ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg/0.8 ml solution for injection for paediatric use.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.8 ml single dose vial contains 40 mg of adalimumab.

Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Humira in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Humira has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Humira is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Paediatric plaque psoriasis

Humira is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Paediatric Crohn's disease

Humira is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Adolescent hidradenitis suppurativa

Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Paediatric Uveitis

Humira is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

4.2 Posology and method of administration

Humira treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which Humira is indicated. Ophthalmologists are advised to consult with an appropriate specialist before initiation of treatment with Humira (see section 4.4). Patients treated with Humira should be given the special alert card.

After proper training in injection technique, patients may self-inject with Humira if their physician determines that it is appropriate and with medical follow-up as necessary.

Posology

Paediatric population

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis from 2 to 12 years of age

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 2-12 years, is 24 mg/m² body surface area up to a maximum single dose of 20 mg adalimumab (for patients aged 2-<4) and up to a maximum single dose of 40mg adalimumab (for patients aged 4-12) administered every other week via subcutaneous injection. The volume for injection is selected based on the patients' height and weight (Table 1).

Table 1. Humira Dose in Millilitres (ml) by Height and Weight of Patients for Polyarticular Juvenile Idiopathic Arthritis and Enthesitis-Related Arthritis

Height (cm)	Total Body Weight (kg)												
	10	**15**	**20**	**25**	**30**	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**
80	0.2	0.3	0.3	0.3									
90	0.2	0.3	0.3	0.4	0.4	0.4							
100	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.5					
110	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.6		
120	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.7
130		0.4	0.4	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.7	0.7
140		0.4	0.4	0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.7	0.7	0.8*
150			0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.7	0.7	0.8*	0.8*
160			0.5	0.5	0.6	0.6	0.7	0.7	0.7	0.8*	0.8*	0.8*	0.8*
170				0.6	0.6	0.6	0.7	0.7	0.8*	0.8*	0.8*	0.8*	0.8*
180					0.6	0.7	0.7	0.8*	0.8*	0.8*	0.8*	0.8*	0.8*

*Maximum single dose is 40 mg (0.8 ml)

Polyarticular juvenile idiopathic arthritis from 13 years of age

For patients from 13 years of age, a dose of 40 mg is administered every other week regardless of body surface area.

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

There is no relevant use of Humira in patients aged less than 2 years for this indication.

Enthesitis-related arthritis

The recommended dose of Humira for patients with enthesitis-related arthritis 6 years of age and older is 24 mg/m² body surface area up to a maximum single dose of 40 mg adalimumab administered every other week via subcutaneous injection. The volume for injection is selected based on the patients' height and weight (Table 1).

Humira has not been studied in patients with enthesitis-related arthritis aged less than 6 years.

Paediatric plaque psoriasis

The recommended Humira dose is 0.8 mg per kg body weight (up to a maximum of 40 mg per dose) administered subcutaneously weekly for the first two doses and every other week thereafter. Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.

If retreatment with Humira is indicated, the above guidance on dose and treatment duration should be followed.

The safety of Humira in paediatric patients with plaque psoriasis has been assessed for a mean of 13 months.

There is no relevant use of Humira in children aged less than 4 years for this indication.

The volume for injection is selected based on the patients' weight (Table 2).

Table 2: Humira Dose in Millilitres (ml) by Weight for Patients with Paediatric Psoriasis

Body Weight (kg)	Paediatric Psoriasis Dose
13 – 16	0.2 ml (10 mg)
17 – 22	0.3 ml (15 mg)
23 – 28	0.4 ml (20 mg)
29 – 34	0.5 ml (25 mg)
35 – 40	0.6 ml (30 mg)
41 – 46	0.7 ml (35 mg)
47+	0.8 ml (40 mg)

Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)

There are no clinical trials with Humira in adolescent patients with HS. The posology of Humira in these patients has been determined from pharmacokinetic modelling and simulation (see section 5.2).

The recommended Humira dose is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via subcutaneous injection.

In adolescent patients with inadequate response to Humira 40 mg every other week, an increase in dosing frequency to 40 mg every week may be considered.

Antibiotics may be continued during treatment with Humira if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Humira.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

Should treatment be interrupted, Humira may be re-introduced as appropriate.

The benefit and risk of continued long-term treatment should be periodically evaluated (see adult data in section 5.1).

There is no relevant use of Humira in children aged less than 12 years in this indication.

Paediatric Crohn's disease

Paediatric Crohn's disease patients < 40 kg:

The recommended Humira induction dose regimen for paediatric subjects with moderately to severely active Crohn's disease is 40 mg at Week 0 followed by 20 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 80 mg at Week 0 (dose can be administered as two injections in one day), 40 mg at Week 2 can be used, with the awareness that the risk for adverse events may be higher with use of the higher induction dose.

After induction treatment, the recommended dose is 20 mg every other week via subcutaneous injection. Some subjects who experience insufficient response may benefit from an increase in dosing frequency to 20 mg Humira every week.

Paediatric Crohn's disease patients ≥ 40 kg:

The recommended Humira induction dose regimen for paediatric subjects with moderately to severely active Crohn's disease is 80 mg at Week 0 followed by 40 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), 80 mg at Week 2 can be used, with the awareness that the risk for adverse events may be higher with use of the higher induction dose.

After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Some subjects who experience insufficient response may benefit from an increase in dosing frequency to 40 mg Humira every week.

Continued therapy should be carefully considered in a subject not responding by Week 12.

There is no relevant use of Humira in children aged less than 6 years for this indication.

Paediatric Uveitis

In paediatric uveitis, there is no experience in the treatment with Humira without concomitant treatment with methotrexate.

Paediatric uveitis patients < 30 kg:

The recommended dose of Humira is 20 mg every other week in combination with methotrexate.

When Humira therapy is initiated, a loading dose of 40 mg may be administered one week prior to the start of maintenance therapy. No clinical data are available on the use of a Humira loading dose in children < 6 years of age (see section 5.2).

Paediatric uveitis patients ≥ 30 kg:

The recommended dose of Humira is 40 mg every other week in combination with methotrexate.

When Humira therapy is initiated, a loading dose of 80 mg may be administered one week prior to the start of maintenance therapy.

There is no relevant use of Humira in children aged less than 2 years in this indication.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis (see section 5.1).

Renal and/or hepatic impairment

Humira has not been studied in these patient populations. No dose recommendations can be made.

Method of administration

Humira is administered by subcutaneous injection. Full instructions for use are provided in the package leaflet.

A 40 mg pen and a 40 mg prefilled syringe are also available for patients to administer a full 40 mg dose.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active tuberculosis or other severe infections such as sepsis, and opportunistic infections (see section 4.4).

Moderate to severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections

Patients taking TNF-antagonists are more susceptible to serious infections. Impaired lung function may increase the risk for developing infections. Patients must therefore be monitored closely for infections, including tuberculosis, before, during and after treatment with Humira. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period.

Treatment with Humira should not be initiated in patients with active infections including chronic or localised infections until infections are controlled. In patients who have been exposed to tuberculosis

and patients who have travelled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with Humira should be considered prior to initiating therapy (see *Other opportunistic infections*).

Patients who develop a new infection while undergoing treatment with Humira, should be monitored closely and undergo a complete diagnostic evaluation. Administration of Humira should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of Humira in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications.

Serious infections

Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis have been reported in patients receiving Humira.

Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia. Hospitalisation or fatal outcomes associated with infections have been reported.

Tuberculosis

Tuberculosis, including reactivation and new onset of tuberculosis, has been reported in patients receiving Humira. Reports included cases of pulmonary and extra-pulmonary (i.e. disseminated) tuberculosis.

Before initiation of therapy with Humira, all patients must be evaluated for both active or inactive ("latent") tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients (local recommendations may apply). It is recommended that the conduct and results of these tests are recorded in the patient alert card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Humira therapy must not be initiated (see section 4.3).

In all situations described below, the benefit/risk balance of therapy should be very carefully considered.

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted.

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylaxis treatment before the initiation of Humira, and in accordance with local recommendations.

Use of anti-tuberculosis prophylaxis treatment should also be considered before the initiation of Humira in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with Humira. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with Humira.

Patients should be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (e.g., persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with Humira.

Other opportunistic infections

Opportunistic infections, including invasive fungal infections have been observed in patients receiving Humira. These infections have not consistently been recognised in patients taking TNF-antagonists and this has resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.

For patients who develop the signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock an invasive fungal infection should be suspected and administration of Humira should be promptly discontinued. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections.

Hepatitis B reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including Humira, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had a fatal outcome. Patients should be tested for HBV infection before initiating treatment with Humira. For patients who test positive for hepatitis B infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Carriers of HBV who require treatment with Humira should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data from treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, Humira should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurological events

TNF-antagonists including Humira have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of Humira in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of Humira should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of Humira therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Allergic reactions

Serious allergic reactions associated with Humira were rare during clinical trials. Non-serious allergic reactions associated with Humira were uncommon during clinical trials. Reports of serious allergic reactions including anaphylaxis have been received following Humira administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Humira should be discontinued immediately and appropriate therapy initiated.

Immunosuppression

In a study of 64 patients with rheumatoid arthritis that were treated with Humira, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T-, B, - NK-cells, monocyte/macrophages, and neutrophils.

Malignancies and lymphoproliferative disorders

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare. In the post marketing setting, cases of leukaemia have been reported in patients treated with a TNF-antagonist. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. With the current knowledge, a possible risk for the development of lymphomas, leukaemia, and other malignancies in patients treated with a TNF-antagonist cannot be excluded.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including adalimumab in the post marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Rare postmarketing cases of hepatosplenic T-cell lymphoma have been identified in patients treated with adalimumab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Some of these hepatosplenic T-cell lymphomas with Humira have occurred in young adult patients on concomitant treatment with azathioprine or 6-mercaptopurine used for inflammatory bowel disease. The potential risk with the combination of azathioprine or 6-mercaptopurine and Humira should be carefully considered. A risk for the development of hepatosplenic T-cell lymphoma in patients treated with Humira cannot be excluded (see section 4.8).

No studies have been conducted that include patients with a history of malignancy or in whom treatment with Humira is continued following development of malignancy. Thus additional caution should be exercised in considering Humira treatment of these patients (see section 4.8).

All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with Humira. Melanoma and Merkel cell carcinoma have also been reported in patients treated with TNF-antagonists including adalimumab (see section 4.8).

In an exploratory clinical trial evaluating the use of another TNF-antagonist, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking.

With current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.

Haematologic reactions

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF-antagonists. Adverse events of the haematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been reported with Humira. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor) while on Humira. Discontinuation of Humira therapy should be considered in patients with confirmed significant haematologic abnormalities.

Vaccinations

Similar antibody responses to the standard 23-valent pneumococcal vaccine and the influenza trivalent virus vaccination were observed in a study in 226 adult subjects with rheumatoid arthritis who were treated with adalimumab or placebo. No data are available on the secondary transmission of infection by live vaccines in patients receiving Humira.

It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy.

Patients on Humira may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Congestive heart failure

In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving Humira. Humira should be used with caution in patients with mild heart failure (NYHA class I/II). Humira is contraindicated in moderate to severe heart failure (see section 4.3). Treatment with Humira must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes

Treatment with Humira may result in the formation of autoimmune antibodies. The impact of long-term treatment with Humira on the development of autoimmune diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Humira and is positive for antibodies against double-stranded DNA, further treatment with Humira should not be given (see section 4.8).

Concurrent administration of biologic DMARDS or TNF-antagonists

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-antagonist, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF-antagonists. Therefore, the combination of adalimumab and anakinra is not recommended. (See section 4.5).

Concomitant administration of adalimumab with other biologic DMARDS (e.g, anakinra and abatacept) or other TNF-antagonists is not recommended based upon the possible increased risk for infections, including serious infections and other potential pharmacological interactions. (See section 4.5).

Surgery

There is limited safety experience of surgical procedures in patients treated with Humira. The long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Humira should be closely monitored for infections, and

appropriate actions should be taken. There is limited safety experience in patients undergoing arthroplasty while receiving Humira.

Small bowel obstruction

Failure to respond to treatment for Crohn's disease may indicate the presence of fixed fibrotic stricture that may require surgical treatment. Available data suggest that Humira does not worsen or cause strictures.

Elderly

The frequency of serious infections among Humira treated subjects over 65 years of age (3.7%) was higher than for those under 65 years of age (1.5%). Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly.

Paediatric population

See Vaccinations above.

4.5 Interaction with other medicinal products and other forms of interaction

Humira has been studied in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis patients taking Humira as monotherapy and those taking concomitant methotrexate. Antibody formation was lower when Humira was given together with methotrexate in comparison with use as monotherapy. Administration of Humira without methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab (see section 5.1).

The combination of Humira and anakinra is not recommended (see section 4.4 "Concurrent administration of biologic DMARDS or TNF-antagonists").

The combination of Humira and abatacept is not recommended (see section 4.4 "Concurrent administration of biologic DMARDS or TNF-antagonists").

4.6 Fertility, pregnancy and lactation

Women of child bearing potential/Contraception in males and females

Women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and continue its use for at least five months after the last Humira treatment.

Pregnancy

For Humira, limited clinical data on exposed pregnancies are available

In a developmental toxicity study conducted in monkeys, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. Preclinical data on postnatal toxicity of adalimumab are not available (see section 5.3).

Due to its inhibition of TNFα, adalimumab administered during pregnancy could affect normal immune responses in the newborn. Administration of adalimumab is not recommended during pregnancy.

Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Breast feeding

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion.

However, because human immunoglobulins are excreted in milk, women must not breast-feed for at least five months after the last Humira treatment.

Fertility

Preclinical data on fertility effects of adalimumab are not available.

4.7 Effects on ability to drive and use machines

Humira may have a minor influence on the ability to drive and use machines. Vertigo and visual impairment may occur following administration of Humira (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Humira was studied in 9,506 patients in pivotal controlled and open label trials for up to 60 months or more. These trials included rheumatoid arthritis patients with short term and long standing disease, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis) as well as axial spondyloarthritis (ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients. The pivotal controlled studies involved 6,089 patients receiving Humira and 3,801 patients receiving placebo or active comparator during the controlled period.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of pivotal studies was 5.9% for patients taking Humira and 5.4% for control treated patients.

The most commonly reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain.

Serious adverse reactions have been reported for Humira. TNF-antagonists, such as Humira affect the immune system and their use may affect the body's defence against infection and cancer.
Fatal and life-threatening infections (including sepsis, opportunistic infections and TB), HBV reactivation and various malignancies (including leukaemia, lymphoma and HSTCL) have also been reported with use of Humira.

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia, aplastic anaemia, central and peripheral demyelinating events and reports of lupus, lupus-related conditions and Stevens-Johnson syndrome.

Paediatric population

Undesirable effects in paediatric patients

In general, the adverse events in paediatric patients were similar in frequency and type to those seen in adult patients.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience and are displayed by system organ class and frequency in Table 3 below: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to< 1/100); rare (≥ 1/10,000 to < 1/1,000); and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The highest frequency seen among the various indications has been included. An asterisk (*) appears in the SOC column if further information is found elsewhere in sections 4.3, 4.4 and 4.8.

Table 3
Undesirable Effects

System Organ Class	Frequency	Adverse Reaction
Infections and infestations*	Very common	respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections, joint infections
	Uncommon	neurological infections (including viral meningitis), opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), bacterial infections, eye infections, diverticulitis[1)]
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Common	skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma), benign neoplasm

System Organ Class	Frequency	Adverse Reaction
	Uncommon	lymphoma**, solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma**
	Rare	leukaemia[1)]
	Not known	hepatosplenic T-cell lymphoma[1)], Merkel cell carcinoma (neuroendocrine carcinoma of the skin)[1)]
Blood and the lymphatic system disorders*	Very common	leukopenia (including neutropenia and agranulocytosis), anaemia
	Common	leucocytosis, thrombocytopenia
	Uncommon	idiopathic thrombocytopenic purpura
	Rare	pancytopenia
Immune system disorders*	Common	hypersensitivity, allergies (including seasonal allergy)
	Uncommon	sarcoidosis[1)], vasculitis
	Rare	anaphylaxis[1)]
Metabolism and nutrition disorders	Very common	lipids increased
	Common	hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia, hyperglycaemia, hypophosphatemia, dehydration
Psychiatric disorders	Common	mood alterations (including depression), anxiety, insomnia
Nervous system disorders*	Very common	headache

System Organ Class	Frequency	Adverse Reaction
	Common	paraesthesias (including hypoesthesia), migraine, nerve root compression
	Uncommon	cerebrovascular accident[1)], tremor, neuropathy
	Rare	multiple sclerosis, demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome) [1)]
Eye disorders	Common	visual impairment, conjunctivitis, blepharitis, eye swelling
	Uncommon	diplopia
Ear and labyrinth disorders	Common	vertigo
	Uncommon	deafness, tinnitus
Cardiac disorders*	Common	tachycardia
	Uncommon	myocardial infarction[1)], arrhythmia, congestive heart failure
	Rare	cardiac arrest
Vascular disorders	Common	hypertension, flushing, haematoma
	Uncommon	aortic aneurysm, vascular arterial occlusion, thrombophlebitis
Respiratory, thoracic and mediastinal disorders*	Common	asthma, dyspnoea, cough

System Organ Class	Frequency	Adverse Reaction
	Uncommon	pulmonary embolism[1)], interstitial lung disease, chronic obstructive pulmonary disease, pneumonitis, pleural effusion[1)]
	Rare	pulmonary fibrosis[1)]
Gastrointestinal disorders	Very common	abdominal pain, nausea and vomiting
	Common	GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	pancreatitis, dysphagia, face oedema
	Rare	intestinal perforation[1)]
Hepato-biliary disorders*	Very Common	elevated liver enzymes
	Uncommon	cholecystitis and cholelithiasis, hepatic steatosis, bilirubin increased
	Rare	hepatitis reactivation of hepatitis B[1)] autoimmune hepatitis[1)]
	Not known	liver failure[1)]
Skin and subcutaneous tissue disorders	Very Common	rash (including exfoliative rash)
	Common	worsening or new onset of psoriasis (including palmoplantar pustular psoriasis)[1)], urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis, hyperhidrosis, alopecia[1)], pruritus
	Uncommon	night sweats, scar

System Organ Class	Frequency	Adverse Reaction
	Rare	erythema multiforme[1)], Stevens-Johnson syndrome[1)], angioedema[1)], cutaneous vasculitis[1)]
	Not known	worsening of symptoms of dermatomyositis[1)]
Musculoskeletal and connective tissue disorders	Very common	musculoskeletal pain
	Common	muscle spasms (including blood creatine phosphokinase increased)
	Uncommon	rhabdomyolysis, systemic lupus erythematosus
	Rare	lupus-like syndrome[1)]
Renal and urinary disorders	Common	renal impairment, haematuria
	Uncommon	nocturia
Reproductive system and breast disorders	Uncommon	erectile dysfunction
General disorders and administration site conditions*	Very Common	injection site reaction (including injection site erythema)
	Common	chest pain, oedema, pyrexia[1)]
	Uncommon	inflammation
Investigations*	Common	coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), autoantibody test positive (including double stranded DNA antibody), blood lactate dehydrogenase increased
Injury, poisoning and procedural complications	Common	impaired healing

* further information is found elsewhere in sections 4.3, 4.4 and 4.8
** including open label extension studies
[1)] including spontaneous reporting data

Description of selected adverse reactions

Injection site reactions

In the pivotal controlled trials in adults and children, 12.9% of patients treated with Humira developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 7.2% of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Infections

In the pivotal controlled trials in adults and children, the rate of infection was 1.51 per patient year in the Humira treated patients and 1.46 per patient year in the placebo and active control-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, and sinusitis. Most patients continued on Humira after the infection resolved.

The incidence of serious infections was 0.04 per patient year in Humira treated patients and 0.03 per patient year in placebo and active control − treated patients.

In controlled and open label adult and paediatric studies with Humira, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extra-pulmonary locations) and invasive opportunistic infections (e.g. disseminated or extrapulmonary histoplasmosis, blastomycosis, coccidioidomycosis, pneumocystis, candidiasis, aspergillosis and listeriosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

Malignancies and lymphoproliferative disorders

No malignancies were observed in 249 paediatric patients with an exposure of 655.6 patient years during Humira trials in patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis). In addition, no malignancies were observed in 192 paediatric patients with an exposure of 498.1 patient years during Humira trials in paediatric patients with Crohn's disease. No malignancies were observed in 77 paediatric patients with an exposure of 80.0 patient years during a Humira trial in paediatric patients with chronic plaque psoriasis. No malignancies were observed in 60 paediatric patients with an exposure of 58.4 patient years during a Humira trial in paediatric patients with uveitis.

During the controlled portions of pivotal Humira trials in adults of at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.8 (4.4, 10.5) per 1,000 patient-years among 5,291 Humira treated patients *versus* a rate of 6.3 (3.4, 11.8) per 1,000 patient-years among 3,444 control patients (median duration of treatment was 4.0 months for Humira and 3.8 months for control-treated patients). The rate (95% confidence interval) of non-melanoma skin cancers was 8.8 (6.0, 13.0) per 1,000 patient-years among Humira-treated patients and 3.2 (1.3, 7.6) per 1,000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) of 2.7 (1.4, 5.4) per 1,000 patient-years among Humira-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients. The rate (95% confidence interval) of lymphomas was 0.7 (0.2, 2.7) per 1,000 patient-years among Humira-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients.

When combining controlled portions of these trials and ongoing and completed open label extension studies with a median duration of approximately 3.3 years including 6,427 patients and over 26,439 patient-years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 8.5 per 1,000 patient years. The observed rate of non-melanoma skin

cancers is approximately 9.6 per 1,000 patient years, and the observed rate of lymphomas is approximately 1.3 per 1,000 patient years.

In post-marketing experience from January 2003 to December 2010, predominantly in patients with rheumatoid arthritis, the reported rate of malignancies is approximately 2.7 per 1,000 patient treatment years. The reported rates for non-melanoma skin cancers and lymphomas are approximately 0.2 and 0.3 per 1,000 patient treatment years, respectively (see section 4.4).

Rare post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with adalimumab (see section 4.4).

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis studies I − V. In these trials, 11.9% of patients treated with Humira and 8.1% of placebo and active control − treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at Week 24. Two patients out of 3,441 treated with Humira in all rheumatoid arthritis and psoriatic arthritis studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms.

Hepato-biliary events

In controlled Phase 3 trials of Humira in patients with rheumatoid arthritis and psoriatic arthritis with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.7% of Humira-treated patients and 1.6% of control-treated patients.

In controlled Phase 3 trials of Humira in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations ≥ 3 x ULN occurred in 6.1% of Humira-treated patients and 1.3% of control-treated patients. Most ALT elevations occurred with concomitant methotrexate use. No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial of Humira in patients with polyarticular juvenile idiopathic arthritis who were 2 to <4 years.

In controlled Phase 3 trials of Humira in patients with Crohn's disease and ulcerative colitis with a control period ranging from 4 to 52 weeks. ALT elevations ≥ 3 x ULN occurred in 0.9% of Humira-treated patients and 0.9% of controlled-treated patients.

In the Phase 3 trial of Humira in patients with paediatric Crohn's disease which evaluated efficacy and safety of two body weight adjusted maintenance dose regimens following body weight adjusted induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients of whom 4 were receiving concomitant immunosuppressants at baseline.

In controlled Phase 3 trials of Humira in patients with plaque Psoriasis with a control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of Humira-treated patients and 1.8% of control-treated patients.

No ALT elevations ≥ 3 X ULN occurred in the Phase 3 trial of Humira in paediatric patients with plaque psoriasis.

In controlled trials of Humira (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in patients with hidradenitis suppurativa with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of Humira-treated patients and 0.6% of control-treated patients.

Across all indications in clinical trials patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have also been post-marketing reports of liver failure as well as less severe liver disorders that may precede liver failure, such as hepatitis including autoimmune hepatitis in patients receiving adalimumab.

Concurrent treatment with azathioprine/6-mercaptopurine

In adult Crohn's disease studies, higher incidences of malignant and serious infection-related adverse events were seen with the combination of Humira and azathioprine/6-mercaptopurine compared with Humira alone.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No dose-limiting toxicity was observed during clinical trials. The highest dose level evaluated has been multiple intravenous doses of 10 mg/kg, which is approximately 15 times the recommended dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors. ATC code: L04AB04

Mechanism of action

Adalimumab binds specifically to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of0.1-0.2 nM).

Pharmacodynamic effects

After treatment with Humira, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL-6) was observed, compared to baseline in patients with rheumatoid arthritis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after Humira administration. Patients treated with Humira usually experienced improvement in haematological signs of chronic inflammation.

A rapid decrease in CRP levels was also observed in patients with polyarticular juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis and hidradenitis suppurativa after treatment with Humira. In patients with Crohn's disease, a reduction of the number of cells expressing inflammatory markers in the colon including a significant reduction of expression of TNFα was seen. Endoscopic studies in intestinal mucosa have shown evidence of mucosal healing in adalimumab treated patients.

Clinical efficacy and safety

Juvenile idiopathic arthritis (JIA)

Polyarticular juvenile idiopathic arthritis (pJIA)

The safety and efficacy of Humira was assessed in two studies (pJIA I and II) in children with active polyarticular or polyarticular course juvenile idiopathic arthritis, who had a variety of JIA onset types (most frequently rheumatoid-factor negative or positive polyarthritis and extended oligoarthritis).

pJIA I

The safety and efficacy of Humira were assessed in a multicentre, randomised, double-blind, parallel − group study in 171 children (4-17 years old) with polyarticular JIA. In the open-label lead in phase (OL LI) patients were stratified into two groups, MTX (methotrexate)-treated or non- MTX-treated. Patients who were in the non-MTX stratum were either naïve to or had been withdrawn from MTX at least two weeks prior to study drug administration. Patients remained on stable doses of NSAIDs and or prednisone (≤ 0.2 mg /kg/day or 10 mg/day maximum). In the OL LI phase all patients received 24 mg/m^2 up to a maximum of 40 mg Humira every other week for 16 weeks. The distribution of patients by age and minimum, median and maximum dose received during the OL LI phase is presented in Table 4.

Table 4
Distribution of patients by age and adalimumab dose received during the OL LI phase

Age Group	**Number of patients at Baseline n (%)**	**Minimum, median and maximum dose**
4 to 7 years	31 (18.1)	10, 20 and 25 mg
8 to 12 years	71 (41.5)	20, 25 and 40 mg
13 to 17 years	69 (40.4)	25, 40 and 40 mg

Patients demonstrating a Pediatric ACR 30 response at Week 16 were eligible to be randomised into the double blind (DB) phase and received either Humira 24 mg/m^2 up to a maximum of 40 mg, or placebo every other week for an additional 32 weeks or until disease flare. Disease flare criteria were defined as a worsening of ≥ 30% from baseline in ≥ 3 of 6 Pediatric ACR core criteria, ≥ 2 active joints, and improvement of > 30% in no more than 1 of the 6 criteria. After 32 weeks or at disease flare, patients were eligible to enrol into the open label extension phase.

Table 5
Ped ACR 30 Responses in the JIA study

Stratum	**MTX**		**Without MTX**	
Phase				
OL-LI 16 weeks				
Ped ACR 30 response (n/N)	94.1% (80/85)		74.4% (64/86)	
Efficacy Outcomes				
Double Blind 32 weeks	Humira / MTX (N = 38)	Placebo / MTX (N = 37)	Humira (N = 30)	Placebo (N = 28)
Disease flares at the end of 32weeks[a] (n/N)	36.8% (14/38)	64.9% (24/37)[b]	43.3% (13/30)	71.4% (20/28)[c]
Median time to disease flare	>32 weeks	20 weeks	>32 weeks	14 weeks

[a] Ped ACR 30/50/70 responses Week 48 significantly greater than those of placebo treated patients
[b] p = 0.015
[c] p = 0.031

Amongst those who responded at Week 16 (n=144), the Pediatric ACR 30/50/70/90 responses were maintained for up to six years in the OLE phase in patients who received Humira throughout the study. Over all 19 subjects, of which 11 of the baseline age group 4 to 12 and 8 of the baseline age group 13 to 17 years were treated 6 years or longer.

Overall responses were generally better and, fewer patients developed antibodies when treated with the combination of Humira and MTX compared to Humira alone. Taking these results into consideration, Humira is recommended for use in combination with MTX and for use as monotherapy in patients for whom MTX use is not appropriate (see section 4.2).

pJIA II

The safety and efficacy of Humira was assessed in an open-label, multicentre study in 32 children (2 - <4 years old or aged 4 and above weighing < 15 kg) with moderately to severely active polyarticular JIA. The patients received 24 mg/m^2 body surface area (BSA) of Humira up to a maximum of 20 mg every other week as a single dose via SC injection for at least 24 weeks. During the study, most subjects used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs.

At Week 12 and Week 24, PedACR30 response was 93.5% and 90.0%, respectively, using the observed data approach. The proportions of subjects with PedACR50/70/90 at Week 12 and Week 24 were 90.3%/61.3%/38.7% and 83.3%/73.3%/36.7%, respectively. Amongst those who responded (Pediatric ACR 30) at Week 24 (n=27 out of 30 patients), the Pediatric ACR 30 responses were maintained for up to 60 weeks in the OLE phase in patients who received Humira throughout this time period. Overall, 20 subjects were treated for 60 weeks or longer.

Enthesitis-related arthritis

The safety and efficacy of Humira were assessed in a multicentre, randomised, double-blind study in 46 paediatric patients (6 to 17 years old) with moderate enthesitis-related arthritis. Patients were randomised to receive either 24 mg/m^2 body surface area (BSA) of Humira up to a maximum of 40 mg, or placebo every other week for 12 weeks. The double-blind period is followed by an open-label (OL) period during which patients received 24 mg/m^2 BSA of Humira up to a maximum of 40 mg every other week subcutaneously for up to an additional 192 weeks. The primary endpoint was

the percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with loss of motion plus pain and/or tenderness), which was achieved with mean percent decrease of -62.6% (median percent change -88.9%) in patients in the Humira group compared to -11.6% (median percent change -50.0%) in patients in the placebo group. Improvement in number of active joints with arthritis was maintained during the OL period through Week 156 for the 26 of 31 (84%) patients in the Humira group who remained inthe study. Although not statistically significant, the majority of patients demonstrated clinical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count (TJC), swollen joint count (SJC), Pediatric ACR 50 response, and Pediatric ACR 70 response.

Adults with rheumatoid arthritis

Humira was evaluated in over 3,000 patients in all rheumatoid arthritis clinical trials. The efficacy and safety of Humira were assessed in five randomised, double-blind and well-controlled studies. Some patients were treated for up to 120 months duration.

RA study I evaluated 271 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had failed therapy with at least one disease-modifying, anti rheumatic drug and had insufficient efficacy with methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 10 to 25 mg every week. Doses of 20, 40 or 80 mg of Humira or placebo were given every other week for 24 weeks.

RA study II evaluated 544 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old and had failed therapy with at least one disease-modifying, anti-rheumatic drugs. Doses of 20 or 40 mg of Humira were given by subcutaneous injection every other week with placebo on alternative weeks or every week for 26 weeks; placebo was given every week for the same duration. No other disease-modifying anti-rheumatic drugs were allowed.

RA study III evaluated 619 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, and who had an ineffective response to methotrexate at doses of 12.5 to 25 mg or have been intolerant to 10 mg of methotrexate every week. There were three groups in this study. The first received placebo injections every week for 52 weeks. The second received 20 mg of Humira every week for 52 weeks. The third group received 40 mg of Humira every other week with placebo injections on alternate weeks. Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of Humira/MTX was administered every other week up to 10 years.

RA study IV primarily assessed safety in 636 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old. Patients were permitted to be either disease-modifying, anti-rheumatic drug-naïve or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. These therapies include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine and/or gold salts. Patients were randomised to 40 mg of Humira or placebo every other week for 24 weeks.

RA study V evaluated 799 methotrexate-naïve, adult patients with moderate to severely active early rheumatoid arthritis (mean disease duration less than 9 months). This study evaluated the efficacy of Humira 40 mg every other week/methotrexate combination therapy, Humira 40 mg every other week monotherapy and methotrexate monotherapy in reducing the signs and symptoms and rate of progression of joint damage in rheumatoid arthritis for 104 weeks. Upon completion of the first 104 weeks, 497 patients enrolled in an open-label extension phase in which 40 mg of Humira was administered every other week up to 10 years.

The primary end point in RA studies I, II and III and the secondary endpoint in RA study IV was the percent of patients who achieved an ACR 20 response at Week 24 or 26. The primary endpoint in RA study V was the percent of patients who achieved an ACR 50 response at Week 52. RA studies III

and V had an additional primary endpoint at 52 weeks of retardation of disease progression (as detected by X-ray results). RA study III also had a primary endpoint of changes in quality of life.

ACR response

The percent of Humira-treated patients achieving ACR 20, 50 and 70 responses was consistent across RA studies I, II and III. The results for the 40 mg every other week dose are summarised in Table 6.

Table 6 ACR Responses in Placebo-Controlled Trials (Percent of Patients)

Response	RA Study I[a]**		RA Study II[a]**		RA Study III[a]**	
	Placebo/ MTX[c] n=60	Humira[b]/ MTX[c] n=63	Placebo n=110	Humira[b] n=113	Placebo/ MTX[c] n=200	Humira[b]/ MTX[c] n=207
ACR 20						
6 months	13.3%	65.1%	19.1%	46.0%	29.5%	63.3%
12 months	NA	NA	NA	NA	24.0%	58.9%
ACR 50						
6 months	6.7%	52.4%	8.2%	22.1%	9.5%	39.1%
12 months	NA	NA	NA	NA	9.5%	41.5%
ACR 70						
6 months	3.3%	23.8%	1.8%	12.4%	2.5%	20.8%
12 months	NA	NA	NA	NA	4.5%	23.2%

[a] RA study I at 24 weeks, RA study II at 26 weeks , and RA study III at 24 and 52 weeks
[b] 40 mg Humira administered every other week
[c] MTX = methotrexate
**p < 0.01, Humira *versus* placebo

In RA studies I-IV, all individual components of the ACR response criteria (number of tender and swollen joints, physician and patient assessment of disease activity and pain, disability index (HAQ) scores and CRP (mg/dl) values) improved at 24 or 26 weeks compared to placebo. In RA study III, these improvements were maintained throughout 52 weeks.

In the open-label extension for RA study III, most patients who were ACR responders maintained response when followed for up to 10 years. Of 207 patients who were randomised to Humira 40 mg every other week, 114 patients continued on Humira 40 mg every other week for 5 years. Among those, 86 patients (75.4%) had ACR 20 responses; 72 patients (63.2%) had ACR 50 responses; and 41 patients (36%) had ACR 70 responses. Of 207 patients, 81 patients continued on Humira 40 mg every other week for 10 years. Among those, 64 patients (79.0%) had ACR 20 responses; 56 patients (69.1%) had ACR 50 responses; and 43 patients (53.1%) had ACR 70 responses.

In RA study IV, the ACR 20 response of patients treated with Humira plus standard of care was statistically significantly better than patients treated with placebo plus standard of care ($p < 0.001$).

In RA studies I-IV, Humira-treated patients achieved statistically significant ACR 20 and 50 responses compared to placebo as early as one to two weeks after initiation of treatment.

In RA study V with early rheumatoid arthritis patients who were methotrexate naïve, combination therapy with Humira and methotrexate led to faster and significantly greater ACR responses than methotrexate monotherapy and Humira monotherapy at Week 52 and responses were sustained at Week 104 (see Table 7).

Table 7 ACR Responses in RA Study V
(percent of patients)

Response	MTX n=257	Humira n=274	Humira/MTX n=268	p-value[a]	p-value[b]	p-value[c]
ACR 20						
Week 52	62.6%	54.4%	72.8%	0.013	< 0.001	0.043
Week 104	56.0%	49.3%	69.4%	0.002	< 0.001	0.140
ACR 50						
Week 52	45.9%	41.2%	61.6%	< 0.001	< 0.001	0.317
Week 104	42.8%	36.9%	59.0%	< 0.001	< 0.001	0.162
ACR 70						
Week 52	27.2%	25.9%	45.5%	< 0.001	< 0.001	0.656
Week 104	28.4%	28.1%	46.6%	< 0.001	< 0.001	0.864

[a] p-value is from the pairwise comparison of methotrexate monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test.
[b] p-value is from the pairwise comparison of Humira monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test
[c] p-value is from the pairwise comparison of Humira monotherapy and methotrexate monotherapy using the Mann-Whitney U test

In the open-label extension for RA study V, ACR response rates were maintained when followed for up to 10 years. Of 542 patients who were randomised to Humira 40 mg every other week, 170 patients continued on Humira 40 mg every other week for 10 years. Among those, 154 patients (90.6%) had ACR 20 responses; 127 patients (74.7%) had ACR 50 responses; and 102 patients (60.0%) had ACR 70 responses.

At Week 52, 42.9% of patients who received Humira/methotrexate combination therapy achieved clinical remission (DAS28 (CRP) < 2.6) compared to 20.6% of patients receiving methotrexate monotherapy and 23.4% of patients receiving Humira monotherapy. Humira/methotrexate combination therapy was clinically and statistically superior to methotrexate ($p < 0.001$) and Humira monotherapy ($p < 0.001$) in achieving a low disease state in patients with recently diagnosed moderate to severe rheumatoid arthritis. The response for the two monotherapy arms was similar ($p = 0.447$). Of 342 subjects originally randomized to Humira monotherapy or Humira/methotrexate combination therapy who entered the open-label extension study, 171 subjects completed 10 years of Humira treatment. Among those, 109 subjects (63.7%) were reported to be in remission at 10 years.

Radiographic response

In RA study III, where Humira treated patients had a mean duration of rheumatoid arthritis of approximately 11 years, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score. Humira/methotrexate patients demonstrated significantly less radiographic progression than patients receiving methotrexate alone at 6 and 12 months (see Table 8).

In the open-label extension of RA Study III, the reduction in rate of progression of structural damage is maintained for 8 and 10 years in a subset of patients. At 8 years, 81 of 207 patients originally treated with 40 mg Humira every other week were evaluated radiographically. Among those, 48 patients showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less. At 10 years, 79 of 207 patients originally treated with 40 mg Humira every other week were evaluated radiographically. Among those, 40 patients showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less.

Table 8 Radiographic Mean Changes Over 12 Months in RA Study III

	Placebo/ MTX[a]	Humira/MTX 40 mg every other week	Placebo/MTX-Humira/MTX (95% Confidence Interval[b])	p-value
Total Sharp Score	2.7	0.1	2.6 (1.4, 3.8)	< 0.001[c]
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	< 0.001
JSN[d] score	1.0	0.1	0.9 (0.3, 1.4)	0.002

[a]methotrexate
[b]95% confidence intervals for the differences in change scores between methotrexate and Humira.
[c]Based on rank analysis
[d]Joint Space Narrowing

In RA study V, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (see Table 9).

Table 9 Radiographic Mean Changes at Week 52 in RA Study V

	MTX n=257 (95% confidence interval)	Humira n=274 (95% confidence interval)	Humira/MTX n=268 (95% confidence interval)	p-value[a]	p-value[b]	p-value[c]
Total Sharp Score	5.7 (4.2-7.3)	3.0 (1.7-4.3)	1.3 (0.5-2.1)	< 0.001	0.0020	< 0.001
Erosion score	3.7 (2.7-4.7)	1.7 (1.0-2.4)	0.8 (0.4-1.2)	< 0.001	0.0082	< 0.001
JSN score	2.0 (1.2-2.8)	1.3 (0.5-2.1)	0.5 (0-1.0)	< 0.001	0.0037	0.151

[a] p-value is from the pairwise comparison of methotrexate monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test.
[b] p-value is from the pairwise comparison of Humira monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test
[c] p-value is from the pairwise comparison of Humira monotherapy and methotrexate monotherapy using the Mann-Whitney U test

Following 52 weeks and 104 weeks of treatment, the percentage of patients without progression (change from baseline in modified Total Sharp Score ≤ 0.5) was significantly higher with Humira/methotrexate combination therapy (63.8% and 61.2% respectively) compared to methotrexate monotherapy (37.4% and 33.5% respectively, $p < 0.001$) and Humira monotherapy (50.7%, $p < 0.002$ and 44.5%, $p < 0.001$ respectively).

In the open-label extension of RA study V, the mean change from baseline at Year 10 in the modified Total Sharp Score was 10.8, 9.2 and 3.9 in patients originally randomized to methotrexate monotherapy, Humira monotherapy and Humira/methotrexate combination therapy, respectively. The corresponding proportions of patients with no radiographic progression were 31.3%, 23.7% and 36.7% respectively.

Quality of life and physical function

Health-related quality of life and physical function were assessed using the disability index of the Health Assessment Questionnaire (HAQ) in the four original adequate and well-controlled trials, which was a pre-specified primary endpoint at Week 52 in RA study III. All doses/schedules of Humira in all four studies showed statistically significantly greater improvement in the disability index of the HAQ from baseline to Month 6 compared to placebo and in RA study III the same was

seen at Week 52. Results from the Short Form Health Survey (SF 36) for all doses/schedules of Humira in all four studies support these findings, with statistically significant physical component summary (PCS) scores, as well as statistically significant pain and vitality domain scores for the 40 mg every other week dose. A statistically significant decrease in fatigue as measured by functional assessment of chronic illness therapy (FACIT) scores was seen in all three studies in which it was assessed (RA studies I, III, IV).

In RA study III, most subjects who achieved improvement in physical function and continued treatment maintained improvement through Week 520 (120 months) of open-label treatment. Improvement in quality of life was measured up to Week 156 (36 months) and improvement was maintained through that time.

In RA study V, the improvement in the HAQ disability index and the physical component of the SF 36 showed greater improvement ($p < 0.001$) for Humira/methotrexate combination therapy *versus* methotrexate monotherapy and Humira monotherapy at Week 52, which was maintained through Week 104. Among the 250 subjects who completed the open-label extension study, improvements in physical function were maintained through 10 years of treatment.

Paediatric plaque psoriasis

The efficacy of Humira was assessed in a randomised, double-blind, controlled study of 114 paediatric patients from 4 years of age with severe chronic plaque psoriasis (as defined by a Physician's Global Assessment (PGA) ≥ 4 or > 20% BSA involvement or > 10% BSA involvement with very thick lesions or Psoriasis Area and Severity Index (PASI) ≥ 20 or ≥ 10 with clinically relevant facial, genital, or hand/ foot involvement) who were inadequately controlled with topical therapy and heliotherapy or phototherapy.

Patients received Humira 0.8 mg/kg eow (up to 40 mg), 0.4 mg/kg eow (up to 20 mg), or methotrexate 0.1 – 0.4 mg/kg weekly (up to 25 mg). At week 16, more patients randomised to Humira 0.8 mg/kg had positive efficacy responses (e.g., PASI 75) than those randomised to 0.4 mg/kg eow or MTX.

Table 10: Paediatric Plaque Psoriasis Efficacy Results at 16 Weeks

	MTX[a] N=37	Humira 0.8 mg/kg eow N=38
PASI 75[b]	12 (32.4%)	22 (57.9%)
PGA: Clear/minimal[c]	15 (40.5%)	23 (60.5%)

[a] MTX = methotrexate
[b] P=0.027, Humira 0.8 mg/kg versus MTX
[c] P=0.083, Humira 0.8 mg/kg versus MTX

Patients who achieved PASI 75 and PGA clear or minimal were withdrawn from treatment for up to 36 weeks and monitored for loss of disease control (i.e. a worsening of PGA by at least 2 grades). Patients were then re-treated with adalimumab 0.8 mg/kg eow for an additional 16 weeks and response rates observed during retreatment were similar to the previous double-blind period: PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects).

In the open label period of the study, PASI 75 and PGA clear or minimal responses were maintained for up to an additional 52 weeks with no new safety findings.

Adult plaque psoriasis

The safety and efficacy of Humira were studied in adult patients with chronic plaque psoriasis (≥ 10% BSA involvement and PASI ≥ 12 or ≥ 10) who were candidates for systemic therapy or phototherapy

in randomised, double-blind studies. 73% of patients enrolled in Psoriasis Studies I and II had received prior systemic therapy or phototherapy. The safety and efficacy of Humira were also studied in adult patients with moderate to severe chronic plaque psoriasis with concomitant hand and/or foot psoriasis who were candidates for systemic therapy in a randomised double-blind study (Psoriasis Study III).

Psoriasis Study I (REVEAL) evaluated 1,212 patients within three treatment periods. In period A, patients received placebo or Humira at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. After 16weeks of therapy, patients who achieved at least a PASI 75 response (PASI score improvement of at least 75% relative to baseline), entered period B and received open-label 40 mg Humira every other week. Patients who maintained ≥PASI 75 response at Week 33 and were originally randomised to active therapy in Period A, were re-randomised in period C to receive 40 mg Humira every other week or placebo for an additional 19 weeks. Across all treatment groups, the mean baseline PASI score was 18.9 and the baseline PGA score ranged from "moderate" (53% of subjects included) to "severe" (41%) to "very severe" (6%).

Psoriasis Study II (CHAMPION) compared the efficacy and safety of Humira *versus* methotrexate and placebo in 271 patients. Patients received placebo, an initial dose of MTX 7.5 mg and thereafter dose increases up to Week 12, with a maximum dose of 25 mg or an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) for 16 weeks. There are no data available comparing Humira and MTX beyond 16 weeks of therapy. Patients receiving MTX who achieved a ≥PASI 50 response at Week 8 and/or 12 did not receive further dose increases. Across all treatment groups, the mean baseline PASI score was 19.7 and the baseline PGA score ranged from "mild" (<1%) to "moderate" (48%) to "severe" (46%) to "very severe" (6%).

Patients participating in all Phase 2 and Phase 3 psoriasis studies were eligible to enrol into an open-label extension trial, where Humira was given for at least an additional 108 weeks.

In Psoriasis Studies I and II, a primary endpoint was the proportion of patients who achieved a PASI 75 response from baseline at Week 16 (see Tables 11 and 12).

Table 11
Ps Study I (REVEAL) - Efficacy Results at 16 Weeks

	Placebo N=398 n (%)	**Humira 40 mg eow N=814 n (%)**
≥PASI 75[a]	26 (6.5)	578 (70.9)[b]
PASI 100	3 (0.8)	163 (20.0)[b]
PGA: Clear/minimal	17 (4.3)	506 (62.2)[b]

[a] Percent of patients achieving PASI75 response was calculated as centre-adjusted rate
[b] p<0.001, Humira vs. placebo

Table 12
Ps Study II (CHAMPION) Efficacy Results at 16 Weeks

	Placebo N=53 n (%)	**MTX N=110 n (%)**	**Humira 40 mg eow N=108 n (%)**
≥PASI 75	10 (18.9)	39 (35.5)	86 (79.6) [a, b]
PASI 100	1 (1.9)	8 (7.3)	18 (16.7) [c, d]
PGA: Clear/minimal	6 (11.3)	33 (30.0)	79 (73.1) [a, b]

[a] p<0.001 Humira vs. placebo
[b] p<0.001 Humira vs. methotrexate
[c] p<0.01 Humira vs. placebo
[d] p<0.05 Humira vs. methotrexate

In Psoriasis Study I, 28% of patients who were PASI 75 responders and were re-randomised to placebo at Week 33 compared to 5% continuing on Humira, p<0.001, experienced "loss of adequate response" (PASI score after Week 33 and on or before Week 52 that resulted in a <PASI 50 response relative to baseline with a minimum of a 6-point increase in PASI score relative to Week 33). Of the patients who lost adequate response after re-randomisation to placebo who then enrolled into the open-label extension trial, 38% (25/66) and 55% (36/66) regained PASI 75 response after 12 and 24 weeks of re-treatment, respectively.

A total of 233 PASI 75 responders at Week 16 and Week 33 received continuous Humira therapy for 52 weeks in Psoriasis Study I, and continued Humira in the open-label extension trial. PASI 75 and PGA of clear or minimal response rates in these patients were 74.7% and 59.0%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks). In an analysis in which all patients who dropped out of the study for adverse events or lack of efficacy, or who dose-escalated, were considered non-responders, PASI 75 and PGA of clear or minimal response rates in these patients were 69.6% and 55.7%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. During the withdrawal period, symptoms of psoriasis returned over time with a median time to relapse (decline to PGA "moderate" or worse) of approximately 5 months. None of these patients experienced rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the retreatment period had a response of PGA "clear" or "minimal" after 16 weeks of retreatment, irrespective of whether they relapsed during withdrawal (69.1%[123/178] and 88.8% [95/107] for patients who relapsed and who did not relapse during the withdrawal period, respectively). A similar safety profile was observed during retreatment as before withdrawal.

Significant improvements at Week 16 from baseline compared to placebo (Studies I and II) and MTX (Study II) were demonstrated in the DLQI (Dermatology Life Quality Index). In Study I, improvements in the physical and mental component summary scores of the SF-36 were also significant compared to placebo.

In an open-label extension study, for patients who dose escalated from 40 mg every other week to 40 mg weekly due to a PASI response below 50%, 26.4% (92/349) and 37.8% (132/349) of patients achieved PASI 75 response at Week 12 and 24, respectively.

Psoriasis Study III (REACH) compared the efficacy and safety of Humira *versus* placebo in 72 patients with moderate to severe chronic plaque psoriasis and hand and/or foot psoriasis. Patients received an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) or placebo for 16 weeks. At Week 16, a statistically significantly greater proportion

of patients who received Humira achieved PGA of 'clear' or 'almost clear' for the hands and/or feet compared to patients who received placebo (30.6% versus 4.3%, respectively [P = 0.014]).

Psoriasis Study IV compared efficacy and safety of Humira versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open-label Humira treatment for an additional 26 weeks. Nail psoriasis assessments included the Modified Nail Psoriasis Severity Index (mNAPSI), the Physician's Global Assessment of Fingernail Psoriasis (PGA-F) and the Nail Psoriasis Severity Index (NAPSI) (see Table 13). Humira demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement (BSA≥10% (60% of patients) and BSA<10% and ≥5% (40% of patients)).

Table 13
Ps Study IV Efficacy Results at 16, 26 and 52 Weeks

Endpoint	Week 16 Placebo-Controlled		Week 26 Placebo-Controlled		Week 52 Open-label
	Placebo N=108	Humira 40 mg eow N=109	Placebo N=108	Humira 40 mg eow N=109	Humira 40 mg eow N=80
≥ mNAPSI 75 (%)	2.9	26.0[a]	3.4	46.6[a]	65.0
PGA-F clear/minimal and ≥2-grade improvement (%)	2.9	29.7[a]	6.9	48.9[a]	61.3
Percent Change in Total Fingernail NAPSI (%)	-7.8	-44.2 [a]	-11.5	-56.2[a]	-72.2
[a] p<0.001, Humira *vs.* placebo					

Humira treated patients showed statistically significant improvements at Week 26 compared with placebo in the DLQI.

Adolescent hidradenitis suppurativa

There are no clinical trials with Humira in adolescent patients with HS. Efficacy of adalimumab for the treatment of adolescent patients with HS is predicted based on the demonstrated efficacy and exposure-response relationship in adult HS patients and the likelihood that the disease course, pathophysiology, and drug effects are substantially similar to that of adults at the same exposure levels. Safety of the recommended adalimumab dose in the adolescent HS population is based on cross-indication safety profile of adalimumab in both adults and paediatric patients at similar or more frequent doses (see section 5.2).

Adult hidradenitis suppurativa

The safety and efficacy of Humira were assessed in randomised, double-blind, placebo-controlled studies and an open-label extension study in adult patients with moderate to severe hidradenitis suppurativa (HS) who were intolerant, had a contraindication or an inadequate response to at least a 3-month trial of systemic antibiotic therapy. The patients in HS-I and HS-II had Hurley Stage II or III disease with at least 3 abscesses or inflammatory nodules.

Study HS-I (PIONEER I) evaluated 307 patients with 2 treatment periods. In Period A, patients received placebo or Humira at an initial dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every week starting at Week 4 to Week 11. Concomitant antibiotic use was not allowed during the study. After 12 weeks of therapy, patients who had received Humira in Period A were re-randomised in Period B to 1 of 3 treatment groups (Humira 40 mg every week, Humira 40 mg every other week, or placebo from Week 12 to Week 35). Patients who had been randomised to placebo in Period A were assigned to receive Humira 40 mg every week in Period B.

Study HS-II (PIONEER II) evaluated 326 patients with 2 treatment periods. In Period A, patients received placebo or Humira at an initial dose of 160 mg at Week 0 and 80 mg at Week 2 and 40 mg every week starting at Week 4 to Week 11. 19.3% of patients had continued baseline oral antibiotic therapy during the study. After 12 weeks of therapy, patients who had received Humira in Period A were re-randomised in Period B to 1 of 3 treatment groups (Humira 40 mg every week, Humira 40 mg every other week, or placebo from Week 12 to Week 35). Patients who had been randomised to placebo in Period A were assigned to receive placebo in Period B.

Patients participating in Studies HS-I and HS-II were eligible to enroll into an open-label extension study in which Humira 40mg was administered every week. Mean exposure in all adalimumab population was 762 days. Throughout all 3 studies patients used topical antiseptic wash daily.

Clinical Response

Reduction of inflammatory lesions and prevention of worsening of abscesses and draining fistulas was assessed using Hidradenitis Suppurativa Clinical Response (HiSCR; at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count relative to Baseline). Reduction in HS-related skin pain was assessed using a Numeric Rating Scale in patients who entered the study with an initial baseline score of 3 or greater on a 11 point scale.

At Week 12, a significantly higher proportion of patients treated with Humira versus placebo achieved HiSCR. At Week 12, a significantly higher proportion of patients in Study HS-II experienced a clinically relevant decrease in HS-related skin pain (see Table 14). Patients treated with Humira had significantly reduced risk of disease flare during the initial 12 weeks of treatment.

Table 14: Efficacy Results at 12 Weeks, HS Studies I and II

	HS Study I		**HS Study II**	
	Placebo	**Humira 40 mg Weekly**	**Placebo**	**Humira 40 mg Weekly**
Hidradenitis Suppurativa Clinical Response (HiSCR)[a]	N = 154 40 (26.0%)	N = 153 64 (41.8%) *	N=163 45 (27.6%)	N=163 96 (58.9%) ***
≥30% Reduction in Skin Pain[b]	N = 109 27 (24.8%)	N = 122 34 (27.9%)	N=111 23 (20.7%)	N=105 48 (45.7%) ***

* $P < 0.05$, *** $P < 0.001$, Humira versus placebo

[a] Among all randomised patients.

[b] Among patients with baseline HS-related skin pain assessment ≥ 3, based on Numeric Rating Scale 0 – 10; 0 = no skin pain, 10 = skin pain as bad as you can imagine.

Treatment with Humira 40 mg every week significantly reduced the risk of worsening of abscesses and draining fistulas. Approximately twice the proportion of patients in the placebo group in the first 12 weeks of Studies HS-I and HS-II, compared with those in the Humira group experienced worsening of abscesses (23.0% vs 11.4%, respectively) and draining fistulas (30.0% vs 13.9%, respectively).

Greater improvements at Week 12 from baseline compared to placebo were demonstrated in skin-specific health-related quality of life, as measured by the Dermatology Life Quality Index (DLQI; Studies HS-I and HS-II), patient global satisfaction with medication treatment as measured by the Treatment Satisfaction Questionnaire - medication (TSQM; Studies HS-I and HS-II), and physical health as measured by the physical component summary score of the SF-36 (Study HS-I).

In patients with at least a partial response to Humira 40 mg weekly at Week 12, the HiSCR rate at Week 36 was higher in patients who continued weekly Humira than in patients in whom dosing frequency was reduced to every other week, or in whom treatment was withdrawn (see Table 15).

Table 15: Proportion of Patients[a] Achieving HiSCR[b] at Weeks 24 and 36 After Treatment Reassignment from Weekly Humira at Week 12

	Placebo (treatment withdrawal) N = 73	Humira 40 mg every other week N = 70	Humira 40 mg weekly N = 70
Week 24	24 (32.9%)	36 (51.4%)	40 (57.1%)
Week 36	22 (30.1%)	28 (40.0%)	39 (55.7%)

[a] Patients with at least a partial response to Humira 40 mg weekly after 12 weeks of treatment.
[b] Patients meeting protocol-specified criteria for loss of response or no improvement were required to discontinue from the studies and were counted as nonresponders.

Among patients who were at least partial responders at Week 12, and who received continuous weekly Humira therapy, the HiSCR rate at Week 48 was 68.3% and at Week 96 was 65.1%. Longer term treatment with Humira 40 mg weekly for 96 weeks identified no new safety findings.

Among patients whose Humira treatment was withdrawn at Week 12 in Studies HS-I and HS-II, the HiSCR rate 12 weeks after re-introduction of Humira 40 mg weekly returned to levels similar to that observed before withdrawal (56.0 %).

Paediatric Crohn's disease

Humira was assessed in a multicentre, randomised, double-blind clinical trial designed to evaluate the efficacy and safety of induction and maintenance treatment with doses dependent on body weight (< 40 kg or ≥ 40 kg) in 192 paediatric subjects between the ages of 6 and 17 (inclusive) years, with moderate to severe Crohn´s disease (CD) defined as Paediatric Crohn's Disease Activity Index (PCDAI) score > 30. Subjects had to have failed conventional therapy (including a corticosteroid and/or an immunomodulator) for CD. Subjects may also have previously lost response or been intolerant to infliximab.

All subjects received open-label induction therapy at a dose based on their Baseline body weight: 160 mg at Week 0 and 80 mg at Week 2 for subjects ≥ 40 kg, and 80 mg and 40 mg, respectively, for subjects < 40 kg.

At Week 4, subjects were randomised 1:1 based on their body weight at the time to either the Low Dose or Standard Dose maintenance regimens as shown in Table 16.

Table 16
Maintenance regimen

Patient Weight	Low dose	Standard dose
< 40 kg	10 mg eow	20 mg eow
≥ 40 kg	20 mg eow	40 mg eow

Efficacy results

The primary endpoint of the study was clinical remission at Week 26, defined as PCDAI score ≤ 10.

Clinical remission and clinical response (defined as reduction in PCDAI score of at least 15 points from Baseline) rates are presented in Table 17. Rates of discontinuation of corticosteroids or immunomodulators are presented in Table 18.

Table 17 **Paediatric CD Study** **PCDAI Clinical Remission and Response**			
	Standard Dose 40/20 mg eow N = 93	**Low Dose 20/10 mg eow N = 95**	**P value***
Week 26			
Clinical remission	38.7%	28.4%	0.075
Clinical response	59.1%	48.4%	0.073
Week 52			
Clinical remission	33.3%	23.2%	0.100
Clinical response	41.9%	28.4%	0.038
* p value for Standard Dose *versus* Low Dose comparison.			

Table 18 Paediatric CD Study Discontinuation of Corticosteroids or Immunomodulators and Fistula Remission			
	Standard Dose 40/20 mg eow	**Low Dose 20/10 mg eow**	**P value[1]**
Discontinued corticosteroids	**N= 33**	**N=38**	
Week 26	84.8%	65.8%	0.066
Week 52	69.7%	60.5%	0.420
Discontinuation of Immunomodulators[2]	**N=60**	**N=57**	
Week 52	30.0%	29.8%	0.983
Fistula remission[3]	**N=15**	**N=21**	
Week 26	46.7%	38.1%	0.608
Week 52,	40.0%	23.8%	0.303

[1] p value for Standard Dose *versus* Low Dose comparison.

[2] Immunosuppressant therapy could only be discontinued at or after Week 26 at the investigator's discretion if the subject met the clinical response criterion

[3] defined as a closure of all fistulas that were draining at Baseline for at least 2 consecutive post-Baseline visits

Statistically significant increases (improvement) from Baseline to Week 26 and 52 in Body Mass Index and height velocity were observed for both treatment groups.

Statistically and clinically significant improvements from Baseline were also observed in both treatment groups for quality of life parameters (including IMPACT III).

One hundred patients (n=100) from the Paediatric CD Study continued in an open-label long-term extension study. After 5 years of adalimumab therapy, 74.0% (37/50) of the 50 patients remaining in the study continued to be in clinical remission, and 92.0% (46/50) of patients continued to be in clinical response per PCDAI.

Adult Crohn's disease

The safety and efficacy of Humira were assessed in over 1500 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomised, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 80% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies, CD Study I (CLASSIC I) and CD Study II (GAIN). In CD Study I, 299 TNF-antagonist naive patients were randomised to one of four treatment groups; placebo at Weeks 0 and 2, 160 mg Humira at Week 0 and 80 mg at Week 2, 80 mg at Week 0 and 40 mg at Week 2, and 40 mg at Week 0 and 20 mg at Week 2. In CD Study II, 325 patients who had lost response or were intolerant to infliximab were randomised to receive either 160 mg Humira at Week 0 and 80 mg at Week 2 or placebo at Weeks 0 and 2. The primary non-responders were excluded from the studies and therefore these patients were not further evaluated.

Maintenance of clinical remission was evaluated in CD study III (CHARM). In CD Study III, 854 patients received open-label 80 mg at Week 0 and 40 mg at Week 2. At Week 4 patients were randomised to 40 mg every other week, 40 mg every week, or placebo with a total study duration of 56 weeks. Patients in clinical response (decrease in CDAI ≥ 70) at Week 4 were stratified and analysed separately from those not in clinical response at Week 4. Corticosteroid taper was permitted after Week 8.

CD study I and CD study II induction of remission and response rates are presented in Table 19.

Table 19
Induction of Clinical Remission and Response
(Percent of Patients)

	CD Study I: Infliximab Naive Patients			**CD Study II: Infliximab Experienced Patients**	
	Placebo N=74	**Humira 80/40 mg N = 75**	**Humira 160/80 mg N=76**	**Placebo N=166**	**Humira 160/80 mg N=159**
Week 4					
Clinical remission	12%	24%	36%*	7%	21%*
Clinical response (CR-100)	24%	37%	49%**	25%	38%**

All p-values are pairwise comparisons of proportions for Humira *versus* placebo

* $p < 0.001$

** $p < 0.01$

Similar remission rates were observed for the 160/80 mg and 80/40 mg induction regimens by Week 8 and adverse events were more frequently noted in the 160/80 mg group.

In CD Study III, at Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. Of those in clinical response at Week 4, 48% had been previously exposed to other TNF-antagonists. Maintenance of remission and response rates are presented in Table 20. Clinical remission results remained relatively constant irrespective of previous TNF-antagonist exposure.

Disease-related hospitalisations and surgeries were statistically significantly reduced with adalimumab compared with placebo at Week 56.

Table 20
Maintenance of Clinical Remission and Response
(Percent of Patients)

	Placebo	**40 mg Humira every other week**	**40 mg Humira every week**
Week 26	**N=170**	**N=172**	**N=157**
Clinical remission	17%	40%*	47%*
Clinical response (CR-100)	27%	52%*	52%*
Patients in steroid-free remission for >=90 days[a]	3% (2/66)	19% (11/58)**	15% (11/74)**
Week 56	**N=170**	**N=172**	**N=157**
Clinical remission	12%	36%*	41%*
Clinical response (CR-100)	17%	41%*	48%*
Patients in steroid-free remission for >=90 days[a]	5% (3/66)	29% (17/58)*	20% (15/74)**

* $p < 0.001$ for Humira *versus* placebo pairwise comparisons of proportions

** $p < 0.02$ for Humira *versus* placebo pairwise comparisons of proportions

[a] Of those receiving corticosteroids at baseline

Among patients who were not in response at Week 4, 43% of Humira maintenance patients responded by Week 12 compared to 30% of placebo maintenance patients. These results suggest that some patients who have not responded by Week 4 benefit from continued maintenance therapy through Week 12. Therapy continued beyond 12 weeks did not result in significantly more responses (see section 4.2).

117/276 patients from CD study I and 272/777 patients from CD studies II and III were followed through at least 3 years of open-label adalimumab therapy. 88 and 189 patients, respectively, continued to be in clinical remission. Clinical response (CR-100) was maintained in 102 and 233 patients, respectively.

Quality of life

In CD Study I and CD Study II, statistically significant improvement in the disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at Week 4 in patients randomised to Humira 80/40 mg and 160/80 mg compared to placebo and was seen at Weeks 26 and 56 in CD Study III as well among the adalimumab treatment groups compared to the placebo group.

Paediatric Uveitis

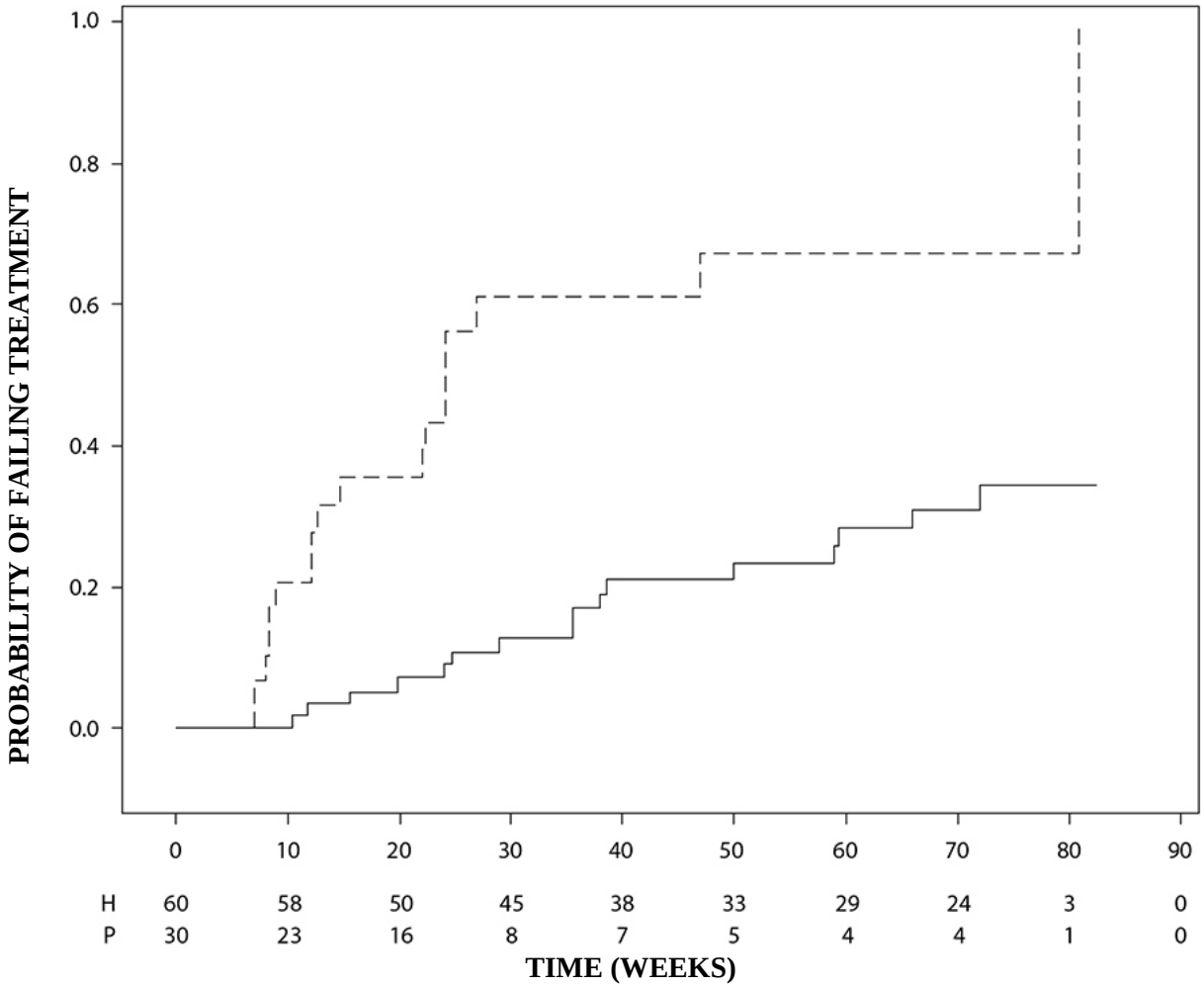
The safety and efficacy of Humira was assessed in a randomized, double-masked, controlled study of 90 paediatric patients from 2 to < 18 years of age with active JIA-associated noninfectious anterior uveitis who were refractory to at least 12 weeks of methotrexate treatment. Patients received either placebo or 20 mg adalimumab (if < 30 kg) or 40 mg adalimumab (if ≥ 30 kg) every other week in combination with their baseline dose of methotrexate.

The primary endpoint was 'time to treatment failure'. The criteria determining treatment failure were worsening or sustained non-improvement in ocular inflammation, partial improvement with development of sustained ocular co-morbidities or worsening of ocular co-morbidities, non-permitted use of concomitant medications, and suspension of treatment for an extended period of time.

Clinical Response

Adalimumab significantly delayed the time to treatment failure, as compared to placebo (See Figure 1, $P < 0.0001$ from log rank test).The median time to treatment failure was 24.1 weeks for subjects treated with placebo, whereas the median time to treatment failure was not estimable for subjects treated with adalimumab because less than one-half of these subjects experienced treatment failure. Adalimumab significantly decreased the risk of treatment failure by 75% relative to placebo, as shown by the hazard ratio (HR = 0.25 [95% CI: 0.12, 0.49]).

Figure 1: Kaplan-Meier Curves Summarizing Time to Treatment Failure in the Paediatric Uveitis Study



Note: P = Placebo (Number at Risk); H = HUMIRA (Number at Risk).

Adult Uveitis

The safety and efficacy of Humira were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis, excluding patients with isolated anterior uveitis, in two randomised, double-masked, placebo-controlled studies (UV I and II). Patients received placebo or Humira at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. Concomitant stable doses of one non-biologic immunosuppressant were permitted.

Study UV I evaluated 217 patients with active uveitis despite treatment with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). All patients received a 2-week standardised dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by Week 15.

Study UV II evaluated 226 patients with inactive uveitis requiring chronic corticosteroid treatment (oral prednisone 10 to 35 mg/day) at baseline to control their disease. Patients subsequently underwent a mandatory taper schedule, with complete corticosteroid discontinuation by Week 19.

The primary efficacy endpoint in both studies was ´time to treatment failure´. Treatment failure was defined by a multi-component outcome based on inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber (AC) cell grade, vitreous haze (VH) grade and best corrected visual acuity (BCVA).

Clinical Response

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with Humira versus patients receiving placebo (See Table 21). Both studies demonstrated an early and sustained effect of Humira on the treatment failure rate versus placebo (see Figure 2).

Table 21
Time to Treatment Failure in Studies UV I and UV II

Analysis Treatment	N	Failure N (%)	Median Time to Failure (months)	HR[a]	CI 95% for HR[a]	*P* Value[b]
Time to Treatment Failure At or After Week 6 in Study UV I						
Primary analysis (ITT)						
Placebo	107	84 (78.5)	3.0	--	--	--
Adalimumab	110	60 (54.5)	5.6	0.50	0.36, 0.70	< 0.001
Time to Treatment Failure At or After Week 2 in Study UV II						
Primary analysis (ITT)						
Placebo	111	61 (55.0)	8.3	--	--	--
Adalimumab	115	45 (39.1)	NE[c]	0.57	0.39, 0.84	0.004

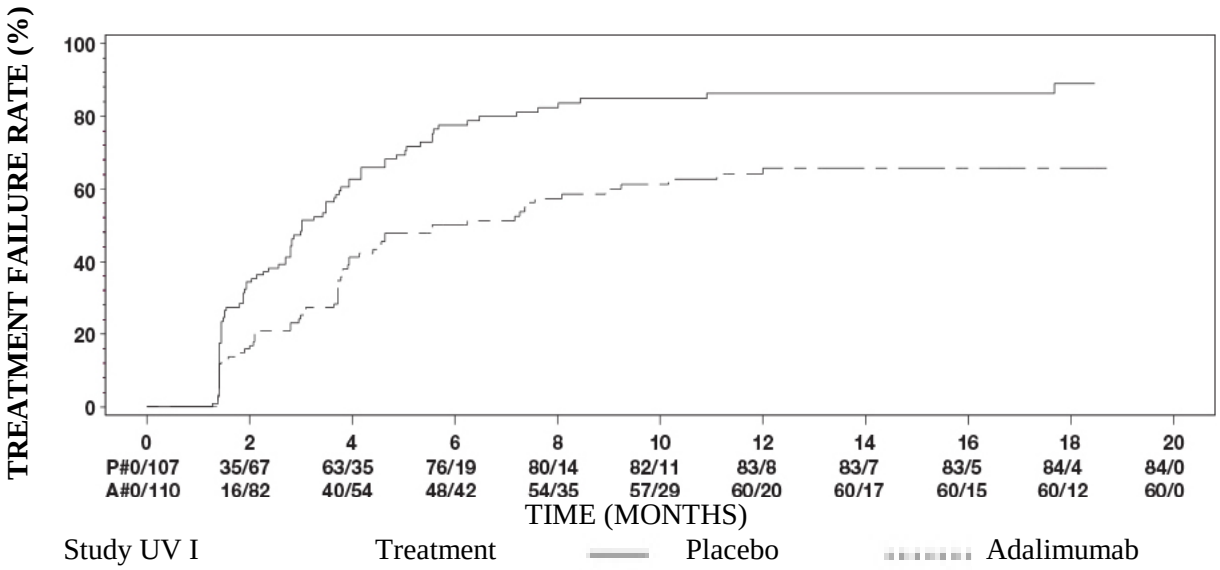
Note: Treatment failure at or after Week 6 (Study UV I), or at or after Week 2 (Study UV II), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

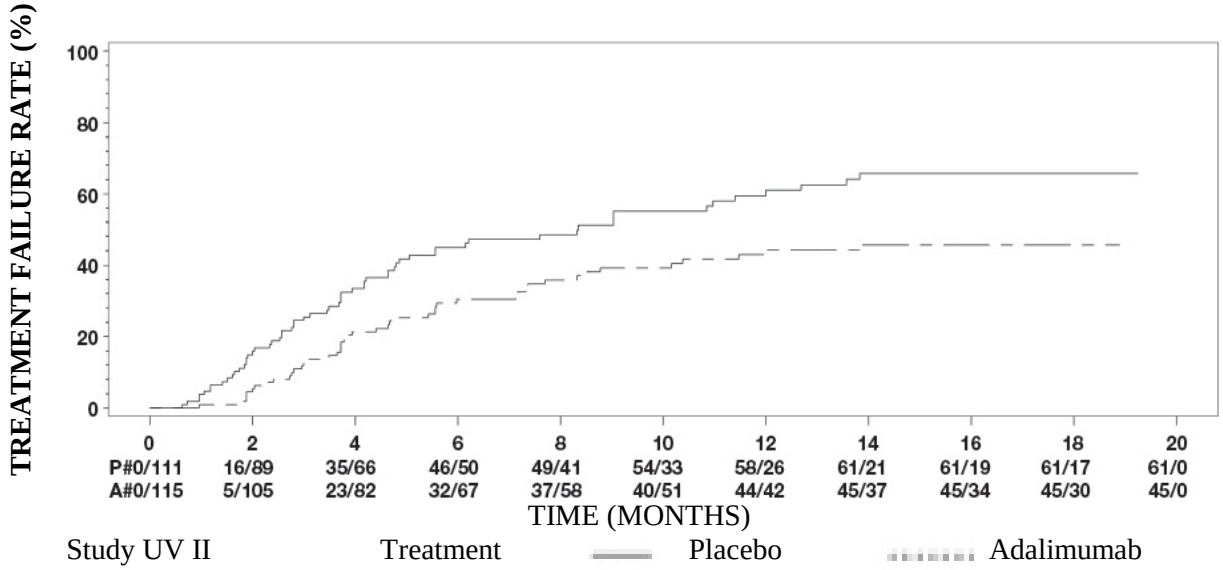
[a] HR of adalimumab vs placebo from proportional hazards regression with treatment as factor.

[b] 2-sided *P* value from log rank test.

[c] NE = not estimable. Fewer than half of at-risk subjects had an event.

Figure 2: Kaplan-Meier Curves Summarizing Time to Treatment Failure on or after Week 6 (Study UV I) or Week 2 (Study UV II)





Note: P# = Placebo (Number of Events/Number at Risk); A# = HUMIRA (Number of Events/Number at Risk).

In Study UV I statistically significant differences in favour of adalimumab versus placebo were observed for each component of treatment failure. In Study UV II, statistically significant differences were observed for visual acuity only, but the other components were numerically in favour of adalimumab.

Quality of Life

Patient reported outcomes regarding vision-related functioning were measured in both clinical studies, using the NEI VFQ-25. Humira was numerically favoured for the majority of subscores with statistically significant mean differences for general vision, ocular pain, near vision, mental health, and total score in Study UV I, and for general vision and mental health in Study UV II. Vision related effects were not numerically in favour of Humira for colour vision in Study UVI and for colour vision, peripheral vision and near vision in Study UV II.

Immunogenicity

Formation of anti-adalimumab antibodies is associated with increased clearance and reduced efficacy of adalimumab. There is no apparent correlation between the presence of anti-adalimumab antibodies and the occurrence of adverse events.

In patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years, anti- adalimumab antibodies were identified in 15.8% (27/171) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 25.6% (22/86) compared to 5.9% (5/85) when adalimumab was used as add-on to methotrexate.

In patients with enthesitis-related arthritis, anti-adalimumab antibodies were identified in 10.9% (5/46) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 13.6% (3/22), compared to 8.3% (2/24) when adalimumab was used as add-on to methotrexate.

Patients in rheumatoid arthritis studies I, II and III were tested at multiple time points for anti-adalimumab antibodies during the 6 to 12 month period. In the pivotal trials, anti-adalimumab antibodies were identified in 5.5% (58/1053) of patients treated with adalimumab, compared to 0.5% (2/370) on placebo. In patients not given concomitant methotrexate, the incidence was 12.4%, compared to 0.6% when adalimumab was used as add-on to methotrexate.

In patients with paediatric psoriasis, anti-adalimumab antibodies were identified in 5/38 subjects (13%) treated with 0.8 mg/kg adalimumab monotherapy.

In adult patients with psoriasis, anti-adalimumab antibodies were identified in 77/920 subjects (8.4%) treated with adalimumab monotherapy.

In patients with moderately to severely active paediatric Crohn's disease, the rate of anti-adalimumab antibody development in patients receiving adalimumab was 3.3%.

Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of the studies with Humira in one or more subsets of the paediatric population in ulcerative colitis, see section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption and distribution

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with polyarticular juvenile idiopathic arthritis (JIA) who were 4 to 17 years the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5.6 ± 5.6 μg/ml (102% CV) for adalimumab without concomitant methotrexate and 10.9 ± 5.2 μg/ml (47.7% CV) with concomitant methotrexate.

In patients with polyarticular JIA who were 2 to <4 years old or aged 4 and above weighing <15 kg dosed with adalimumab 24 mg/m^2, the mean trough steady-state serum adalimumab concentrations was 6.0 ± 6.1 μg/ml (101% CV) for adalimumab without concomitant methotrexate and 7.9 ± 5.6 μg/ml (71.2% CV) with concomitant methotrexate.

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with enthesitis-related arthritis who were 6 to 17 years, the mean trough steady-state (values measured at Week 24) serum adalimumab concentrations were 8.8 ± 6.6 μg/ml for adalimumab without concomitant methotrexate and 11.8 ± 4.3 μg/ml with concomitant methotrexate.

In paediatric patients with moderate to severe CD, the open-label adalimumab induction dose was 160/80 mg or 80/40 mg at Weeks 0 and 2, respectively, dependent on a body weight cut-off of 40 kg. At Week 4, patients were randomised 1:1 to either the Standard Dose (40/20 mg eow) or Low Dose (20/10 mg eow) maintenance treatment groups based on their body weight. The mean (±SD) serum adalimumab trough concentrations achieved at Week 4 were 15.7 ± 6.6 μg/ml for patients ≥ 40 kg (160/80 mg) and 10.6 ± 6.1 μg/ml for patients < 40 kg (80/40 mg).

For patients who stayed on their randomised therapy, the mean (±SD) adalimumab trough concentrations at Week 52 were 9.5 ± 5.6 μg/ml for the Standard Dose group and 3.5 ± 2.2 μg/ml for the Low Dose group. The mean trough concentrations were maintained in patients who continued to receive adalimumab treatment eow for 52 weeks. For patients who dose escalated from eow to weekly regimen, the mean (±SD) serum concentrations of adalimumab at Week 52 were 15.3 ± 11.4 μg/ml (40/20 mg, weekly) and 6.7 ± 3.5 μg/ml (20/10 mg, weekly).

Following the administration of 0.8 mg/kg (up to a maximum of 40 mg) subcutaneously every other week to paediatric patients with chronic plaque psoriasis, the mean ± SD steady-state adalimumab trough concentration was approximately 7.4 ± 5.8 μg/ml (79% CV).

Adalimumab exposure in adolescent HS patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent HS dosing schedule is 40 mg every other week. Since exposure to adalimumab can be affected by body size, adolescents with higher body weight and inadequate response may benefit from receiving the recommended adult dose of 40 mg every week.

Adalimumab exposure in paediatric uveitis patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). No clinical exposure data are available on the use of a loading dose in children < 6 years. The predicted exposures indicate that in the absence of methotrexate, a loading dose may lead to an initial increase in systemic exposure.

Adults

After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. After single intravenous doses ranging from 0.25 to 10 mg/kg, concentrations were dose proportional. After doses of 0.5 mg/kg (~40 mg), clearances ranged from 11 to 15 ml/hour, the distribution volume (V_{ss}) ranged from 5 to 6 litres and the mean terminal phase half-life was approximately two weeks. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31-96% of those in serum.

Following subcutaneous administration of 40 mg of adalimumab every other week in adult rheumatoid arthritis (RA) patients the mean steady-state trough concentrations were approximately 5 μg/ml (without concomitant methotrexate) and 8 to 9 μg/ml (with concomitant methotrexate), respectively. The serum adalimumab trough levels at steady-state increased roughly proportionally with dose following 20, 40 and 80 mg subcutaneous dosing every other week and every week.

In adult patients with psoriasis, the mean steady-state trough concentration was 5 μg/ml during adalimumab 40 mg every other week monotherapy treatment.

Elimination

Population pharmacokinetic analyses with data from over 1,300 RA patients revealed a trend toward higher apparent clearance of adalimumab with increasing body weight. After adjustment for weight differences, gender and age appeared to have a minimal effect on adalimumab clearance. The serum levels of free adalimumab (not bound to anti-adalimumab antibodies, AAA) were observed to be lower in patients with measurable AAA.

Hepatic or renal impairment

Humira has not been studied in patients with hepatic or renal impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity.

An embryo-foetal developmental toxicity/perinatal developmental study has been performed in cynomologous monkeys at 0, 30 and 100 mg/kg (9-17 monkeys/group) and has revealed no evidence of harm to the foetuses due to adalimumab. Neither carcinogenicity studies, nor a standard assessment of fertility and postnatal toxicity, were performed with adalimumab due to the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and to the development of neutralising antibodies in rodents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Citric acid monohydrate
Sodium citrate
Sodium dihydrogen phosphate dihydrate
Disodium phosphate dihydrate
Sodium chloride
Polysorbate 80
Sodium hydroxide
Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Humira 40 mg solution for injection in single-use vial (type I glass), fitted with rubber stoppers, aluminium crimps and flip-off seals.

1 Pack of 2 boxes each containing:
1 vial (0.8 ml sterile solution), 1 empty sterile injection syringe, 1 needle, 1 vial adapter and 2 alcohol pads.

6.6 Special precautions for disposal

Humira does not contain preservatives. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB

United Kingdom

8. MARKETING AUTHORISATION NUMBER

EU/1/03/256/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 September 2003
Date of latest renewal: 8 September 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe
Humira 40 mg solution for injection in pre-filled syringe with needleguard
Humira 40 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Humira 40 mg solution for injection in pre-filled syringe / Humira 40 mg solution for injection in pre-filled syringe with needleguard
Each 0.8 ml single dose pre-filled syringe contains 40 mg of adalimumab.

Humira 40 mg solution for injection in pre-filled pen
Each 0.8 ml single dose pre-filled pen contains 40 mg of adalimumab.

Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Humira in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Humira has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Humira in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Humira can be given as

monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Humira has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Humira is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Humira is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS

Humira is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Psoriatic arthritis

Humira is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Humira has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see Section 5.1) and to improve physical function.

Psoriasis

Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis

Humira is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Crohn’s disease

Humira is indicated for treatment of moderately to severely active Crohn’s disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Humira is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

Humira is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Uveitis

Humira is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Paediatric Uveitis

Humira is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

4.2 Posology and method of administration

Humira treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which Humira is indicated. Ophthalmologists are advised to consult with an appropriate specialist before initiation of treatment with Humira (see section 4.4). Patients treated with Humira should be given the special alert card.

After proper training in injection technique, patients may self-inject with Humira if their physician determines that it is appropriate and with medical follow-up as necessary.

During treatment with Humira, other concomitant therapies (e.g., corticosteroids and/or immunomodulatory agents) should be optimised.

Posology

Rheumatoid arthritis

The recommended dose of Humira for adult patients with rheumatoid arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Methotrexate should be continued during treatment with Humira.

Glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics can be continued during treatment with Humira. Regarding combination with disease modifying anti-rheumatic drugs other than methotrexate see sections 4.4 and 5.1.

In monotherapy, some patients who experience a decrease in their response may benefit from an increase in dose intensity to 40 mg adalimumab every week.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period.

Dose interruption

There may be a need for dose interruption, for instance before surgery or if a serious infection occurs.

Available data suggest that re-introduction of Humira after discontinuation for 70 days or longer resulted in the same magnitudes of clinical response and similar safety profile as before dose interruption.

Ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS and psoriatic arthritis

The recommended dose of Humira for patients with ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS and for patients with psoriatic arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period.

Psoriasis

The recommended dose of Humira for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose.

Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.

Beyond 16 weeks, patients with inadequate response may benefit from an increase in dosing frequency to 40 mg every week. The benefits and risks of continued weekly Humira therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosing frequency (see section 5.1). If adequate response is achieved with an increased dosing frequency, the dose may subsequently be reduced to 40 mg every other week.

Hidradenitis suppurativa

The recommended Humira dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later at Day 15 (given as two 40 mg injections in one day). Two weeks later (Day 29) continue with a dose of 40 mg every week. Antibiotics may be continued during treatment with Humira if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Humira.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

Should treatment be interrupted, Humira 40 mg every week may be re-introduced (see section 5.1).

The benefit and risk of continued long-term treatment should be periodically evaluated (see section 5.1).

Crohn's disease

The recommended Humira induction dose regimen for adult patients with moderately to severely active Crohn's disease is 80 mg at Week 0 followed by 40 mg at Week 2. In case there is a need for a

more rapid response to therapy, the regimen 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), 80 mg at Week 2, can be used with the awareness that the risk for adverse events is higher during induction.

After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Alternatively, if a patient has stopped Humira and signs and symptoms of disease recur, Humira may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg Humira every week.

Some patients who have not responded by Week 4 may benefit from continued maintenance therapy through Week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Ulcerative colitis

The recommended Humira induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days) and 80 mg at Week 2. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg Humira every week.

Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment. Humira therapy should not be continued in patients failing to respond within this time period.

Uveitis

The recommended dose of Humira for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. There is limited experience in the initiation of treatment with Humira alone. Treatment with Humira can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with Humira.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis (see section 5.1).

<u>Elderly</u>

No dose adjustment is required.

<u>Renal and/or hepatic impairment</u>

Humira has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis from 2 to 12 years of age

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 2 - 12 years, is 24 mg/m² body surface area up to a maximum single dose of 20 mg adalimumab (for patients aged 2- <4) and up to a maximum single dose of 40 mg adalimumab (for patients aged 4-12) administered every other week via subcutaneous injection. The volume for injection is selected based on the patients' height and weight (Table 1). A 40 mg/0.8 ml paediatric vial is available for patients who need to administer less than the full 40 mg dose.

Table 1. Humira Dose in Millilitres (ml) by Height and Weight of Patients for Polyarticular Juvenile Idiopathic Arthritis and Enthesitis-Related Arthritis

Height (cm)	Total Body Weight (kg)												
	10	**15**	**20**	**25**	**30**	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**
80	0.2	0.3	0.3	0.3									
90	0.2	0.3	0.3	0.4	0.4	0.4							
100	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.5					
110	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.6		
120	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.7
130		0.4	0.4	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.7	0.7
140		0.4	0.4	0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.7	0.7	0.8*
150			0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.7	0.7	0.8*	0.8*
160			0.5	0.5	0.6	0.6	0.7	0.7	0.7	0.8*	0.8*	0.8*	0.8*
170				0.6	0.6	0.6	0.7	0.7	0.8*	0.8*	0.8*	0.8*	0.8*
180					0.6	0.7	0.7	0.8*	0.8*	0.8*	0.8*	0.8*	0.8*

*Maximum single dose is 40 mg (0.8 ml)

Polyarticular juvenile idiopathic arthritis from 13 years of age

For patients from 13 years of age, a dose of 40 mg is administered every other week regardless of body surface area.

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

There is no relevant use of Humira in patients aged <2 years for this indication.

Enthesitis-related arthritis

The recommended dose of Humira for patients with enthesitis-related arthritis 6 years of age and older is 24 mg/m² body surface area up to a maximum single dose of 40 mg adalimumab administered every other week via subcutaneous injection. The volume for injection is selected based on the patients' height and weight (Table 1).

Humira has not been studied in patients with enthesitis-related arthritis aged less than 6 years.

Paediatric plaque psoriasis

The recommended Humira dose is 0.8 mg per kg body weight (up to a maximum of 40 mg per dose) administered subcutaneously weekly for the first two doses and every other week thereafter.

Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.

If retreatment with Humira is indicated, the above guidance on dose and treatment duration should be followed.

The safety of Humira in paediatric patients with plaque psoriasis has been assessed for a mean of 13 months.

There is no relevant use of Humira in children aged less than 4 years for this indication.

The volume for injection is selected based on the patients' weight (Table 2).

Table 2: Humira Dose in Millilitres (ml) by Weight for Patients with Paediatric Psoriasis

Body Weight (kg)	Paediatric Psoriasis Dose
13 – 16	0.2 ml (10 mg)
17 – 22	0.3 ml (15 mg)
23 – 28	0.4 ml (20 mg)
29 – 34	0.5 ml (25 mg)
35 – 40	0.6 ml (30 mg)
41 – 46	0.7 ml (35 mg)
47+	0.8 ml (40 mg)

Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)

There are no clinical trials with Humira in adolescent patients with HS. The posology of Humira in these patients has been determined from pharmacokinetic modelling and simulation (see section 5.2).

The recommended Humira dose is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via subcutaneous injection.

In adolescent patients with inadequate response to Humira 40 mg every other week, an increase in dosing frequency to 40 mg every week may be considered.

Antibiotics may be continued during treatment with Humira if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Humira.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

Should treatment be interrupted, Humira may be re-introduced as appropriate.

The benefit and risk of continued long-term treatment should be periodically evaluated (see adult data in section 5.1)

There is no relevant use of Humira in children aged less than 12 years in this indication.

Paediatric Crohn's disease

Paediatric Crohn's disease patients < 40 kg:

The recommended Humira induction dose regimen for paediatric subjects with moderately to severely active Crohn's disease is 40 mg at Week 0 followed by 20 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 80 mg at Week 0 (dose can be administered as two injections in one day), 40 mg at Week 2 can be used, with the awareness that the risk for adverse events may be higher with use of the higher induction dose.

After induction treatment, the recommended dose is 20 mg every other week via subcutaneous injection. Some subjects who experience insufficient response may benefit from an increase in dosing frequency to 20 mg Humira every week.

Paediatric Crohn's disease patients ≥ 40 kg:

The recommended Humira induction dose regimen for paediatric subjects with moderately to severely active Crohn's disease is 80 mg at Week 0 followed by 40 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), 80 mg at Week 2 can be used, with the awareness that the risk for adverse events may be higher with use of the higher induction dose.

After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Some subjects who experience insufficient response may benefit from an increase in dosing frequency to 40 mg Humira every week.

Continued therapy should be carefully considered in a subject not responding by Week 12.

There is no relevant use of Humira in children aged below 6 years for this indication.

Paediatric Uveitis

In paediatric uveitis, there is no experience in the treatment with Humira without concomitant treatment with methotrexate.

Paediatric uveitis patients < 30 kg:

The recommended dose of Humira is 20 mg every other week in combination with methotrexate.

When Humira therapy is initiated, a loading dose of 40 mg may be administered one week prior to the start of maintenance therapy. No clinical data are available on the use of a Humira loading dose in children < 6 years of age (see section 5.2).

Paediatric uveitis patients ≥ 30 kg:

The recommended dose of Humira is 40 mg every other week in combination with methotrexate.

When Humira therapy is initiated, a loading dose of 80 mg may be administered one week prior to the start of maintenance therapy.

There is no relevant use of Humira in children aged less than 2 years in this indication.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis (see section 5.1).

Paediatric ulcerative colitis

The safety and efficacy of Humira in children aged 4-17 years have not yet been established. No data are available. There is no relevant use of Humira in children aged <4 years for this indication.

Psoriatic arthritis and axial spondyloarthritis including ankylosing spondylitis

There is no relevant use of Humira in the paediatric population for the indications of ankylosing spondylitis and psoriatic arthritis.

Method of administration

Humira is administered by subcutaneous injection. Full instructions for use are provided in the package leaflet.

A 40 mg paediatric vial is available for patients who need to administer less than the full 40 mg dose.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active tuberculosis or other severe infections such as sepsis, and opportunistic infections (see section 4.4).

Moderate to severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections

Patients taking TNF-antagonists are more susceptible to serious infections. Impaired lung function may increase the risk for developing infections. Patients must therefore be monitored closely for infections, including tuberculosis, before, during and after treatment with Humira. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period.

Treatment with Humira should not be initiated in patients with active infections including chronic or localised infections until infections are controlled. In patients who have been exposed to tuberculosis and patients who have travelled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with Humira should be considered prior to initiating therapy (see *Other opportunistic infections*).

Patients who develop a new infection while undergoing treatment with Humira, should be monitored closely and undergo a complete diagnostic evaluation. Administration of Humira should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of Humira in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications.

Serious infections

Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis have been reported in patients receiving Humira.

Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia. Hospitalisation or fatal outcomes associated with infections have been reported.

Tuberculosis

Tuberculosis, including reactivation and new onset of tuberculosis, has been reported in patients receiving Humira. Reports included cases of pulmonary and extra-pulmonary (i.e. disseminated) tuberculosis.

Before initiation of therapy with Humira, all patients must be evaluated for both active or inactive ("latent") tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients (local recommendations may apply). It is recommended that the conduct and results of these tests are recorded in the patient alert card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Humira therapy must not be initiated (see section 4.3).

In all situations described below, the benefit/risk balance of therapy should be very carefully considered.

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted.

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylaxis treatment before the initiation of Humira, and in accordance with local recommendations.

Use of anti-tuberculosis prophylaxis treatment should also be considered before the initiation of Humira in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with Humira. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with Humira.

Patients should be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (e.g., persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with Humira.

Other opportunistic infections

Opportunistic infections, including invasive fungal infections have been observed in patients receiving Humira. These infections have not consistently been recognised in patients taking TNF-antagonists and this has resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.

For patients who develop the signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock an invasive fungal infection should be suspected and administration of Humira should be promptly discontinued. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections.

Hepatitis B reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including Humira, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had a fatal outcome. Patients should be tested for HBV infection before initiating treatment with Humira. For patients who test positive for hepatitis B infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Carriers of HBV who require treatment with Humira should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data from treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, Humira should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurological events

TNF-antagonists including Humira have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of Humira in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of Humira should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of Humira therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Allergic reactions

Serious allergic reactions associated with Humira were rare during clinical trials. Non-serious allergic reactions associated with Humira were uncommon during clinical trials. Reports of serious allergic reactions including anaphylaxis have been received following Humira administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Humira should be discontinued immediately and appropriate therapy initiated.

Immunosuppression

In a study of 64 patients with rheumatoid arthritis that were treated with Humira, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T-, B, - NK-cells, monocyte/macrophages, and neutrophils.

Malignancies and lymphoproliferative disorders

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare. In the post marketing setting, cases of leukaemia have been reported in patients treated with a TNF-antagonist. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active,

inflammatory disease, which complicates the risk estimation. With the current knowledge, a possible risk for the development of lymphomas, leukaemia, and other malignancies in patients treated with a TNF-antagonist cannot be excluded.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including adalimumab in the post marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Rare postmarketing cases of hepatosplenic T-cell lymphoma have been identified in patients treated with adalimumab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Some of these hepatosplenic T-cell lymphomas with Humira have occurred in young adult patients on concomitant treatment with azathioprine or 6-mercaptopurine used for inflammatory bowel disease. The potential risk with the combination of azathioprine or 6-mercaptopurine and Humira should be carefully considered. A risk for the development of hepatosplenic T-cell lymphoma in patients treated with Humira cannot be excluded (see section 4.8).

No studies have been conducted that include patients with a history of malignancy or in whom treatment with Humira is continued following development of malignancy. Thus additional caution should be exercised in considering Humira treatment of these patients (see section 4.8).

All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with Humira. Melanoma and Merkel cell carcinoma have also been reported in patients treated with TNF-antagonists including adalimumab (see section 4.8).

In an exploratory clinical trial evaluating the use of another TNF-antagonist, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking.

With current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.

Haematologic reactions

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF-antagonists. Adverse events of the haematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been reported with Humira. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor) while on Humira. Discontinuation of Humira therapy should be considered in patients with confirmed significant haematologic abnormalities.

Vaccinations

Similar antibody responses to the standard 23-valent pneumococcal vaccine and the influenza trivalent virus vaccination were observed in a study in 226 adult subjects with rheumatoid arthritis

who were treated with adalimumab or placebo. No data are available on the secondary transmission of infection by live vaccines in patients receiving Humira.

It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy.

Patients on Humira may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Congestive heart failure

In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving Humira. Humira should be used with caution in patients with mild heart failure (NYHA class I/II). Humira is contraindicated in moderate to severe heart failure (see section 4.3). Treatment with Humira must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes

Treatment with Humira may result in the formation of autoimmune antibodies. The impact of long-term treatment with Humira on the development of autoimmune diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Humira and is positive for antibodies against double-stranded DNA, further treatment with Humira should not be given (see section 4.8).

Concurrent administration of biologic DMARDS or TNF-antagonists

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-antagonist, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF-antagonists. Therefore, the combination of adalimumab and anakinra is not recommended. (See section 4.5).

Concomitant administration of adalimumab with other biologic DMARDS (e.g, anakinra and abatacept) or other TNF-antagonists is not recommended based upon the possible increased risk for infections, including serious infections and other potential pharmacological interactions. (See section 4.5).

Surgery

There is limited safety experience of surgical procedures in patients treated with Humira. The long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Humira should be closely monitored for infections, and appropriate actions should be taken. There is limited safety experience in patients undergoing arthroplasty while receiving Humira.

Small bowel obstruction

Failure to respond to treatment for Crohn's disease may indicate the presence of fixed fibrotic stricture that may require surgical treatment. Available data suggest that Humira does not worsen or cause strictures.

Elderly

The frequency of serious infections among Humira treated subjects over 65 years of age (3.7%) was higher than for those under 65 years of age (1.5%). Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly.

Paediatric population

See Vaccinations above.

4.5 Interaction with other medicinal products and other forms of interaction

Humira has been studied in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis patients taking Humira as monotherapy and those taking concomitant methotrexate. Antibody formation was lower when Humira was given together with methotrexate in comparison with use as monotherapy. Administration of Humira without methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab (see section 5.1).

The combination of Humira and anakinra is not recommended (see section 4.4 “Concurrent administration of biologic DMARDS or TNF-antagonists”).

The combination of Humira and abatacept is not recommended (see section 4.4 “Concurrent administration of biologic DMARDS or TNF-antagonists”).

4.6 Fertility, pregnancy and lactation

Women of child bearing potential/Contraception in males and females

Women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and continue its use for at least five months after the last Humira treatment.

Pregnancy

For Humira, limited clinical data on exposed pregnancies are available

In a developmental toxicity study conducted in monkeys, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. Preclinical data on postnatal toxicity of adalimumab are not available (see section 5.3).

Due to its inhibition of TNFα, adalimumab administered during pregnancy could affect normal immune responses in the newborn. Administration of adalimumab is not recommended during pregnancy.

Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother’s last adalimumab injection during pregnancy.

Breast feeding

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion.

However, because human immunoglobulins are excreted in milk, women must not breast-feed for at least five months after the last Humira treatment.

Fertility

Preclinical data on fertility effects of adalimumab are not available.

4.7 Effects on ability to drive and use machines

Humira may have a minor influence on the ability to drive and use machines. Vertigo and visual impairment may occur following administration of Humira (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Humira was studied in 9,506 patients in pivotal controlled and open label trials for up to 60 months or more. These trials included rheumatoid arthritis patients with short term and long standing disease, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis) as well as axial spondyloarthritis (ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients. The pivotal controlled studies involved 6,089 patients receiving Humira and 3,801 patients receiving placebo or active comparator during the controlled period.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of pivotal studies was 5.9% for patients taking Humira and 5.4% for control treated patients.

The most commonly reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain.

Serious adverse reactions have been reported for Humira. TNF-antagonists, such as Humira affect the immune system and their use may affect the body's defence against infection and cancer.
Fatal and life-threatening infections (including sepsis, opportunistic infections and TB), HBV reactivation and various malignancies (including leukaemia, lymphoma and HSTCL) have also been reported with use of Humira.

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia, aplastic anaemia, central and peripheral demyelinating events and reports of lupus, lupus-related conditions and Stevens-Johnson syndrome.

Paediatric population

Undesirable effects in paediatric patients

In general, the adverse events in paediatric patients were similar in frequency and type to those seen in adult patients.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience and are displayed by system organ class and frequency in Table 3 below: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The highest frequency seen among the various indications has been included. An asterisk (*) appears in the SOC column if further information is found elsewhere in sections 4.3, 4.4 and 4.8.

Table 3
Undesirable Effects

System Organ Class	Frequency	Adverse Reaction
Infections and infestations*	Very common	respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections, joint infections
	Uncommon	neurological infections (including viral meningitis), opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), bacterial infections, eye infections, diverticulitis[1)]
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Common	skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma), benign neoplasm
	Uncommon	lymphoma**,

System Organ Class	Frequency	Adverse Reaction
		solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma**
	Rare	leukaemia[1)]
	Not known	hepatosplenic T-cell lymphoma[1)], Merkel cell carcinoma (neuroendocrine carcinoma of the skin)[1)]
Blood and the lymphatic system disorders*	Very common	leukopenia (including neutropenia and agranulocytosis), anaemia
	Common	leucocytosis, thrombocytopenia
	Uncommon	idiopathic thrombocytopenic purpura
	Rare	pancytopenia
Immune system disorders*	Common	hypersensitivity, allergies (including seasonal allergy)
	Uncommon	sarcoidosis[1)], vasculitis
	Rare	anaphylaxis[1)]
Metabolism and nutrition disorders	Very common	lipids increased
	Common	hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia, hyperglycaemia, hypophosphatemia, dehydration
Psychiatric disorders	Common	mood alterations (including depression), anxiety, insomnia
Nervous system disorders*	Very common	headache
	Common	paraesthesias (including hypoesthesia),

System Organ Class	Frequency	Adverse Reaction
		migraine, nerve root compression
	Uncommon	cerebrovascular accident[1)], tremor, neuropathy
	Rare	multiple sclerosis, demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome) [1)]
Eye disorders	Common	visual impairment, conjunctivitis, blepharitis, eye swelling
	Uncommon	diplopia
Ear and labyrinth disorders	Common	vertigo
	Uncommon	deafness, tinnitus
Cardiac disorders*	Common	tachycardia
	Uncommon	myocardial infarction[1)], arrhythmia, congestive heart failure
	Rare	cardiac arrest
Vascular disorders	Common	hypertension, flushing, haematoma
	Uncommon	aortic aneurysm, vascular arterial occlusion, thrombophlebitis
Respiratory, thoracic and mediastinal disorders*	Common	asthma, dyspnoea, cough
	Uncommon	pulmonary embolism[1)], interstitial lung disease, chronic obstructive pulmonary disease, pneumonitis,

System Organ Class	Frequency	Adverse Reaction
		pleural effusion[1)]
	Rare	pulmonary fibrosis[1)]
Gastrointestinal disorders	Very common	abdominal pain, nausea and vomiting
	Common	GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	pancreatitis, dysphagia, face oedema
	Rare	intestinal perforation[1)]
Hepato-biliary disorders*	Very Common	elevated liver enzymes
	Uncommon	cholecystitis and cholelithiasis, hepatic steatosis, bilirubin increased
	Rare	hepatitis reactivation of hepatitis B[1)] autoimmune hepatitis[1)]
	Not known	liver failure[1)]
Skin and subcutaneous tissue disorders	Very Common	rash (including exfoliative rash)
	Common	worsening or new onset of psoriasis(including palmoplantar pustular psoriasis)[1)], urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis, hyperhidrosis, alopecia[1)], pruritus
	Uncommon	night sweats, scar

System Organ Class	Frequency	Adverse Reaction
	Rare	erythema multiforme[1)], Stevens-Johnson syndrome[1)], angioedema[1)], cutaneous vasculitis[1)]
	Not known	worsening of symptoms of dermatomyositis[1)]
Musculoskeletal and connective tissue disorders	Very common	musculoskeletal pain
	Common	muscle spasms (including blood creatine phosphokinase increased)
	Uncommon	rhabdomyolysis, systemic lupus erythematosus
	Rare	lupus-like syndrome[1)]
Renal and urinary disorders	Common	renal impairment, haematuria
	Uncommon	nocturia
Reproductive system and breast disorders	Uncommon	erectile dysfunction
General disorders and administration site conditions*	Very Common	injection site reaction (including injection site erythema)
	Common	chest pain, oedema, pyrexia[1)]
	Uncommon	inflammation
Investigations*	Common	coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), autoantibody test positive (including double stranded DNA antibody), blood lactate dehydrogenase increased
Injury, poisoning and procedural complications	Common	impaired healing

* further information is found elsewhere in sections 4.3, 4.4 and 4.8
** including open label extension studies
[1)] including spontaneous reporting data

Hidradenitis suppurativa

The safety profile for patients with HS treated with Humira weekly was consistent with the known safety profile of Humira.

Uveitis

The safety profile for patients with uveitis treated with Humira every other week was consistent with the known safety profile of Humira.

Description of selected adverse reactions

Injection site reactions

In the pivotal controlled trials in adults and children, 12.9% of patients treated with Humira developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 7.2% of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Infections

In the pivotal controlled trials in adults and children, the rate of infection was 1.51 per patient year in the Humira treated patients and 1.46 per patient year in the placebo and active control-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, and sinusitis. Most patients continued on Humira after the infection resolved.

The incidence of serious infections was 0.04 per patient year in Humira treated patients and 0.03 per patient year in placebo and active control − treated patients.

In controlled and open label adult and paediatric studies with Humira, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extra-pulmonary locations) and invasive opportunistic infections (e.g. disseminated or extrapulmonary histoplasmosis, blastomycosis, coccidioidomycosis, pneumocystis, candidiasis, aspergillosis and listeriosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

Malignancies and lymphoproliferative disorders

No malignancies were observed in 249 paediatric patients with an exposure of 655.6 patient years during Humira trials in patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis). In addition, no malignancies were observed in 192 paediatric patients with an exposure of 498.1 patient years during Humira trials in paediatric patients with Crohn's disease. No malignancies were observed in 77 paediatric patients with an exposure of 80.0 patient years during a Humira trial in paediatric patients with chronic plaque psoriasis. No malignancies were observed in 60 paediatric patients with an exposure of 58.4 patient years during a Humira trial in paediatric patients with uveitis.

During the controlled portions of pivotal Humira trials in adults of at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.8 (4.4, 10.5) per 1,000 patient-years among 5,291 Humira treated patients *versus* a rate of 6.3 (3.4, 11.8) per 1,000 patient-years among 3,444 control patients (median duration of treatment was 4.0 months for Humira and 3.8 months for control-treated patients). The rate (95% confidence interval) of non-melanoma skin cancers was 8.8 (6.0, 13.0) per 1,000 patient-years among Humira-treated patients and 3.2 (1.3,

7.6) per 1,000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) of 2.7 (1.4, 5.4) per 1,000 patient-years among Humira-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients. The rate (95% confidence interval) of lymphomas was 0.7 (0.2, 2.7) per 1,000 patient-years among Humira-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients.

When combining controlled portions of these trials and ongoing and completed open label extension studies with a median duration of approximately 3.3 years including 6,427 patients and over 26,439 patient-years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 8.5 per 1,000 patient years. The observed rate of non-melanoma skin cancers is approximately 9.6 per 1,000 patient years, and the observed rate of lymphomas is approximately 1.3 per 1,000 patient years.

In post-marketing experience from January 2003 to December 2010, predominantly in patients with rheumatoid arthritis, the reported rate of malignancies is approximately 2.7 per 1,000 patient treatment years. The reported rates for non-melanoma skin cancers and lymphomas are approximately 0.2 and 0.3 per 1,000 patient treatment years, respectively (see section 4.4).

Rare post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with adalimumab (see section 4.4).

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis studies I − V. In these trials, 11.9% of patients treated with Humira and 8.1% of placebo and active control − treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at Week 24. Two patients out of 3,441 treated with Humira in all rheumatoid arthritis and psoriatic arthritis studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms.

Hepato-biliary events

In controlled Phase 3 trials of Humira in patients with rheumatoid arthritis and psoriatic arthritis with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.7% of Humira-treated patients and 1.6% of control-treated patients.

In controlled Phase 3 trials of Humira in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations ≥ 3 x ULN occurred in 6.1% of Humira-treated patients and 1.3% of control-treated patients. Most ALT elevations occurred with concomitant methotrexate use. No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial of Humira in patients with polyarticular juvenile idiopathic arthritis who were 2 to <4 years.

In controlled Phase 3 trials of Humira in patients with Crohn's disease and ulcerative colitis with a control period ranging from 4 to 52 weeks. ALT elevations ≥ 3 x ULN occurred in 0.9% of Humira-treated patients and 0.9% of controlled-treated patients.

In the Phase 3 trial of Humira in patients with paediatric Crohn's disease which evaluated efficacy and safety of two body weight adjusted maintenance dose regimens following body weight adjusted induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients of whom 4 were receiving concomitant immunosuppressants at baseline.

In controlled Phase 3 trials of Humira in patients with plaque Psoriasis with a control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of Humira-treated patients and 1.8% of control-treated patients.

No ALT elevations ≥3 X ULN occurred in the Phase 3 trial of Humira in paediatric patients with plaque psoriasis.

In controlled trials of Humira (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in patients with hidradenitis suppurativa with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of Humira-treated patients and 0.6% of control-treated patients.

In controlled trials of Humira (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis up to 80 weeks with a median exposure of 166.5 days and 105.0 days in Humira-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of Humira-treated patients and 2.4% of control-treated patients.

Across all indications in clinical trials patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have also been post-marketing reports of liver failure as well as less severe liver disorders that may precede liver failure, such as hepatitis including autoimmune hepatitis in patients receiving adalimumab.

Concurrent treatment with azathioprine/6-mercaptopurine

In adult Crohn's disease studies, higher incidences of malignant and serious infection-related adverse events were seen with the combination of Humira and azathioprine/6-mercaptopurine compared with Humira alone.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No dose-limiting toxicity was observed during clinical trials. The highest dose level evaluated has been multiple intravenous doses of 10 mg/kg, which is approximately 15 times the recommended dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors. ATC code: L04AB04

Mechanism of action

Adalimumab binds specifically to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of0.1-0.2 nM).

Pharmacodynamic effects

After treatment with Humira, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL-6) was observed, compared to baseline in patients with rheumatoid arthritis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after Humira administration. Patients treated with Humira usually experienced improvement in haematological signs of chronic inflammation.

A rapid decrease in CRP levels was also observed in patients with polyarticular juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis and hidradenitis suppurativa after treatment with Humira. In patients with Crohn's disease, a reduction of the number of cells expressing inflammatory markers in the colon including a significant reduction of expression of TNFα was seen. Endoscopic studies in intestinal mucosa have shown evidence of mucosal healing in adalimumab treated patients.

Clinical efficacy and safety

Rheumatoid arthritis

Humira was evaluated in over 3000 patients in all rheumatoid arthritis clinical trials. The efficacy and safety of Humira were assessed in five randomised, double-blind and well-controlled studies. Some patients were treated for up to 120 months duration.

RA study I evaluated 271 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had failed therapy with at least one disease-modifying, anti rheumatic drug and had insufficient efficacy with methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 10 to 25 mg every week. Doses of 20, 40 or 80 mg of Humira or placebo were given every other week for 24 weeks.

RA study II evaluated 544 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old and had failed therapy with at least one disease-modifying, anti-rheumatic drugs. Doses of 20 or 40 mg of Humira were given by subcutaneous injection every other week with placebo on alternative weeks or every week for 26 weeks; placebo was given every week for the same duration. No other disease-modifying anti-rheumatic drugs were allowed.

RA study III evaluated 619 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, and who had an ineffective response to methotrexate at doses of 12.5 to 25 mg or have been intolerant to 10 mg of methotrexate every week. There were three groups in this study. The first received placebo injections every week for 52 weeks. The second received 20 mg of Humira every week for 52 weeks. The third group received 40 mg of Humira every other week with placebo injections on alternate weeks. Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of Humira/MTX was administered every other week up to 10 years.

RA study IV primarily assessed safety in 636 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old. Patients were permitted to be either disease-modifying, anti-rheumatic drug-naïve or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. These therapies include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine and/or gold salts. Patients were randomised to 40 mg of Humira or placebo every other week for 24 weeks.

RA study V evaluated 799 methotrexate-naïve, adult patients with moderate to severely active early rheumatoid arthritis (mean disease duration less than 9 months). This study evaluated the efficacy of Humira 40 mg every other week/methotrexate combination therapy, Humira 40 mg every other week monotherapy and methotrexate monotherapy in reducing the signs and symptoms and rate of

progression of joint damage in rheumatoid arthritis for 104 weeks. Upon completion of the first 104 weeks, 497 patients enrolled in an open-label extension phase in which 40 mg of Humira was administered every other week up to 10 years.

The primary end point in RA studies I, II and III and the secondary endpoint in RA study IV was the percent of patients who achieved an ACR 20 response at Week 24 or 26. The primary endpoint in RA study V was the percent of patients who achieved an ACR 50 response at Week 52. RA studies III and V had an additional primary endpoint at 52 weeks of retardation of disease progression (as detected by X-ray results). RA study III also had a primary endpoint of changes in quality of life.

ACR response

The percent of Humira-treated patients achieving ACR 20, 50 and 70 responses was consistent across RA studies I, II and III. The results for the 40 mg every other week dose are summarised in Table 4.

Table 4
ACR Responses in Placebo-Controlled Trials
(Percent of Patients)

Response	RA Study I[a]**		RA Study II[a]**		RA Study III[a]**	
	Placebo/ MTX[c] n=60	Humira[b]/ MTX[c] n=63	Placebo n=110	Humira[b] n=113	Placebo/ MTX[c] n=200	Humira[b]/ MTX[c] n=207
ACR 20						
6 months	13.3%	65.1%	19.1%	46.0%	29.5%	63.3%
12 months	NA	NA	NA	NA	24.0%	58.9%
ACR 50						
6 months	6.7%	52.4%	8.2%	22.1%	9.5%	39.1%
12 months	NA	NA	NA	NA	9.5%	41.5%
ACR 70						
6 months	3.3%	23.8%	1.8%	12.4%	2.5%	20.8%
12 months	NA	NA	NA	NA	4.5%	23.2%

[a] RA study I at 24 weeks, RA study II at 26 weeks , and RA study III at 24 and 52 weeks
[b] 40 mg Humira administered every other week
[c] MTX = methotrexate
**p < 0.01, Humira *versus* placebo

In RA studies I-IV, all individual components of the ACR response criteria (number of tender and swollen joints, physician and patient assessment of disease activity and pain, disability index (HAQ) scores and CRP (mg/dl) values) improved at 24 or 26 weeks compared to placebo. In RA study III, these improvements were maintained throughout 52 weeks.

In the open-label extension for RA study III, most patients who were ACR responders maintained response when followed for up to 10 years. Of 207 patients who were randomised to Humira 40 mg every other week, 114 patients continued on Humira 40 mg every other week for 5 years. Among those, 86 patients (75.4%) had ACR 20 responses; 72 patients (63.2%) had ACR 50 responses; and 41 patients (36%) had ACR 70 responses. Of 207 patients, 81 patients continued on Humira 40 mg every other week for 10 years. Among those, 64 patients (79.0%) had ACR 20 responses; 56 patients (69.1%) had ACR 50 responses; and 43 patients (53.1%) had ACR 70 responses.

In RA study IV, the ACR 20 response of patients treated with Humira plus standard of care was statistically significantly better than patients treated with placebo plus standard of care ($p < 0.001$).

In RA studies I-IV, Humira-treated patients achieved statistically significant ACR 20 and 50 responses compared to placebo as early as one to two weeks after initiation of treatment.

In RA study V with early rheumatoid arthritis patients who were methotrexate naïve, combination therapy with Humira and methotrexate led to faster and significantly greater ACR responses than methotrexate monotherapy and Humira monotherapy at Week 52 and responses were sustained at Week 104 (see Table 5).

Table 5
ACR Responses in RA Study V
(percent of patients)

Response	**MTX n=257**	**Humira n=274**	**Humira/MTX n=268**	**p-value[a]**	**p-value[b]**	**p-value[c]**
ACR 20						
Week 52	62.6%	54.4%	72.8%	0.013	< 0.001	0.043
Week 104	56.0%	49.3%	69.4%	0.002	< 0.001	0.140
ACR 50						
Week 52	45.9%	41.2%	61.6%	< 0.001	< 0.001	0.317
Week 104	42.8%	36.9%	59.0%	< 0.001	< 0.001	0.162
ACR 70						
Week 52	27.2%	25.9%	45.5%	< 0.001	< 0.001	0.656
Week 104	28.4%	28.1%	46.6%	< 0.001	< 0.001	0.864

a. p-value is from the pairwise comparison of methotrexate monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test.
b. p-value is from the pairwise comparison of Humira monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test
c. p-value is from the pairwise comparison of Humira monotherapy and methotrexate monotherapy using the Mann-Whitney U test

In the open-label extension for RA study V, ACR response rates were maintained when followed for up to 10 years. Of 542 patients who were randomised to Humira 40 mg every other week, 170 patients continued on Humira 40 mg every other week for 10 years. Among those, 154 patients (90.6%) had ACR 20 responses; 127 patients (74.7%) had ACR 50 responses; and 102 patients (60.0%) had ACR 70 responses.

At Week 52, 42.9% of patients who received Humira/methotrexate combination therapy achieved clinical remission (DAS28 (CRP) < 2.6) compared to 20.6% of patients receiving methotrexate monotherapy and 23.4% of patients receiving Humira monotherapy. Humira/methotrexate combination therapy was clinically and statistically superior to methotrexate ($p < 0.001$) and Humira monotherapy ($p < 0.001$) in achieving a low disease state in patients with recently diagnosed moderate to severe rheumatoid arthritis. The response for the two monotherapy arms was similar ($p = 0.447$). Of 342 subjects originally randomized to Humira monotherapy or Humira/methotrexate combination therapy who entered the open-label extension study, 171 subjects completed 10 years of Humira treatment. Among those, 109 subjects (63.7%) were reported to be in remission at 10 years.

Radiographic response

In RA study III, where Humira treated patients had a mean duration of rheumatoid arthritis of approximately 11 years, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (TSS) and its components, the erosion score and joint space

narrowing score. Humira/methotrexate patients demonstrated significantly less radiographic progression than patients receiving methotrexate alone at 6 and 12 months (see Table 6).

In the open-label extension of RA Study III, the reduction in rate of progression of structural damage is maintained for 8 and 10 years in a subset of patients. At 8 years, 81 of 207 patients originally treated with 40 mg Humira every other week were evaluated radiographically. Among those, 48 patients showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less. At 10 years, 79 of 207 patients originally treated with 40 mg Humira every other week were evaluated radiographically. Among those, 40 patients showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less.

Table 6
Radiographic Mean Changes Over 12 Months in RA Study III

	Placebo/ MTX[a]	Humira/MTX 40 mg every other week	Placebo/MTX-Humira/MTX (95% Confidence Interval[b])	p-value
Total Sharp Score	2.7	0.1	2.6 (1.4, 3.8)	< 0.001[c]
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	< 0.001
JSN[d] score	1.0	0.1	0.9 (0.3, 1.4)	0.002

[a]methotrexate
[b]95% confidence intervals for the differences in change scores between methotrexate and Humira.
[c]Based on rank analysis
[d]Joint Space Narrowing

In RA study V, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (see Table 7).

Table 7
Radiographic Mean Changes at Week 52 in RA Study V

	MTX n=257 (95% confidence interval)	Humira n=274 (95% confidence interval)	Humira/MTX n=268 (95% confidence interval)	p-value[a]	p-value[b]	p-value[c]
Total Sharp Score	5.7 (4.2-7.3)	3.0 (1.7-4.3)	1.3 (0.5-2.1)	< 0.001	0.0020	< 0.001
Erosion score	3.7 (2.7-4.7)	1.7 (1.0-2.4)	0.8 (0.4-1.2)	< 0.001	0.0082	< 0.001
JSN score	2.0 (1.2-2.8)	1.3 (0.5-2.1)	0.5 (0-1.0)	< 0.001	0.0037	0.151

[a] p-value is from the pairwise comparison of methotrexate monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test.
[b] p-value is from the pairwise comparison of Humira monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test
[c] p-value is from the pairwise comparison of Humira monotherapy and methotrexate monotherapy using the Mann-Whitney U test

Following 52 weeks and 104 weeks of treatment, the percentage of patients without progression (change from baseline in modified Total Sharp Score ≤ 0.5) was significantly higher with Humira/methotrexate combination therapy (63.8% and 61.2% respectively) compared to methotrexate monotherapy (37.4% and 33.5% respectively, $p < 0.001$) and Humira monotherapy (50.7%, $p < 0.002$ and 44.5%, $p < 0.001$ respectively).

In the open-label extension of RA study V, the mean change from baseline at Year 10 in the modified Total Sharp Score was 10.8, 9.2 and 3.9 in patients originally randomized to methotrexate monotherapy, Humira monotherapy and Humira/methotrexate combination therapy, respectively. The corresponding proportions of patients with no radiographic progression were 31.3%, 23.7% and 36.7% respectively.

Quality of life and physical function

Health-related quality of life and physical function were assessed using the disability index of the Health Assessment Questionnaire (HAQ) in the four original adequate and well-controlled trials, which was a pre-specified primary endpoint at Week 52 in RA study III. All doses/schedules of Humira in all four studies showed statistically significantly greater improvement in the disability index of the HAQ from baseline to Month 6 compared to placebo and in RA study III the same was seen at Week 52. Results from the Short Form Health Survey (SF 36) for all doses/schedules of Humira in all four studies support these findings, with statistically significant physical component summary (PCS) scores, as well as statistically significant pain and vitality domain scores for the 40 mg every other week dose. A statistically significant decrease in fatigue as measured by functional assessment of chronic illness therapy (FACIT) scores was seen in all three studies in which it was assessed (RA studies I, III, IV).

In RA study III, most subjects who achieved improvement in physical function and continued treatment maintained improvement through Week 520 (120 months) of open-label treatment. Improvement in quality of life was measured up to Week 156 (36 months) and improvement was maintained through that time.

In RA study V, the improvement in the HAQ disability index and the physical component of the SF 36 showed greater improvement ($p < 0.001$) for Humira/methotrexate combination therapy *versus* methotrexate monotherapy and Humira monotherapy at Week 52, which was maintained through Week 104. Among the 250 subjects who completed the open-label extension study, improvements in physical function were maintained through 10 years of treatment.

Juvenile idiopathic arthritis (JIA)

Polyarticular juvenile idiopathic arthritis (pJIA)

The safety and efficacy of Humira was assessed in two studies (pJIA I and II) in children with active polyarticular or polyarticular course juvenile idiopathic arthritis, who had a variety of JIA onset types (most frequently rheumatoid-factor negative or positive polyarthritis and extended oligoarthritis).

pJIA I

The safety and efficacy of Humira were assessed in a multicentre, randomised, double-blind, parallel − group study in 171 children (4-17 years old) with polyarticular JIA. In the open-label lead in phase (OL LI) patients were stratified into two groups, MTX (methotrexate)-treated or non-MTX-treated. Patients who were in the non-MTX stratum were either naïve to or had been withdrawn from MTX at least two weeks prior to study drug administration. Patients remained on stable doses of NSAIDs and or prednisone (≤ 0.2 mg /kg/day or 10 mg/day maximum). In the OL LI phase all patients received 24 mg/m^2 up to a maximum of 40 mg Humira every other week for 16 weeks. The distribution of patients by age and minimum, median and maximum dose received during the OL LI phase is presented in Table 8.

Table 8
Distribution of patients by age and adalimumab dose received during the OL LI phase

Age Group	Number of patients at Baseline n (%)	Minimum, median and maximum dose
4 to 7 years	31 (18.1)	10, 20 and 25 mg
8 to 12 years	71 (41.5)	20, 25 and 40 mg
13 to 17 years	69 (40.4)	25, 40 and 40 mg

Patients demonstrating a Pediatric ACR 30 response at Week 16 were eligible to be randomised into the double blind (DB) phase and received either Humira 24 mg/m^2 up to a maximum of 40 mg, or placebo every other week for an additional 32 weeks or until disease flare. Disease flare criteria were defined as a worsening of ≥ 30% from baseline in ≥ 3 of 6 Pediatric ACR core criteria, ≥ 2 active joints, and improvement of > 30% in no more than 1 of the 6 criteria. After 32 weeks or at disease flare, patients were eligible to enrol into the open label extension phase.

Table 9
Ped ACR 30 Responses in the JIA study

Stratum	MTX		Without MTX	
Phase				
OL-LI 16 weeks				
Ped ACR 30 response (n/N)	94.1% (80/85)		74.4% (64/86)	
Efficacy Outcomes				
Double Blind 32 weeks	Humira /MTX (N = 38)	Placebo / MTX (N = 37)	Humira (N = 30)	Placebo (N = 28)
Disease flares at the end of 32 weeks[a] (n/N)	36.8% (14/38)	64.9% (24/37)[b]	43.3% (13/30)	71.4% (20/28)[c]
Median time to disease flare	>32 weeks	20 weeks	>32 weeks	14 weeks

[a] Ped ACR 30/50/70 responses Week 48 significantly greater than those of placebo treated patients
[b] p = 0.015
[c] p = 0.031

Amongst those who responded at Week 16 (n=144), the Pediatric ACR 30/50/70/90 responses were maintained for up to six years in the OLE phase in patients who received Humira throughout the study. Over all 19 subjects, of which 11 of the baseline age group 4 to 12 and 8 of the baseline age group 13 to 17 years were treated 6 years or longer.

Overall responses were generally better and, fewer patients developed antibodies when treated with the combination of Humira and MTX compared to Humira alone. Taking these results into consideration, Humira is recommended for use in combination with MTX and for use as monotherapy in patients for whom MTX use is not appropriate (see section 4.2).

pJIA II

The safety and efficacy of Humira was assessed in an open-label, multicentre study in 32 children (2 - <4 years old or aged 4 and above weighing < 15 kg) with moderately to severely active polyarticular JIA. The patients received 24 mg/m^2 body surface area (BSA) of Humira up to a maximum of 20 mg

every other week as a single dose via SC injection for at least 24 weeks. During the study, most subjects used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs.

At Week 12 and Week 24, PedACR30 response was 93.5% and 90.0%, respectively, using the observed data approach. The proportions of subjects with PedACR50/70/90 at Week 12 and Week 24 were 90.3%/61.3%/38.7% and 83.3%/73.3%/36.7%, respectively. Amongst those who responded (Pediatric ACR 30) at Week 24 (n=27 out of 30 patients), the Pediatric ACR 30 responses were maintained for up to 60 weeks in the OLE phase in patients who received Humira throughout this time period. Overall, 20 subjects were treated for 60 weeks or longer.

Enthesitis-related arthritis

The safety and efficacy of Humira were assessed in a multicentre, randomised, double-blind study in 46 paediatric patients (6 to 17 years old) with moderate enthesitis-related arthritis. Patients were randomised to receive either 24 mg/m^2 body surface area (BSA) of Humira up to a maximum of 40 mg, or placebo every other week for 12 weeks. The double-blind period is followed by an open-label (OL) period during which patients received 24 mg/m^2 BSA of Humira up to a maximum of 40 mg every other week subcutaneously for up to an additional 192 weeks. The primary endpoint was the percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with loss of motion plus pain and/or tenderness), which was achieved with mean percent decrease of -62.6% (median percent change -88.9%) in patients in the Humira group compared to -11.6% (median percent change -50.0%) in patients in the placebo group. Improvement in number of active joints with arthritis was maintained during the OL period through Week 156 for the 26 of 31 (84%) patients in the Humira group who remained in the study. Although not statistically significant, the majority of patients demonstrated clinical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count (TJC), swollen joint count (SJC), Pediatric ACR 50 response, and Pediatric ACR 70 response.

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Humira 40 mg every other week was assessed in 393 patients in two randomised, 24 week double − blind, placebo − controlled studies in patients with active ankylosing spondylitis (mean baseline score of disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] was 6.3 in all groups) who have had an inadequate response to conventional therapy. Seventy-nine (20.1%) patients were treated concomitantly with disease modifying anti − rheumatic drugs, and 37 (9.4%) patients with glucocorticoids. The blinded period was followed by an open − label period during which patients received Humira 40 mg every other week subcutaneously for up to an additional 28 weeks. Subjects (n=215, 54.7%) who failed to achieve ASAS 20 at Weeks 12, or 16 or 20 received early escape open-label adalimumab 40 mg every other week subcutaneously and were subsequently treated as non-responders in the double-blind statistical analyses.

In the larger AS study I with 315 patients, results showed statistically significant improvement of the signs and symptoms of ankylosing spondylitis in patients treated with Humira compared to placebo. Significant response was first observed at Week 2 and maintained through 24 weeks (Table 10).

Table 10
Efficacy Responses in Placebo-Controlled AS Study – Study I
Reduction of Signs and Symptoms

Response	**Placebo N=107**	**Humira N=208**
ASAS[a] 20		
Week 2	16%	42%***
Week 12	21%	58%***
Week 24	19%	51%***
ASAS 50		
Week 2	3%	16%***
Week 12	10%	38%***
Week 24	11%	35%***
ASAS 70		
Week 2	0%	7%**
Week 12	5%	23%***
Week 24	8%	24%***
BASDAI[b] 50		
Week 2	4%	20%***
Week 12	16%	45%***
Week 24	15%	42%***

***,** Statistically significant at $p < 0.001$, < 0.01 for all comparisons between Humira and placebo at Weeks 2, 12 and 24
[a] Assessments in Ankylosing Spondylitis
[b] Bath Ankylosing Spondylitis Disease Activity Index

Humira treated patients had significantly greater improvement at Week 12 which was maintained through Week 24 in both the SF36 and Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL).

Similar trends (not all statistically significant) were seen in the smaller randomised, double − blind, placebo controlled AS study II of 82 adult patients with active ankylosing spondylitis.

Axial spondyloarthritis without radiographic evidence of AS

Humira 40 mg every other week was assessed in 185 patients in one randomised, 12 week double - blind, placebo - controlled study in patients with active non-radiographic axial spondyloarthitis (mean baseline score of disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] was 6.4 for patients treated with Humira and 6.5 for those on placebo) who have had an inadequate response to or intolerance to ≥ 1 NSAIDs, or a contraindication for NSAIDs.

Thirty-three (18%) of patients were treated concomitantly with disease modifying anti-rheumatic drugs, and 146 (79%) patients with NSAIDs at baseline. The double-blind period was followed by an open-label period during which patients receive Humira 40 mg every other week subcutaneously for up to an additional 144 weeks. Week 12 results showed statistically significant improvement of the signs and symptoms of active non-radiographic axial spondyloarthritis in patients treated with Humira compared to placebo (Table 11).

Table 11
Efficacy Response in Placebo-Controlled Axial SpA Study

Double-Blind Response at Week 12	**Placebo N=94**	**Humira N=91**
ASAS[a] 40	15%	36%***
ASAS 20	31%	52%**
ASAS 5/6	6%	31%***
ASAS Partial Remission	5%	16%*
BASDAI[b] 50	15%	35%**
ASDAS[c,d,e]	-0.3	-1.0***
ASDAS Inactive Disease	4%	24%***
hs-CRP[d,f,g]	-0.3	-4.7***
SPARCC[h] MRI Sacroiliac Joints[d,i]	-0.6	-3.2**
SPARCC MRI Spine[d,j]	-0.2	-1.8**

[a] Assessment of Spondyloarthritis International Society
[b] Bath Ankylosing Spondylitis Disease Activity Index
[c] Ankylosing Spondylitis Disease Activity Score
[d] mean change from baseline
[e] n=91 placebo and n=87 Humira
[f] high sensitivity C-Reactive Protein (mg/L)
[g] n=73 placebo and n=70 Humira
[h] Spondyloarthritis Research Consortium of Canada
[i] n=84 placebo and Humira
[j] n=82 placebo and n=85 Humira
***, **, * Statistically significant at $p < 0.001$, < 0.01, and < 0.05, respectively, for all comparisons between Humira and placebo.

In the open-label extension, improvement in the signs and symptoms was maintained with Humira therapy through Week 156.

Inhibition of inflammation

Significant improvement of signs of inflammation as measured by hs-CRP and MRI of both Sacroiliac Joints and the Spine was maintained in Humira-treated patients through Week 156 and Week 104, respectively.

Quality of life and physical function

Health-related quality of life and physical function were assessed using the HAQ-S and the SF-36 questionnaires. Humira showed statistically significantly greater improvement in the HAQ-S total score and the SF-36 Physical Component Score (PCS) from baseline to Week 12 compared to placebo. Improvement in health-related quality of life and physical function was maintained during the open-label extension through Week 156.

Psoriatic arthritis

Humira, 40 mg every other week, was studied in patients with moderately to severely active psoriatic arthritis in two placebo-controlled studies, PsA studies I and II. PsA study I with 24 week duration, treated 313 adult patients who had an inadequate response to non-steroidal anti-inflammatory drug therapy and of these, approximately 50% were taking methotrexate. PsA study II with 12-week duration, treated 100 patients who had an inadequate response to DMARD therapy. Upon completion of both studies, 383 patients enrolled in an open-label extension study, in which 40 mg Humira was administered every other week.

There is insufficient evidence of the efficacy of Humira in patients with ankylosing spondylitis-like psoriatic arthropathy due to the small number of patients studied.

Table 12
ACR Response in Placebo-Controlled Psoriatic Arthritis Studies
(Percent of Patients)

	PsA Study I		PsA Study II	
Response	Placebo N=162	Humira N=151	Placebo N=49	Humira N=51
ACR 20				
Week 12	14%	58%***	16%	39%*
Week 24	15%	57%***	N/A	N/A
ACR 50				
Week 12	4%	36%***	2%	25%***
Week 24	6%	39%***	N/A	N/A
ACR 70				
Week 12	1%	20%***	0%	14%*
Week 24	1%	23%***	N/A	N/A

*** $p < 0.001$ for all comparisons between Humira and placebo
* $p < 0.05$ for all comparisons between Humira and placebo
N/A not applicable

ACR responses in PsA study I were similar with and without concomitant methotrexate therapy. ACR responses were maintained in the open-label extension study for up to 136 weeks.

Radiographic changes were assessed in the psoriatic arthritis studies. Radiographs of hands, wrists, and feet were obtained at baseline and Week 24 during the double-blind period when patients were on Humira or placebo and at Week 48 when all patients were on open-label Humira. A modified Total Sharp Score (mTSS), which included distal interphalangeal joints (i.e. not identical to the TSS used for rheumatoid arthritis), was used.

Humira treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment as measured by change from baseline in mTSS (mean ± SD) 0.8 ± 2.5 in the placebo group (at Week 24) compared with 0.0 ± 1.9; ($p< 0.001$) in the Humira group (at Week 48).

In subjects treated with Humira with no radiographic progression from baseline to Week 48 (n=102), 84% continued to show no radiographic progression through 144 weeks of treatment.
Humira treated patients demonstrated statistically significant improvement in physical function as assessed by HAQ and Short Form Health Survey (SF 36) compared to placebo at Week 24. Improved physical function continued during the open label extension up to Week 136.

Psoriasis

The safety and efficacy of Humira were studied in adult patients with chronic plaque psoriasis (≥ 10% BSA involvement and Psoriasis Area and Severity Index (PASI) ≥ 12 or ≥ 10) who were candidates for systemic therapy or phototherapy in randomised, double-blind studies. 73% of patients enrolled in Psoriasis Studies I and II had received prior systemic therapy or phototherapy. The safety and efficacy of Humira were also studied in adult patients with moderate to severe chronic plaque psoriasis with concomitant hand and/or foot psoriasis who were candidates for systemic therapy in a randomised double-blind study (Psoriasis Study III).

Psoriasis Study I (REVEAL) evaluated 1,212 patients within three treatment periods. In period A, patients received placebo or Humira at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. After 16 weeks of therapy, patients who achieved at least a PASI 75 response (PASI score improvement of at least 75% relative to baseline), entered period B

and received open-label 40 mg Humira every other week. Patients who maintained ≥PASI 75 response at Week 33 and were originally randomised to active therapy in Period A, were re-randomised in period C to receive 40 mg Humira every other week or placebo for an additional 19 weeks. Across all treatment groups, the mean baseline PASI score was 18.9 and the baseline Physician's Global Assessment (PGA) score ranged from "moderate" (53% of subjects included) to "severe" (41%) to "very severe" (6%).

Psoriasis Study II (CHAMPION) compared the efficacy and safety of Humira *versus* methotrexate and placebo in 271 patients. Patients received placebo, an initial dose of MTX 7.5 mg and thereafter dose increases up to Week 12, with a maximum dose of 25 mg or an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) for 16 weeks. There are no data available comparing Humira and MTX beyond 16 weeks of therapy. Patients receiving MTX who achieved a ≥PASI 50 response at Week 8 and/or 12 did not receive further dose increases. Across all treatment groups, the mean baseline PASI score was 19.7 and the baseline PGA score ranged from "mild" (<1%) to "moderate" (48%) to "severe" (46%) to "very severe" (6%).

Patients participating in all Phase 2 and Phase 3 psoriasis studies were eligible to enrol into an open-label extension trial, where Humira was given for at least an additional 108 weeks.

In Psoriasis Studies I and II, a primary endpoint was the proportion of patients who achieved a PASI 75 response from baseline at Week 16 (see Tables 13 and14).

Table 13
Ps Study I (REVEAL) - Efficacy Results at 16 Weeks

	Placebo N=398 n (%)	**Humira 40 mg eow N=814 n (%)**
≥PASI 75[a]	26 (6.5)	578 (70.9)[b]
PASI 100	3 (0.8)	163 (20.0)[b]
PGA: Clear/minimal	17 (4.3)	506 (62.2)[b]
[a] Percent of patients achieving PASI75 response was calculated as centre-adjusted rate [b] p<0.001, Humira vs. placebo		

Table 14
Ps Study II (CHAMPION) Efficacy Results at 16 Weeks

	Placebo N=53 n (%)	**MTX N=110 n (%)**	**Humira 40 mg eow N=108 n (%)**
≥PASI 75	10 (18.9)	39 (35.5)	86 (79.6) [a, b]
PASI 100	1 (1.9)	8 (7.3)	18 (16.7) [c, d]
PGA: Clear/minimal	6 (11.3)	33 (30.0)	79 (73.1) [a, b]
[a] p<0.001 Humira vs. placebo [b] p<0.001 Humira vs. methotrexate [c] p<0.01 Humira vs. placebo [d] p<0.05 Humira vs. methotrexate			

In Psoriasis Study I, 28% of patients who were PASI 75 responders and were re-randomised to placebo at Week 33 compared to 5% continuing on Humira, p<0.001, experienced "loss of adequate response" (PASI score after Week 33 and on or before Week 52 that resulted in a <PASI 50 response relative to baseline with a minimum of a 6-point increase in PASI score relative to Week 33). Of the patients who lost adequate response after re-randomisation to placebo who then enrolled into the

open-label extension trial, 38% (25/66) and 55% (36/66) regained PASI 75 response after 12 and 24 weeks of re-treatment, respectively.

A total of 233 PASI 75 responders at Week 16 and Week 33 received continuous Humira therapy for 52 weeks in Psoriasis Study I, and continued Humira in the open-label extension trial. PASI 75 and PGA of clear or minimal response rates in these patients were 74.7% and 59.0%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks). In an analysis in which all patients who dropped out of the study for adverse events or lack of efficacy, or who dose-escalated, were considered non-responders, PASI 75 and PGA of clear or minimal response rates in these patients were 69.6% and 55.7%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. During the withdrawal period, symptoms of psoriasis returned over time with a median time to relapse (decline to PGA "moderate" or worse) of approximately 5 months. None of these patients experienced rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the retreatment period had a response of PGA "clear" or "minimal" after 16 weeks of retreatment, irrespective of whether they relapsed during withdrawal (69.1%[123/178] and 88.8% [95/107] for patients who relapsed and who did not relapse during the withdrawal period, respectively). A similar safety profile was observed during retreatment as before withdrawal.

Significant improvements at Week 16 from baseline compared to placebo (Studies I and II) and MTX (Study II) were demonstrated in the DLQI (Dermatology Life Quality Index). In Study I, improvements in the physical and mental component summary scores of the SF-36 were also significant compared to placebo.

In an open-label extension study, for patients who dose escalated from 40 mg every other week to 40 mg weekly due to a PASI response below 50%, 26.4% (92/349) and 37.8% (132/349) of patients achieved PASI 75 response at Week 12 and 24, respectively.

Psoriasis Study III (REACH) compared the efficacy and safety of Humira *versus* placebo in 72 patients with moderate to severe chronic plaque psoriasis and hand and/or foot psoriasis. Patients received an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) or placebo for 16 weeks. At Week 16, a statistically significantly greater proportion of patients who received Humira achieved PGA of 'clear' or 'almost clear' for the hands and/or feet compared to patients who received placebo (30.6% versus 4.3%, respectively [P = 0.014]).

Psoriasis Study IV compared efficacy and safety of Humira versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open-label Humira treatment for an additional 26 weeks. Nail psoriasis assessments included the Modified Nail Psoriasis Severity Index (mNAPSI), the Physician's Global Assessment of Fingernail Psoriasis (PGA-F) and the Nail Psoriasis Severity Index (NAPSI) (see Table 15). Humira demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement (BSA≥10% (60% of patients) and BSA<10% and ≥5% (40% of patients)).

Table 15
Ps Study IV Efficacy Results at 16, 26 and 52 Weeks

Endpoint	Week 16 Placebo-Controlled		Week 26 Placebo-Controlled		Week 52 Open-label
	Placebo N=108	Humira 40 mg eow N=109	Placebo N=108	Humira 40 mg eow N=109	Humira 40 mg eow N=80
≥ mNAPSI 75 (%)	2.9	26.0[a]	3.4	46.6[a]	65.0
PGA-F clear/minimal and ≥2-grade improvement (%)	2.9	29.7[a]	6.9	48.9[a]	61.3

Percent Change in Total Fingernail NAPSI (%)	-7.8	-44.2 [a]	-11.5	-56.2[a]	-72.2
[a] p<0.001, Humira *vs.* placebo					

Humira treated patients showed statistically significant improvements at Week 26 compared with placebo in the DLQI.

Paediatric plaque psoriasis

The efficacy of Humira was assessed in a randomised, double-blind, controlled study of 114 paediatric patients from 4 years of age with severe chronic plaque psoriasis (as defined by a PGA ≥ 4 or > 20% BSA involvement or > 10% BSA involvement with very thick lesions or PASI ≥ 20 or ≥ 10 with clinically relevant facial, genital, or hand/ foot involvement) who were inadequately controlled with topical therapy and heliotherapy or phototherapy.

Patients received Humira 0.8 mg/kg eow (up to 40 mg), 0.4 mg/kg eow (up to 20 mg), or methotrexate 0.1 – 0.4 mg/kg weekly (up to 25 mg). At Week 16, more patients randomised to Humira 0.8 mg/kg had positive efficacy responses (e.g., PASI 75) than those randomised to 0.4 mg/kg eow or MTX.

Table 16: Paediatric Plaque Psoriasis Efficacy Results at 16 Weeks

	MTX[a] N=37	Humira 0.8 mg/kg eow N=38
PASI 75[b]	12 (32.4%)	22 (57.9%)
PGA: Clear/minimal[c]	15 (40.5%)	23 (60.5%)
[a] MTX = methotrexate [b] P=0.027, Humira 0.8 mg/kg versus MTX [c] P=0.083, Humira 0.8 mg/kg versus MTX		

Patients who achieved PASI 75 and PGA clear or minimal were withdrawn from treatment for up to 36 weeks and monitored for loss of disease control (i.e. a worsening of PGA by at least 2 grades). Patients were then re-treated with adalimumab 0.8 mg/kg eow for an additional 16 weeks and response rates observed during retreatment were similar to the previous double-blind period: PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects).

In the open label period of the study, PASI 75 and PGA clear or minimal responses were maintained for up to an additional 52 weeks with no new safety findings.

Hidradenitis suppurativa

The safety and efficacy of Humira were assessed in randomised, double-blind, placebo-controlled studies and an open-label extension study in adult patients with moderate to severe hidradenitis suppurativa (HS) who were intolerant, had a contraindication or an inadequate response to at least a 3-month trial of systemic antibiotic therapy. The patients in HS-I and HS-II had Hurley Stage II or III disease with at least 3 abscesses or inflammatory nodules.

Study HS-I (PIONEER I) evaluated 307 patients with 2 treatment periods. In Period A, patients received placebo or Humira at an initial dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every week starting at Week 4 to Week 11. Concomitant antibiotic use was not allowed during the study. After 12 weeks of therapy, patients who had received Humira in Period A were re-randomised in Period B to 1 of 3 treatment groups (Humira 40 mg every week, Humira 40 mg every other week, or placebo from Week 12 to Week 35). Patients who had been randomised to placebo in Period A were assigned to receive Humira 40 mg every week in Period B.

Study HS-II (PIONEER II) evaluated 326 patients with 2 treatment periods. In Period A, patients received placebo or Humira at an initial dose of 160 mg at Week 0 and 80 mg at Week 2 and 40 mg every week starting at Week 4 to Week 11. 19.3% of patients had continued baseline oral antibiotic therapy during the study. After 12 weeks of therapy, patients who had received Humira in Period A were re-randomised in Period B to 1 of 3 treatment groups (Humira 40 mg every week, Humira 40 mg every other week, or placebo from Week 12 to Week 35). Patients who had been randomised to placebo in Period A were assigned to receive placebo in Period B.

Patients participating in Studies HS-I and HS-II were eligible to enrol into an open-label extension study in which Humira 40mg was administered every week. Mean exposure in all adalimumab population was 762 days. Throughout all 3 studies patients used topical antiseptic wash daily.

Clinical Response

Reduction of inflammatory lesions and prevention of worsening of abscesses and draining fistulas was assessed using Hidradenitis Suppurativa Clinical Response (HiSCR; at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count relative to Baseline). Reduction in HS-related skin pain was assessed using a Numeric Rating Scale in patients who entered the study with an initial baseline score of 3 or greater on a 11 point scale.

At Week 12, a significantly higher proportion of patients treated with Humira versus placebo achieved HiSCR. At Week 12, a significantly higher proportion of patients in Study HS-II experienced a clinically relevant decrease in HS-related skin pain (see Table 17). Patients treated with Humira had significantly reduced risk of disease flare during the initial 12 weeks of treatment.

Table 17: Efficacy Results at 12 Weeks, HS Studies I and II

	HS Study I		**HS Study II**	
	Placebo	**Humira 40 mg Weekly**	**Placebo**	**Humira 40 mg Weekly**
Hidradenitis Suppurativa Clinical Response (HiSCR)[a]	N = 154 40 (26.0%)	N = 153 64 (41.8%) *	N=163 45 (27.6%)	N=163 96 (58.9%) ***
≥30% Reduction in Skin Pain[b]	N = 109 27 (24.8%)	N = 122 34 (27.9%)	N=111 23 (20.7%)	N=105 48 (45.7%) ***

* $P < 0.05$, *** $P < 0.001$, Humira versus placebo

[a] Among all randomised patients.

[b] Among patients with baseline HS-related skin pain assessment ≥ 3, based on Numeric Rating Scale 0 – 10; 0 = no skin pain, 10 = skin pain as bad as you can imagine.

Treatment with Humira 40 mg every week significantly reduced the risk of worsening of abscesses and draining fistulas. Approximately twice the proportion of patients in the placebo group in the first 12 weeks of Studies HS-I and HS-II, compared with those in the Humira group experienced worsening of abscesses (23.0% vs 11.4%, respectively) and draining fistulas (30.0% vs 13.9%, respectively).

Greater improvements at Week 12 from baseline compared to placebo were demonstrated in skin-specific health-related quality of life, as measured by the Dermatology Life Quality Index (DLQI; Studies HS-I and HS-II), patient global satisfaction with medication treatment as measured by the Treatment Satisfaction Questionnaire - medication (TSQM; Studies HS-I and HS-II), and physical health as measured by the physical component summary score of the SF-36 (Study HS-I).

In patients with at least a partial response to Humira 40 mg weekly at Week 12, the HiSCR rate at Week 36 was higher in patients who continued weekly Humira than in patients in whom dosing frequency was reduced to every other week, or in whom treatment was withdrawn (see Table 18).

Table 18: Proportion of Patients[a] Achieving HiSCR[b] at Weeks 24 and 36 After Treatment Reassignment from Weekly Humira at Week 12

	Placebo (treatment withdrawal) N = 73	Humira 40 mg every other week N = 70	Humira 40 mg weekly N = 70
Week 24	24 (32.9%)	36 (51.4%)	40 (57.1%)
Week 36	22 (30.1%)	28 (40.0%)	39 (55.7%)

[a] Patients with at least a partial response to Humira 40 mg weekly after 12 weeks of treatment.

[b] Patients meeting protocol-specified criteria for loss of response or no improvement were required to discontinue from the studies and were counted as nonresponders.

Among patients who were at least partial responders at Week 12, and who received continuous weekly Humira therapy, the HiSCR rate at Week 48 was 68.3% and at Week 96 was 65.1%. Longer term treatment with Humira 40 mg weekly for 96 weeks identified no new safety findings.

Among patients whose Humira treatment was withdrawn at Week 12 in Studies HS-I and HS-II, the HiSCR rate 12 weeks after re-introduction of Humira 40 mg weekly returned to levels similar to that observed before withdrawal (56.0 %).

Adolescent hidradenitis suppurativa

There are no clinical trials with Humira in adolescent patients with HS. Efficacy of adalimumab for the treatment of adolescent patients with HS is predicted based on the demonstrated efficacy and exposure-response relationship in adult HS patients and the likelihood that the disease course, pathophysiology, and drug effects are substantially similar to that of adults at the same exposure levels. Safety of the recommended adalimumab dose in the adolescent HS population is based on cross-indication safety profile of adalimumab in both adults and paediatric patients at similar or more frequent doses (see section 5.2).

Crohn's disease

The safety and efficacy of Humira were assessed in over 1500 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomised, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 80% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies, CD Study I (CLASSIC I) and CD Study II (GAIN). In CD Study I, 299 TNF-antagonist naive patients were randomised to one of four treatment groups; placebo at Weeks 0 and 2, 160 mg Humira at Week 0 and 80 mg at Week 2, 80 mg at Week 0 and 40 mg at Week 2, and 40 mg at Week 0 and 20 mg at Week 2. In CD Study II, 325 patients who had lost response or were intolerant to infliximab were randomised to receive either 160 mg Humira at Week 0 and 80 mg at Week 2 or placebo at Weeks 0 and 2. The primary non-responders were excluded from the studies and therefore these patients were not further evaluated.

Maintenance of clinical remission was evaluated in CD study III (CHARM). In CD Study III, 854 patients received open-label 80 mg at Week 0 and 40 mg at Week 2. At Week 4 patients were randomised to 40 mg every other week, 40 mg every week, or placebo with a total study duration of 56 weeks. Patients in clinical response (decrease in CDAI ≥ 70) at Week 4 were stratified and

analysed separately from those not in clinical response at Week 4. Corticosteroid taper was permitted after Week 8.

CD study I and CD study II induction of remission and response rates are presented in Table 19.

Table 19
Induction of Clinical Remission and Response
(Percent of Patients)

	CD Study I: Infliximab Naive Patients			**CD Study II: Infliximab Experienced Patients**	
	Placebo N=74	**Humira 80/40 mg N = 75**	**Humira 160/80 mg N=76**	**Placebo N=166**	**Humira 160/80 mg N=159**
Week 4					
Clinical remission	12%	24%	36%*	7%	21%*
Clinical response (CR-100)	24%	37%	49%**	25%	38%**

All p-values are pairwise comparisons of proportions for Humira *versus* placebo

* $p < 0.001$

** $p < 0.01$

Similar remission rates were observed for the 160/80 mg and 80/40 mg induction regimens by Week 8 and adverse events were more frequently noted in the 160/80 mg group.

In CD Study III, at Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. Of those in clinical response at Week 4, 48% had been previously exposed to other TNF-antagonists. Maintenance of remission and response rates are presented in Table 20. Clinical remission results remained relatively constant irrespective of previous TNF-antagonist exposure.

Disease-related hospitalisations and surgeries were statistically significantly reduced with adalimumab compared with placebo at Week 56.

Table 20
Maintenance of Clinical Remission and Response
(Percent of Patients)

	Placebo	**40 mg Humira every other week**	**40 mg Humira every week**
Week 26	**N=170**	**N=172**	**N=157**
Clinical remission	17%	40%*	47%*
Clinical response (CR-100)	27%	52%*	52%*
Patients in steroid-free remission for >=90 days[a]	3% (2/66)	19% (11/58)**	15% (11/74)**
Week 56	**N=170**	**N=172**	**N=157**
Clinical remission	12%	36%*	41%*
Clinical response (CR-100)	17%	41%*	48%*
Patients in steroid-free remission for >=90 days[a]	5% (3/66)	29% (17/58)*	20% (15/74)**

* $p < 0.001$ for Humira *versus* placebo pairwise comparisons of proportions

** $p < 0.02$ for Humira *versus* placebo pairwise comparisons of proportions

[a] Of those receiving corticosteroids at baseline

Among patients who were not in response at Week 4, 43% of Humira maintenance patients responded by Week 12 compared to 30% of placebo maintenance patients. These results suggest that some patients who have not responded by Week 4 benefit from continued maintenance therapy through Week 12. Therapy continued beyond 12 weeks did not result in significantly more responses (see section 4.2).

117/276 patients from CD study I and 272/777 patients from CD studies II and III were followed through at least 3 years of open-label adalimumab therapy. 88 and 189 patients, respectively, continued to be in clinical remission. Clinical response (CR-100) was maintained in 102 and 233 patients, respectively.

Quality of life

In CD Study I and CD Study II, statistically significant improvement in the disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at Week 4 in patients randomised to Humira 80/40 mg and 160/80 mg compared to placebo and was seen at Weeks 26 and 56 in CD Study III as well among the adalimumab treatment groups compared to the placebo group.

Paediatric Crohn's disease

Humira was assessed in a multicentre, randomised, double-blind clinical trial designed to evaluate the efficacy and safety of induction and maintenance treatment with doses dependent on body weight (< 40 kg or ≥ 40 kg) in 192 paediatric subjects between the ages of 6 and 17 (inclusive) years, with moderate to severe Crohn´s disease (CD) defined as Paediatric Crohn's Disease Activity Index (PCDAI) score > 30. Subjects had to have failed conventional therapy (including a corticosteroid and/or an immunomodulator) for CD. Subjects may also have previously lost response or been intolerant to infliximab.

All subjects received open-label induction therapy at a dose based on their Baseline body weight: 160 mg at Week 0 and 80 mg at Week 2 for subjects ≥ 40 kg, and 80 mg and 40 mg, respectively, for subjects < 40 kg.

At Week 4, subjects were randomised 1:1 based on their body weight at the time to either the Low Dose or Standard Dose maintenance regimens as shown in Table 21.

Table 21
Maintenance regimen

Patient Weight	**Low dose**	**Standard dose**
< 40 kg	10 mg eow	20 mg eow
≥ 40 kg	20 mg eow	40 mg eow

Efficacy results

The primary endpoint of the study was clinical remission at Week 26, defined as PCDAI score ≤ 10.

Clinical remission and clinical response (defined as reduction in PCDAI score of at least 15 points from Baseline) rates are presented in Table 22. Rates of discontinuation of corticosteroids or immunomodulators are presented in Table 23.

Table 22 Paediatric CD Study PCDAI Clinical Remission and Response			
	Standard Dose 40/20 mg eow N = 93	**Low Dose 20/10 mg eow N = 95**	**P value***
Week 26			
Clinical remission	38.7%	28.4%	0.075
Clinical response	59.1%	48.4%	0.073
Week 52			
Clinical remission	33.3%	23.2%	0.100
Clinical response	41.9%	28.4%	0.038
* p value for Standard Dose *versus* Low Dose comparison.			

Table 23 Paediatric CD Study Discontinuation of Corticosteroids or Immunomodulators and Fistula Remission			
	Standard Dose 40/20 mg eow	**Low Dose 20/10 mg eow**	**P value[1]**
Discontinued corticosteroids	**N= 33**	**N=38**	
Week 26	84.8%	65.8%	0.066
Week 52	69.7%	60.5%	0.420
Discontinuation of Immunomodulators[2]	**N=60**	**N=57**	
Week 52	30.0%	29.8%	0.983
Fistula remission[3]	**N=15**	**N=21**	
Week 26	46.7%	38.1%	0.608
Week 52	40.0%	23.8%	0.303

[1] p value for Standard Dose *versus* Low Dose comparison.
[2] Immunosuppressant therapy could only be discontinued at or after Week 26 at the investigator's discretion if the subject met the clinical response criterion
[3] defined as a closure of all fistulas that were draining at Baseline for at least 2 consecutive post-Baseline visits

Statistically significant increases (improvement) from Baseline to Week 26 and 52 in Body Mass Index and height velocity were observed for both treatment groups.

Statistically and clinically significant improvements from Baseline were also observed in both treatment groups for quality of life parameters (including IMPACT III).

One hundred patients (n=100) from the Paediatric CD Study continued in an open-label long-term extension study. After 5 years of adalimumab therapy, 74.0% (37/50) of the 50 patients remaining in the study continued to be in clinical remission, and 92.0% (46/50) of patients continued to be in clinical response per PCDAI.

Ulcerative colitis

The safety and efficacy of multiple doses of Humira were assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopy subscore of 2 to 3) in randomised, double-blind, placebo-controlled studies.

In study UC-I, 390 TNF-antagonist naïve patients were randomised to receive either placebo at Weeks 0 and 2, 160 mg Humira at Week 0 followed by 80 mg at Week 2, or 80 mg Humira at Week 0 followed by 40 mg at Week 2. After Week 2, patients in both adalimumab arms received

40 mg eow. Clinical remission (defined as Mayo score ≤ 2 with no subscore > 1) was assessed at Week 8.

In study UC-II, 248 patients received 160 mg of Humira at Week 0, 80 mg at Week 2 and 40 mg eow thereafter, and 246 patients received placebo. Clinical results were assessed for induction of remission at Week 8 and for maintenance of remission at Week 52.

Patients induced with 160/80 mg Humira achieved clinical remission versus placebo at Week 8 in statistically significantly greater percentages in study UC-I (18% vs. 9% respectively, p=0.031) and study UC-II (17% vs. 9% respectively, p=0.019). In study UC-II, among those treated with Humira who were in remission at Week 8, 21/41 (51%) were in remission at Week 52.

Results from the overall UC-II study population are shown in Table 24.

Table 24

Response, Remission and Mucosal Healing in Study UC-II

(Percent of Patients)

	Placebo	**Humira 40 mg eow**
Week 52	**N=246**	**N=248**
Clinical Response	18%	30%*
Clinical Remission	9%	17%*
Mucosal Healing	15%	25%*
Steroid-free remission for ≥ 90 days [a]	6% (N=140)	13% * (N=150)
Week 8 and 52		
Sustained Response	12%	24%**
Sustained Remission	4%	8%*
Sustained Mucosal Healing	11%	19%*

Clinical remission is Mayo score ≤ 2 with no subscore > 1;
Clinical response is decrease from baseline in Mayo score ≥3 points and ≥30% plus a decrease in the rectal bleeding subscore [RBS] ≥1 or an absolute RBS of 0 or 1;
*p<0.05 for Humira *vs.* placebo pairwise comparison of proportions
**p<0.001 for Humira *vs.* placebo pairwise comparison of proportions
[a] Of those receiving corticosteroids at baseline

Of those patients who had a response at Week 8, 47% were in response, 29% were in remission, 41% had mucosal healing, and 20% were in steroid-free remission for ≥ 90 days at Week 52.

Approximately 40% of patients in study UC-II had failed prior anti-TNF treatment with infliximab. The efficacy of adalimumab in those patients was reduced compared to that in anti-TNF naïve patients. Among patients who had failed prior anti-TNF treatment, Week 52 remission was achieved by 3% on placebo and 10% on adalimumab.

Patients from studies UC-I and UC-II had the option to roll over into an open-label long-term extension study (UC III). Following 3 years of adalimumab therapy, 75% (301/402) continued to be in clinical remission per partial Mayo score.

Hospitalisation rates

During 52 weeks of studies UC-I and UC-II, lower rates of all-cause hospitalisations and UC-related hospitalisations were observed for the adalimumab-treated arm compared to the placebo arm. The number of all cause hospitalisations in the adalimumab treatment group was 0.18 per patient year *vs*. 0.26 per patient year in the placebo group and the corresponding figures for UC-related hospitalisations were 0.12 per patient year *vs.* 0.22 per patient year.

Quality of life

In study UC-II, treatment with adalimumab resulted in improvements in the Inflammatory Bowel Disease Questionnaire (IBDQ) score.

Uveitis

The safety and efficacy of Humira were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis, excluding patients with isolated anterior uveitis, in two randomised, double-masked, placebo-controlled studies (UV I and II). Patients received placebo or Humira at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. Concomitant stable doses of one non-biologic immunosuppressant were permitted.

Study UV I evaluated 217 patients with active uveitis despite treatment with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). All patients received a 2-week standardised dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by Week 15.

Study UV II evaluated 226 patients with inactive uveitis requiring chronic corticosteroid treatment (oral prednisone 10 to 35 mg/day) at baseline to control their disease. Patients subsequently underwent a mandatory taper schedule, with complete corticosteroid discontinuation by Week 19.

The primary efficacy endpoint in both studies was ´time to treatment failure´. Treatment failure was defined by a multi-component outcome based on inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber (AC) cell grade, vitreous haze (VH) grade and best corrected visual acuity (BCVA).

Clinical Response

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with Humira versus patients receiving placebo (See Table 25). Both studies demonstrated an early and sustained effect of Humira on the treatment failure rate versus placebo (see Figure 1).

Table 25
Time to Treatment Failure in Studies UV I and UV II

Analysis Treatment	**N**	**Failure N (%)**	**Median Time to Failure (months)**	**HR[a]**	**CI 95% for HR[a]**	***P* Value[b]**
Time to Treatment Failure At or After Week 6 in Study UV I						
Primary analysis (ITT)						
Placebo	107	84 (78.5)	3.0	--	--	--
Adalimumab	110	60 (54.5)	5.6	0.50	0.36, 0.70	< 0.001
Time to Treatment Failure At or After Week 2 in Study UV II						
Primary analysis (ITT)						
Placebo	111	61 (55.0)	8.3	--	--	--
Adalimumab	115	45 (39.1)	NE[c]	0.57	0.39, 0.84	0.004

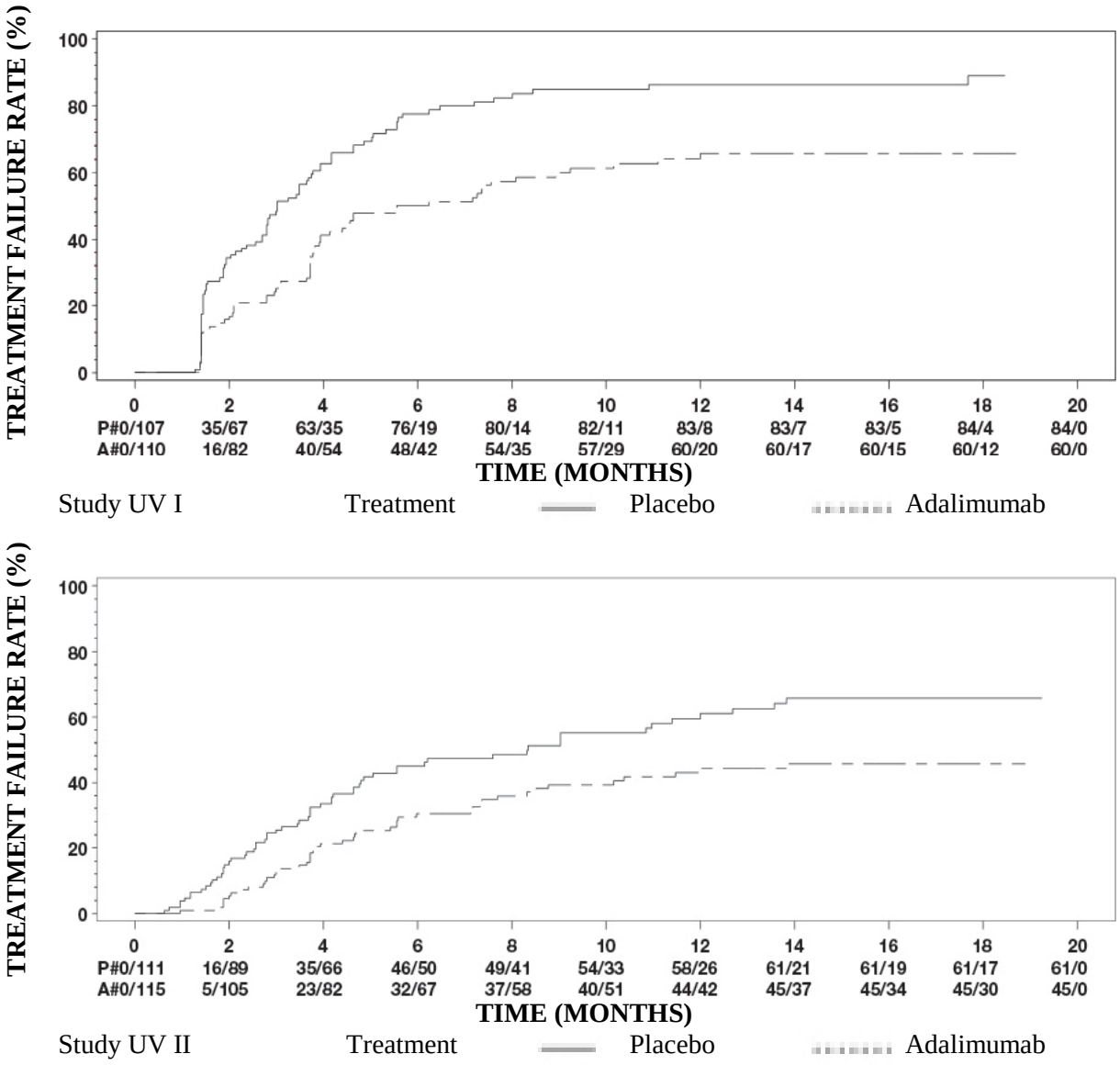
Note: Treatment failure at or after Week 6 (Study UV I), or at or after Week 2 (Study UV II), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

[a] HR of adalimumab vs placebo from proportional hazards regression with treatment as factor.

[b] 2-sided *P* value from log rank test.

[c] NE = not estimable. Fewer than half of at-risk subjects had an event.

Figure 1: Kaplan-Meier Curves Summarizing Time to Treatment Failure on or after Week 6 (Study UV I) or Week 2 (Study UV II)



Note: P# = Placebo (Number of Events/Number at Risk); A# = HUMIRA (Number of Events/Number at Risk).

In Study UV I statistically significant differences in favour of adalimumab versus placebo were observed for each component of treatment failure. In Study UV II, statistically significant differences were observed for visual acuity only, but the other components were numerically in favour of adalimumab.

Quality of Life

Patient reported outcomes regarding vision-related functioning were measured in both clinical studies, using the NEI VFQ-25. Humira was numerically favoured for the majority of subscores with statistically significant mean differences for general vision, ocular pain, near vision, mental health, and total score in Study UV I, and for general vision and mental health in Study UV II. Vision related effects were not numerically in favour of Humira for colour vision in Study UVI and for colour vision, peripheral vision and near vision in Study UV II.

Paediatric Uveitis

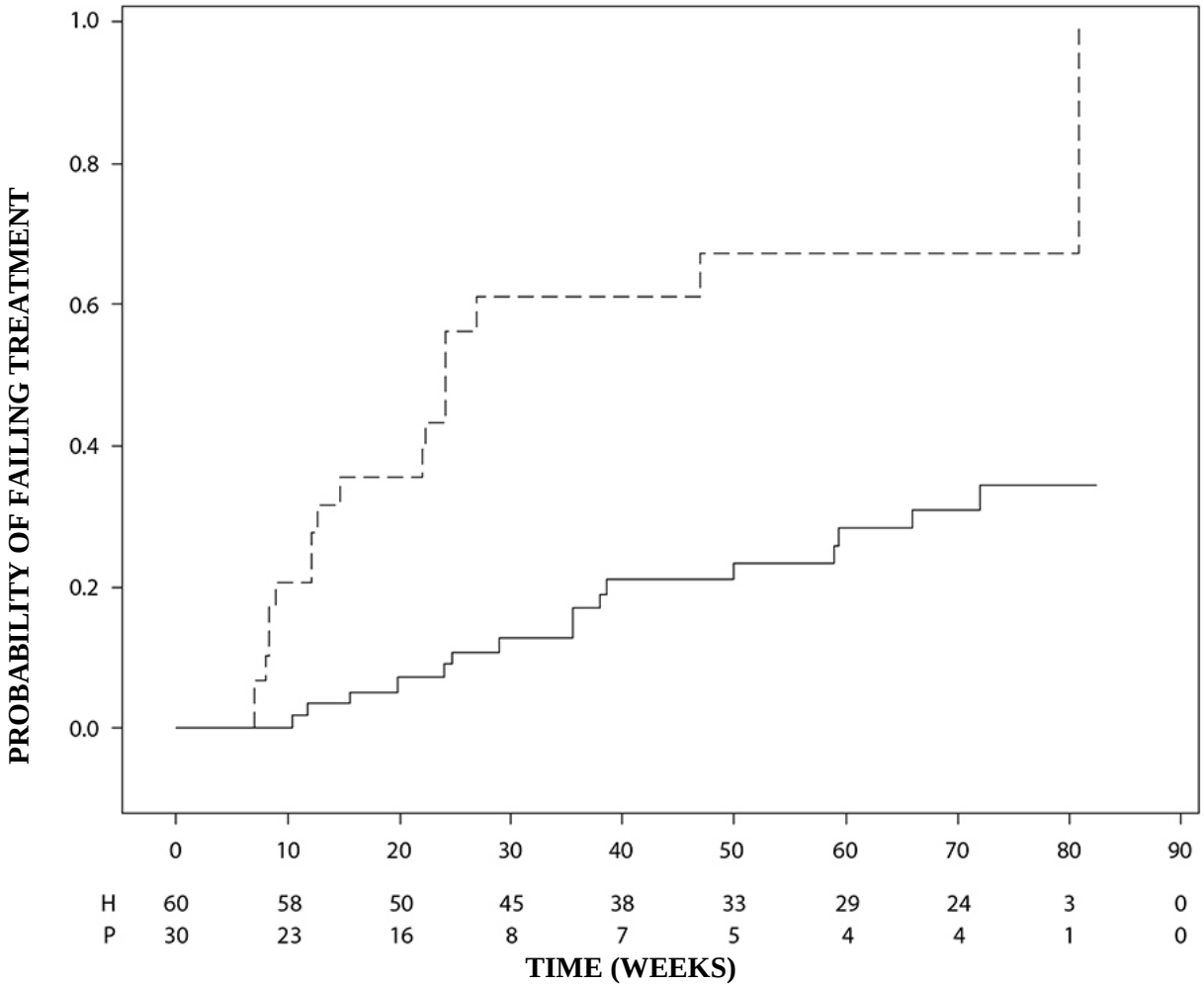
The safety and efficacy of Humira was assessed in a randomized, double-masked, controlled study of 90 paediatric patients from 2 to < 18 years of age with active JIA-associated noninfectious anterior uveitis who were refractory to at least 12 weeks of methotrexate treatment. Patients received either placebo or 20 mg adalimumab (if < 30 kg) or 40 mg adalimumab (if ≥ 30 kg) every other week in combination with their baseline dose of methotrexate.

The primary endpoint was 'time to treatment failure'. The criteria determining treatment failure were worsening or sustained non-improvement in ocular inflammation, partial improvement with development of sustained ocular co-morbidities or worsening of ocular co-morbidities, non-permitted use of concomitant medications, and suspension of treatment for an extended period of time.

Clinical Response

Adalimumab significantly delayed the time to treatment failure, as compared to placebo (See Figure 2, P < 0.0001 from log rank test).The median time to treatment failure was 24.1 weeks for subjects treated with placebo, whereas the median time to treatment failure was not estimable for subjects treated with adalimumab because less than one-half of these subjects experienced treatment failure. Adalimumab significantly decreased the risk of treatment failure by 75% relative to placebo, as shown by the hazard ratio (HR = 0.25 [95% CI: 0.12, 0.49]).

Figure 2: Kaplan-Meier Curves Summarizing Time to Treatment Failure in the Paediatric Uveitis Study



Note: P = Placebo (Number at Risk); H = HUMIRA (Number at Risk).

Immunogenicity

Formation of anti-adalimumab antibodies is associated with increased clearance and reduced efficacy of adalimumab. There is no apparent correlation between the presence of anti-adalimumab antibodies and the occurrence of adverse events.

Patients in rheumatoid arthritis studies I, II and III were tested at multiple time points for anti-adalimumab antibodies during the 6 to 12 month period. In the pivotal trials, anti-adalimumab antibodies were identified in 5.5% (58/1053) of patients treated with adalimumab, compared to 0.5% (2/370) on placebo. In patients not given concomitant methotrexate, the incidence was 12.4%, compared to 0.6% when adalimumab was used as add-on to methotrexate.

In patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years, anti-adalimumab antibodies were identified in 15.8% (27/171) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 25.6% (22/86) compared to 5.9% (5/85) when adalimumab was used as add-on to methotrexate.

In patients with enthesitis-related arthritis, anti-adalimumab antibodies were identified in 10.9% (5/46) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 13.6% (3/22), compared to 8.3% (2/24) when adalimumab was used as add-on to methotrexate.

In patients with psoriatic arthritis, anti-adalimumab antibodies were identified in 38/376 subjects (10%) treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 13.5% (24/178 subjects), compared to 7% (14 of 198 subjects) when adalimumab was used as add-on to methotrexate.

In patients with ankylosing spondylitis anti-adalimumab antibodies were identified in 17/204 subjects (8.3%) treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 16/185 (8.6%), compared to 1/19 (5.3%) when adalimumab was used as add-on to methotrexate.

In patients with Crohn's disease, anti-adalimumab antibodies were identified in 7/269 subjects (2.6%) and in 19/487 subjects (3.9%) with ulcerative colitis.

In adult patients with psoriasis, anti-adalimumab antibodies were identified in 77/920 subjects (8.4%) treated with adalimumab monotherapy.

In adult plaque psoriasis patients on long term adalimumab monotherapy who participated in a withdrawal and retreatment study, the rate of antibodies to adalimumab after retreatment (11 of 482 subjects, 2.3%) was similar to the rate observed prior to withdrawal (11 of 590 subjects, 1.9%).

In patients with paediatric psoriasis, anti-adalimumab antibodies were identified in 5/38 subjects (13%) treated with 0.8 mg/kg adalimumab monotherapy.

In patients with moderate to severe hidradenitis suppurativa, anti-adalimumab antibodies were identified in 10/99 subjects (10.1%) treated with adalimumab.

In patients with moderately to severely active paediatric Crohn's disease, the rate of anti-adalimumab antibody development in patients receiving adalimumab was 3.3%.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab.

Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of the studies with Humira in one or more subsets of the paediatric population in ulcerative colitis, see section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption and distribution

After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. After single intravenous doses ranging from 0.25 to 10 mg/kg, concentrations were dose proportional. After doses of 0.5 mg/kg (~40 mg), clearances ranged from 11 to 15 ml/hour, the distribution volume (V_{ss}) ranged from 5 to 6 litres and the mean terminal phase half-life was approximately two weeks. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31-96% of those in serum.

Following subcutaneous administration of 40 mg of adalimumab every other week in adult rheumatoid arthritis (RA) patients the mean steady-state trough concentrations were approximately

5 μg/ml (without concomitant methotrexate) and 8 to 9 μg/ml (with concomitant methotrexate), respectively. The serum adalimumab trough levels at steady-state increased roughly proportionally with dose following 20, 40 and 80 mg subcutaneous dosing every other week and every week.

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with polyarticular juvenile idiopathic arthritis (JIA) who were 4 to 17 years the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5.6 ± 5.6 μg/ml (102% CV) for adalimumab without concomitant methotrexate and 10.9 ± 5.2 μg/ml (47.7% CV) with concomitant methotrexate.

In patients with polyarticular JIA who were 2 to <4 years old or aged 4 and above weighing <15 kg dosed with adalimumab 24 mg/m^2 , the mean trough steady-state serum adalimumab concentrations was 6.0 ± 6.1 μg/ml (101% CV) for adalimumab without concomitant methotrexate and 7.9 ± 5.6 μg/ml (71.2% CV) with concomitant methotrexate.

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with enthesitis-related arthritis who were 6 to 17 years, the mean trough steady-state (values measured at Week 24) serum adalimumab concentrations were 8.8 ± 6.6 μg/ml for adalimumab without concomitant methotrexate and 11.8 ± 4.3 μg/ml with concomitant methotrexate.

In adult patients with psoriasis, the mean steady-state trough concentration was 5 μg/ml during adalimumab 40 mg every other week monotherapy treatment.

Following the administration of 0.8 mg/kg (up to a maximum of 40 mg) subcutaneously every other week to paediatric patients with chronic plaque psoriasis, the mean ± SD steady-state adalimumab trough concentration was approximately 7.4 ± 5.8 μg/ml (79% CV).

In adult patients with hidradenitis suppurativa, a dose of 160 mg Humira on Week 0 followed by 80 mg on Week 2 achieved serum adalimumab trough concentrations of approximately 7 to 8 μg/ml at Week 2 and Week 4. The mean steady-state trough concentration at Week 12 through Week 36 were approximately 8 to 10 μg/ml during adalimumab 40 mg every week treatment.

Adalimumab exposure in adolescent HS patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent HS dosing schedule is 40 mg every other week. Since exposure to adalimumab can be affected by body size, adolescents with higher body weight and inadequate response may benefit from receiving the recommended adult dose of 40 mg every week.

In patients with Crohn's disease, the loading dose of 80 mg Humira on Week 0 followed by 40 mg Humira on Week 2 achieves serum adalimumab trough concentrations of approximately 5.5 μg/ml during the induction period. A loading dose of 160 mg Humira on Week 0 followed by 80 mg Humira on Week 2 achieves serum adalimumab trough concentrations of approximately 12 μg/ml during the induction period. Mean steady-state trough levels of approximately 7 μg/ml were observed in Crohn's disease patients who received a maintenance dose of 40 mg Humira every other week.

In paediatric patients with moderate to severe CD, the open-label adalimumab induction dose was 160/80 mg or 80/40 mg at Weeks 0 and 2, respectively, dependent on a body weight cut-off of 40 kg. At Week 4, patients were randomised 1:1 to either the Standard Dose (40/20 mg eow) or Low Dose (20/10 mg eow) maintenance treatment groups based on their body weight. The mean (±SD) serum adalimumab trough concentrations achieved at Week 4 were 15.7±6.6 μg/ml for patients ≥ 40 kg (160/80 mg) and 10.6±6.1 μg/ml for patients < 40 kg (80/40 mg).

For patients who stayed on their randomised therapy, the mean (±SD) adalimumab trough concentrations at Week 52 were 9.5±5.6μg/ml for the Standard Dose group and 3.5±2.2 μg/ml for the

Low Dose group. The mean trough concentrations were maintained in patients who continued to receive adalimumab treatment eow for 52 weeks. For patients who dose escalated from eow to weekly regimen, the mean (±SD) serum concentrations of adalimumab at Week 52 were 15.3±11.4 μg/ml (40/20 mg, weekly) and 6.7±3.5 μg/ml (20/10 mg, weekly).

In patients with ulcerative colitis, a loading dose of 160 mg Humira on Week 0 followed by 80 mg Humira on Week 2 achieves serum adalimumab trough concentrations of approximately 12 μg/ml during the induction period. Mean steady-state trough levels of approximately 8 μg/ml were observed in ulcerative colitis patients who received a maintenance dose of 40 mg Humira every other week.

In patients with uveitis, a loading dose of 80 mg adalimumab on Week 0 followed by 40 mg adalimumab every other week starting at Week 1, resulted in mean steady-state concentrations of approximately 8 to 10 μg/mL.

Adalimumab exposure in paediatric uveitis patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). No clinical exposure data are available on the use of a loading dose in children < 6 years. The predicted exposures indicate that in the absence of methotrexate, a loading dose may lead to an initial increase in systemic exposure.

Elimination

Population pharmacokinetic analyses with data from over 1,300 RA patients revealed a trend toward higher apparent clearance of adalimumab with increasing body weight. After adjustment for weight differences, gender and age appeared to have a minimal effect on adalimumab clearance. The serum levels of free adalimumab (not bound to anti-adalimumab antibodies, AAA) were observed to be lower in patients with measurable AAA.

Hepatic or renal impairment

Humira has not been studied in patients with hepatic or renal impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity.

An embryo-foetal developmental toxicity/perinatal developmental study has been performed in cynomologous monkeys at 0, 30 and 100 mg/kg (9-17 monkeys/group) and has revealed no evidence of harm to the foetuses due to adalimumab. Neither carcinogenicity studies, nor a standard assessment of fertility and postnatal toxicity, were performed with adalimumab due to the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and to the development of neutralising antibodies in rodents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Citric acid monohydrate
Sodium citrate
Sodium dihydrogen phosphate dihydrate
Disodium phosphate dihydrate
Sodium chloride

Polysorbate 80
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the pre-filled syringe or pre-filled pen in its outer carton in order to protect from light.

A single Humira pre-filled syringe or pre-filled pen may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. The syringe or pen must be protected from light, and discarded if not used within the 14-day period.

6.5 Nature and contents of container

Humira 40 mg solution for injection in pre-filled syringe
Humira 40 mg solution for injection in single-use pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

Packs of:
- 1 pre-filled syringe (0.8 ml sterile solution) with 1 alcohol pad in a blister.
- 2 pre-filled syringes (0.8 ml sterile solution), each with 1 alcohol pad, in a blister.
- 4 pre-filled syringes (0.8 ml sterile solution), each with 1 alcohol pad, in a blister.
- 6 pre-filled syringes (0.8 ml sterile solution), each with 1 alcohol pad, in a blister.

Humira 40 mg solution for injection in pre-filled syringe with needleguard
Humira 40 mg solution for injection in single-use pre-filled syringe (type I glass) with needleguard for hospital and caregiver use. The syringe is made from type 1 glass with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

Packs of:
1 pre-filled syringe with needleguard (0.8 ml sterile solution) in a blister, and 1 alcohol pad.

Humira 40 mg solution for injection in pre-filled pen
Humira 40 mg solution for injection in single-use pre-filled pen for patient use containing a pre-filled syringe. The syringe inside the pen is made from type 1 glass with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

Packs of:
- 1 pre-filled pen (0.8 ml sterile solution), with 2 alcohol pads in a blister.
- 2 pre-filled pens (0.8 ml sterile solution), each with 1 alcohol pad, in a blister.
- 4 pre-filled pens (0.8 ml sterile solution), each with 1 alcohol pad, in a blister.
- 6 pre-filled pens (0.8 ml sterile solution), each with 1 alcohol pad, in a blister.

Not all presentations or pack sizes may be marketed.

6.6 Special precautions for disposal

Humira does not contain preservatives. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

Humira 40 mg solution for injection in pre-filled syringe
EU/1/03/256/002
EU/1/03/256/003
EU/1/03/256/004
EU/1/03/256/005

Humira 40 mg solution for injection in pre-filled syringe with needleguard
EU/1/03/256/006

Humira 40 mg solution for injection in pre-filled pen
EU/1/03/256/007
EU/1/03/256/008
EU/1/03/256/009
EU/1/03/256/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 September 2003
Date of latest renewal: 08 September 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe
Humira 40 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Humira 40 mg solution for injection in pre-filled syringe
Each 0.4 ml single dose pre-filled syringe contains 40 mg of adalimumab.

Humira 40 mg solution for injection in pre-filled pen
Each 0.4 ml single dose pre-filled pen contains 40 mg of adalimumab.

Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Humira in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Humira has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Humira in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is

inappropriate (for the efficacy in monotherapy see section 5.1). Humira has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Humira is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Humira is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS

Humira is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Psoriatic arthritis

Humira is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Humira has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see Section 5.1) and to improve physical function.

Psoriasis

Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis

Humira is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Crohn’s disease

Humira is indicated for treatment of moderately to severely active Crohn’s disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Humira is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

Humira is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Uveitis

Humira is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Paediatric Uveitis

Humira is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

4.2 Posology and method of administration

Humira treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which Humira is indicated. Ophthalmologists are advised to consult with an appropriate specialist before initiation of treatment with Humira (see section 4.4). Patients treated with Humira should be given the special alert card.

After proper training in injection technique, patients may self-inject with Humira if their physician determines that it is appropriate and with medical follow-up as necessary.

During treatment with Humira, other concomitant therapies (e.g., corticosteroids and/or immunomodulatory agents) should be optimised.

Posology

Rheumatoid arthritis

The recommended dose of Humira for adult patients with rheumatoid arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Methotrexate should be continued during treatment with Humira.

Glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics can be continued during treatment with Humira. Regarding combination with disease modifying anti-rheumatic drugs other than methotrexate see sections 4.4 and 5.1.

In monotherapy, some patients who experience a decrease in their response may benefit from an increase in dose intensity to 40 mg adalimumab every week.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period.

Dose interruption

There may be a need for dose interruption, for instance before surgery or if a serious infection occurs.

Available data suggest that re-introduction of Humira after discontinuation for 70 days or longer resulted in the same magnitudes of clinical response and similar safety profile as before dose interruption.

Ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS and psoriatic arthritis

The recommended dose of Humira for patients with ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS and for patients with psoriatic arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period.

Psoriasis

The recommended dose of Humira for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose.

Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.

Beyond 16 weeks, patients with inadequate response may benefit from an increase in dosing frequency to 40 mg every week. The benefits and risks of continued weekly Humira therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosing frequency (see section 5.1). If adequate response is achieved with an increased dosing frequency, the dose may subsequently be reduced to 40 mg every other week.

Hidradenitis suppurativa

The recommended Humira dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later at Day 15 (given as two 40 mg injections in one day). Two weeks later (Day 29) continue with a dose of 40 mg every week. Antibiotics may be continued during treatment with Humira if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Humira.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

Should treatment be interrupted, Humira 40 mg every week may be re-introduced (see section 5.1).

The benefit and risk of continued long-term treatment should be periodically evaluated (see section 5.1).

Crohn's disease

The recommended Humira induction dose regimen for adult patients with moderately to severely active Crohn's disease is 80 mg at Week 0 followed by 40 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), 80 mg at Week 2, can be used with the awareness that the risk for adverse events is higher during induction.

After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Alternatively, if a patient has stopped Humira and signs and symptoms of disease recur, Humira may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg Humira every week.

Some patients who have not responded by Week 4 may benefit from continued maintenance therapy through Week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Ulcerative colitis

The recommended Humira induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days) and 80 mg at Week 2. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg Humira every week.

Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment. Humira therapy should not be continued in patients failing to respond within this time period.

Uveitis

The recommended dose of Humira for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. There is limited experience in the initiation of treatment with Humira alone. Treatment with Humira can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with Humira.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis (see section 5.1).

Elderly

No dose adjustment is required.

Renal and/or hepatic impairment

Humira has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis from 2 to 12 years of age

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 2 - 12 years, is 24 mg/m² body surface area up to a maximum single dose of 20 mg adalimumab (for patients aged 2 - < 4) and up to a maximum single dose of 40 mg adalimumab (for patients aged 4-12) administered every other week via subcutaneous injection. The volume for injection is selected based on the patients' height and weight. A 40 mg/0.8 ml paediatric vial is available for patients who need to administer less than the full 40 mg dose. For paediatric dosing information for patients aged 2-12 years, see Summary of Product Characteristics for Humira 40 mg/0.8 ml solution for injection for paediatric use.

Polyarticular juvenile idiopathic arthritis from 13 years of age

For patients from 13 years of age, a dose of 40 mg is administered every other week regardless of body surface area.

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

There is no relevant use of Humira in patients aged < 2 years for this indication.

Enthesitis-related arthritis

The recommended dose of Humira for patients with enthesitis-related arthritis 6 years of age and older is 24 mg/m² body surface area up to a maximum single dose of 40 mg adalimumab administered every other week via subcutaneous injection. The volume for injection is selected based on the patients' height and weight. A 40 mg/0.8 ml paediatric vial is available for patients who need to administer less than the full 40 mg dose. For paediatric dosing information, see Summary of Product Characteristics for Humira 40 mg/0.8 ml solution for injection for paediatric use.

Humira has not been studied in patients with enthesitis-related arthritis aged less than 6 years.

Paediatric plaque psoriasis

The recommended Humira dose is 0.8 mg per kg body weight (up to a maximum of 40 mg per dose) administered subcutaneously weekly for the first two doses and every other week thereafter. Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.

If retreatment with Humira is indicated, the above guidance on dose and treatment duration should be followed.

The safety of Humira in paediatric patients with plaque psoriasis has been assessed for a mean of 13 months.

There is no relevant use of Humira in children aged less than 4 years for this indication.

The volume for injection is selected based on the patients' weight. A 40 mg/0.8 ml paediatric vial is available for patients who need to administer less than the full 40 mg dose. For paediatric dosing information, see Summary of Product Characteristics for Humira 40 mg/0.8 ml solution for injection for paediatric use.

Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)

There are no clinical trials with Humira in adolescent patients with HS. The posology of Humira in these patients has been determined from pharmacokinetic modelling and simulation (see section 5.2).

The recommended Humira dose is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via subcutaneous injection.

In adolescent patients with inadequate response to Humira 40 mg every other week, an increase in dosing frequency to 40 mg every week may be considered.

Antibiotics may be continued during treatment with Humira if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Humira.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

Should treatment be interrupted, Humira may be re-introduced as appropriate.

The benefit and risk of continued long-term treatment should be periodically evaluated (see adult data in section 5.1)

There is no relevant use of Humira in children aged less than 12 years in this indication.

Paediatric Crohn's disease

Paediatric Crohn's disease patients < 40 kg:

The recommended Humira induction dose regimen for paediatric subjects with moderately to severely active Crohn's disease is 40 mg at Week 0 followed by 20 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 80 mg at Week 0 (dose can be administered as two injections in one day), 40 mg at Week 2 can be used, with the awareness that the risk for adverse events may be higher with use of the higher induction dose.

After induction treatment, the recommended dose is 20 mg every other week via subcutaneous injection. Some subjects who experience insufficient response may benefit from an increase in dosing frequency to 20 mg Humira every week.

Paediatric Crohn's disease patients ≥ 40 kg:

The recommended Humira induction dose regimen for paediatric subjects with moderately to severely active Crohn's disease is 80 mg at Week 0 followed by 40 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), 80 mg at Week 2 can be used, with the awareness that the risk for adverse events may be higher with use of the higher induction dose.

After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Some subjects who experience insufficient response may benefit from an increase in dosing frequency to 40 mg Humira every week.

Continued therapy should be carefully considered in a subject not responding by Week 12.

There is no relevant use of Humira in children aged below 6 years for this indication.

Paediatric Uveitis

In paediatric uveitis, there is no experience in the treatment with Humira without concomitant treatment with methotrexate.

Paediatric uveitis patients < 30 kg:

The recommended dose of Humira is 20 mg every other week in combination with methotrexate.

When Humira therapy is initiated, a loading dose of 40 mg may be administered one week prior to the start of maintenance therapy. No clinical data are available on the use of a Humira loading dose in children < 6 years of age (see section 5.2).

Paediatric uveitis patients ≥ 30 kg:

The recommended dose of Humira is 40 mg every other week in combination with methotrexate.

When Humira therapy is initiated, a loading dose of 80 mg may be administered one week prior to the start of maintenance therapy.

There is no relevant use of Humira in children aged less than 2 years in this indication.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis (see section 5.1).

Paediatric ulcerative colitis

The safety and efficacy of Humira in children aged 4-17 years have not yet been established. No data are available. There is no relevant use of Humira in children aged < 4 years for this indication.

Psoriatic arthritis and axial spondyloarthritis including ankylosing spondylitis

There is no relevant use of Humira in the paediatric population for the indications of ankylosing spondylitis and psoriatic arthritis.

Method of administration

Humira is administered by subcutaneous injection. Full instructions for use are provided in the package leaflet.

A 40 mg paediatric vial is available for patients who need to administer less than the full 40 mg dose.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active tuberculosis or other severe infections such as sepsis, and opportunistic infections (see section 4.4).

Moderate to severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections

Patients taking TNF-antagonists are more susceptible to serious infections. Impaired lung function may increase the risk for developing infections. Patients must therefore be monitored closely for infections, including tuberculosis, before, during and after treatment with Humira. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period.

Treatment with Humira should not be initiated in patients with active infections including chronic or localised infections until infections are controlled. In patients who have been exposed to tuberculosis and patients who have travelled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with Humira should be considered prior to initiating therapy (see *Other opportunistic infections*).

Patients who develop a new infection while undergoing treatment with Humira, should be monitored closely and undergo a complete diagnostic evaluation. Administration of Humira should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of Humira in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications.

Serious infections

Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis have been reported in patients receiving Humira.

Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia. Hospitalisation or fatal outcomes associated with infections have been reported.

Tuberculosis

Tuberculosis, including reactivation and new onset of tuberculosis, has been reported in patients receiving Humira. Reports included cases of pulmonary and extra-pulmonary (i.e. disseminated) tuberculosis.

Before initiation of therapy with Humira, all patients must be evaluated for both active or inactive ("latent") tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients (local recommendations may apply). It is recommended that the conduct and results of these tests are recorded in the patient alert card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Humira therapy must not be initiated (see section 4.3).

In all situations described below, the benefit/risk balance of therapy should be very carefully considered.

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted.

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylaxis treatment before the initiation of Humira, and in accordance with local recommendations.

Use of anti-tuberculosis prophylaxis treatment should also be considered before the initiation of Humira in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with Humira. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with Humira.

Patients should be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (e.g., persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with Humira.

Other opportunistic infections

Opportunistic infections, including invasive fungal infections have been observed in patients receiving Humira. These infections have not consistently been recognised in patients taking TNF-antagonists and this has resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.

For patients who develop the signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock an invasive fungal infection should be suspected and administration of Humira should be promptly discontinued. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections.

Hepatitis B reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including Humira, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had a fatal outcome. Patients should be tested for HBV infection before initiating treatment with Humira. For patients who test positive for hepatitis B infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Carriers of HBV who require treatment with Humira should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data from treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, Humira should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurological events

TNF-antagonists including Humira have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of Humira in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of Humira should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate

uveitis prior to the initiation of Humira therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Allergic reactions

Serious allergic reactions associated with Humira were rare during clinical trials. Non-serious allergic reactions associated with Humira were uncommon during clinical trials. Reports of serious allergic reactions including anaphylaxis have been received following Humira administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Humira should be discontinued immediately and appropriate therapy initiated.

Immunosuppression

In a study of 64 patients with rheumatoid arthritis that were treated with Humira, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T-, B, - NK-cells, monocyte/macrophages, and neutrophils.

Malignancies and lymphoproliferative disorders

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare. In the post marketing setting, cases of leukaemia have been reported in patients treated with a TNF-antagonist. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. With the current knowledge, a possible risk for the development of lymphomas, leukaemia, and other malignancies in patients treated with a TNF-antagonist cannot be excluded.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including adalimumab in the post marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Rare postmarketing cases of hepatosplenic T-cell lymphoma have been identified in patients treated with adalimumab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Some of these hepatosplenic T-cell lymphomas with Humira have occurred in young adult patients on concomitant treatment with azathioprine or 6-mercaptopurine used for inflammatory bowel disease. The potential risk with the combination of azathioprine or 6-mercaptopurine and Humira should be carefully considered. A risk for the development of hepatosplenic T-cell lymphoma in patients treated with Humira cannot be excluded (see section 4.8).

No studies have been conducted that include patients with a history of malignancy or in whom treatment with Humira is continued following development of malignancy. Thus additional caution should be exercised in considering Humira treatment of these patients (see section 4.8).

All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with Humira. Melanoma and Merkel cell carcinoma have also been reported in patients treated with TNF-antagonists including adalimumab (see section 4.8).

In an exploratory clinical trial evaluating the use of another TNF-antagonist, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control

patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking.

With current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.

Haematologic reactions

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF-antagonists. Adverse events of the haematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been reported with Humira. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor) while on Humira. Discontinuation of Humira therapy should be considered in patients with confirmed significant haematologic abnormalities.

Vaccinations

Similar antibody responses to the standard 23-valent pneumococcal vaccine and the influenza trivalent virus vaccination were observed in a study in 226 adult subjects with rheumatoid arthritis who were treated with adalimumab or placebo. No data are available on the secondary transmission of infection by live vaccines in patients receiving Humira.

It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy.

Patients on Humira may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother’s last adalimumab injection during pregnancy.

Congestive heart failure

In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving Humira. Humira should be used with caution in patients with mild heart failure (NYHA class I/II). Humira is contraindicated in moderate to severe heart failure (see section 4.3). Treatment with Humira must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes

Treatment with Humira may result in the formation of autoimmune antibodies. The impact of long-term treatment with Humira on the development of autoimmune diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Humira and is positive for antibodies against double-stranded DNA, further treatment with Humira should not be given (see section 4.8).

Concurrent administration of biologic DMARDS or TNF-antagonists

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-antagonist, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar

toxicities may also result from the combination of anakinra and other TNF-antagonists. Therefore, the combination of adalimumab and anakinra is not recommended. (See section 4.5).

Concomitant administration of adalimumab with other biologic DMARDS (e.g, anakinra and abatacept) or other TNF-antagonists is not recommended based upon the possible increased risk for infections, including serious infections and other potential pharmacological interactions. (See section 4.5).

Surgery

There is limited safety experience of surgical procedures in patients treated with Humira. The long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Humira should be closely monitored for infections, and appropriate actions should be taken. There is limited safety experience in patients undergoing arthroplasty while receiving Humira.

Small bowel obstruction

Failure to respond to treatment for Crohn's disease may indicate the presence of fixed fibrotic stricture that may require surgical treatment. Available data suggest that Humira does not worsen or cause strictures.

Elderly

The frequency of serious infections among Humira treated subjects over 65 years of age (3.7%) was higher than for those under 65 years of age (1.5%). Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly.

Paediatric population

See Vaccinations above.

4.5 Interaction with other medicinal products and other forms of interaction

Humira has been studied in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis patients taking Humira as monotherapy and those taking concomitant methotrexate. Antibody formation was lower when Humira was given together with methotrexate in comparison with use as monotherapy. Administration of Humira without methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab (see section 5.1).

The combination of Humira and anakinra is not recommended (see section 4.4 "Concurrent administration of biologic DMARDS or TNF-antagonists").

The combination of Humira and abatacept is not recommended (see section 4.4 "Concurrent administration of biologic DMARDS or TNF-antagonists").

4.6 Fertility, pregnancy and lactation

Women of child bearing potential/Contraception in males and females

Women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and continue its use for at least five months after the last Humira treatment.

Pregnancy

For Humira, limited clinical data on exposed pregnancies are available

In a developmental toxicity study conducted in monkeys, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. Preclinical data on postnatal toxicity of adalimumab are not available (see section 5.3).

Due to its inhibition of TNFα, adalimumab administered during pregnancy could affect normal immune responses in the newborn. Administration of adalimumab is not recommended during pregnancy.

Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Breast feeding

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion.

However, because human immunoglobulins are excreted in milk, women must not breast-feed for at least five months after the last Humira treatment.

Fertility

Preclinical data on fertility effects of adalimumab are not available.

4.7 Effects on ability to drive and use machines

Humira may have a minor influence on the ability to drive and use machines. Vertigo and visual impairment may occur following administration of Humira (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Humira was studied in 9,506 patients in pivotal controlled and open label trials for up to 60 months or more. These trials included rheumatoid arthritis patients with short term and long standing disease, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis) as well as axial spondyloarthritis (ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients. The pivotal controlled studies involved 6,089 patients receiving Humira and 3,801 patients receiving placebo or active comparator during the controlled period.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of pivotal studies was 5.9% for patients taking Humira and 5.4% for control treated patients.

The most commonly reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain.

Serious adverse reactions have been reported for Humira. TNF-antagonists, such as Humira affect the immune system and their use may affect the body's defence against infection and cancer.

Fatal and life-threatening infections (including sepsis, opportunistic infections and TB), HBV reactivation and various malignancies (including leukaemia, lymphoma and HSTCL) have also been reported with use of Humira.

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia, aplastic anaemia, central and peripheral demyelinating events and reports of lupus, lupus-related conditions and Stevens-Johnson syndrome.

Paediatric population

Undesirable effects in paediatric patients

In general, the adverse events in paediatric patients were similar in frequency and type to those seen in adult patients.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience and are displayed by system organ class and frequency in Table 1 below: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The highest frequency seen among the various indications has been included. An asterisk (*) appears in the SOC column if further information is found elsewhere in sections 4.3, 4.4 and 4.8.

Table 1
Undesirable Effects

System Organ Class	Frequency	Adverse Reaction
Infections and infestations*	Very common	respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections, joint infections
	Uncommon	neurological infections (including viral meningitis),

System Organ Class	Frequency	Adverse Reaction
		opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), bacterial infections, eye infections, diverticulitis[1)]
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Common	skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma), benign neoplasm
	Uncommon	lymphoma**, solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma**
	Rare	leukaemia[1)]
	Not known	hepatosplenic T-cell lymphoma[1)] Merkel cell carcinoma (neuroendocrine carcinoma of the skin)[1)]
Blood and the lymphatic system disorders*	Very common	leukopenia (including neutropenia and agranulocytosis), anaemia
	Common	leucocytosis, thrombocytopenia
	Uncommon	idiopathic thrombocytopenic purpura
	Rare	pancytopenia
Immune system disorders*	Common	hypersensitivity, allergies (including seasonal allergy)
	Uncommon	sarcoidosis[1)], vasculitis
	Rare	anaphylaxis[1)]
Metabolism and nutrition disorders	Very common	lipids increased

System Organ Class	Frequency	Adverse Reaction
	Common	hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia, hyperglycaemia, hypophosphatemia, dehydration
Psychiatric disorders	Common	mood alterations (including depression), anxiety, insomnia
Nervous system disorders*	Very common	headache
	Common	paraesthesias (including hypoesthesia), migraine, nerve root compression
	Uncommon	cerebrovascular accident[1)], tremor, neuropathy
	Rare	multiple sclerosis, demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome) [1)]
Eye disorders	Common	visual impairment, conjunctivitis, blepharitis, eye swelling
	Uncommon	diplopia
Ear and labyrinth disorders	Common	vertigo
	Uncommon	deafness, tinnitus
Cardiac disorders*	Common	tachycardia
	Uncommon	myocardial infarction[1)], arrhythmia, congestive heart failure
	Rare	cardiac arrest

System Organ Class	Frequency	Adverse Reaction
Vascular disorders	Common	hypertension, flushing, haematoma
	Uncommon	aortic aneurysm, vascular arterial occlusion, thrombophlebitis
Respiratory, thoracic and mediastinal disorders*	Common	asthma, dyspnoea, cough
	Uncommon	pulmonary embolism[1)], interstitial lung disease, chronic obstructive pulmonary disease, pneumonitis, pleural effusion[1)]
	Rare	pulmonary fibrosis[1)]
Gastrointestinal disorders	Very common	abdominal pain, nausea and vomiting
	Common	GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	pancreatitis, dysphagia, face oedema
	Rare	intestinal perforation[1)]
Hepato-biliary disorders*	Very Common	elevated liver enzymes
	Uncommon	cholecystitis and cholelithiasis, hepatic steatosis, bilirubin increased
	Rare	hepatitis reactivation of hepatitis B[1)] autoimmune hepatitis[1)]
	Not known	liver failure[1)]
Skin and subcutaneous	Very Common	rash (including exfoliative rash)

System Organ Class	Frequency	Adverse Reaction
tissue disorders	Common	worsening or new onset of psoriasis(including palmoplantar pustular psoriasis)[1)], urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis, hyperhidrosis, alopecia[1)], pruritus
	Uncommon	night sweats, scar
	Rare	erythema multiforme[1)], Stevens-Johnson syndrome[1)], angioedema[1)], cutaneous vasculitis[1)]
	Not known	worsening of symptoms of dermatomyositis[1)]
Musculoskeletal and connective tissue disorders	Very common	musculoskeletal pain
	Common	muscle spasms (including blood creatine phosphokinase increased)
	Uncommon	rhabdomyolysis, systemic lupus erythematosus
	Rare	lupus-like syndrome[1)]
Renal and urinary disorders	Common	renal impairment, haematuria
	Uncommon	nocturia
Reproductive system and breast disorders	Uncommon	erectile dysfunction
General disorders and administration site conditions*	Very Common	injection site reaction (including injection site erythema)
	Common	chest pain, oedema, pyrexia[1)]
	Uncommon	inflammation
Investigations*	Common	coagulation and bleeding disorders (including activated partial thromboplastin time prolonged),

System Organ Class	Frequency	Adverse Reaction
		autoantibody test positive (including double stranded DNA antibody), blood lactate dehydrogenase increased
Injury, poisoning and procedural complications	Common	impaired healing

* further information is found elsewhere in sections 4.3, 4.4 and 4.8
** including open label extension studies
[1)] including spontaneous reporting data

Hidradenitis suppurativa

The safety profile for patients with HS treated with Humira weekly was consistent with the known safety profile of Humira.

Uveitis

The safety profile for patients with uveitis treated with Humira every other week was consistent with the known safety profile of Humira.

Description of selected adverse reactions

Injection site reactions

In the pivotal controlled trials in adults and children, 12.9% of patients treated with Humira developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 7.2% of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Infections

In the pivotal controlled trials in adults and children, the rate of infection was 1.51 per patient year in the Humira treated patients and 1.46 per patient year in the placebo and active control-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, and sinusitis. Most patients continued on Humira after the infection resolved.

The incidence of serious infections was 0.04 per patient year in Humira treated patients and 0.03 per patient year in placebo and active control − treated patients.

In controlled and open label adult and paediatric studies with Humira, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extra-pulmonary locations) and invasive opportunistic infections (e.g. disseminated or extrapulmonary histoplasmosis, blastomycosis, coccidioidomycosis, pneumocystis, candidiasis, aspergillosis and listeriosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

Malignancies and lymphoproliferative disorders

No malignancies were observed in 249 paediatric patients with an exposure of 655.6 patient years during Humira trials in patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis). In addition, no malignancies were observed in 192 paediatric patients with an exposure of 498.1 patient years during Humira trials in paediatric patients with

Crohn's disease. No malignancies were observed in 77 paediatric patients with an exposure of 80.0 patient years during a Humira trial in paediatric patients with chronic plaque psoriasis. No malignancies were observed in 60 paediatric patients with an exposure of 58.4 patient years during a Humira trial in paediatric patients with uveitis.

During the controlled portions of pivotal Humira trials in adults of at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.8 (4.4, 10.5) per 1,000 patient-years among 5,291 Humira treated patients *versus* a rate of 6.3 (3.4, 11.8) per 1,000 patient-years among 3,444 control patients (median duration of treatment was 4.0 months for Humira and 3.8 months for control-treated patients). The rate (95% confidence interval) of non-melanoma skin cancers was 8.8 (6.0, 13.0) per 1,000 patient-years among Humira-treated patients and 3.2 (1.3, 7.6) per 1,000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) of 2.7 (1.4, 5.4) per 1,000 patient-years among Humira-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients. The rate (95% confidence interval) of lymphomas was 0.7 (0.2, 2.7) per 1,000 patient-years among Humira-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients.

When combining controlled portions of these trials and ongoing and completed open label extension studies with a median duration of approximately 3.3 years including 6,427 patients and over 26,439 patient-years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 8.5 per 1,000 patient years. The observed rate of non-melanoma skin cancers is approximately 9.6 per 1,000 patient years, and the observed rate of lymphomas is approximately 1.3 per 1,000 patient years.

In post-marketing experience from January 2003 to December 2010, predominantly in patients with rheumatoid arthritis, the reported rate of malignancies is approximately 2.7 per 1,000 patient treatment years. The reported rates for non-melanoma skin cancers and lymphomas are approximately 0.2 and 0.3 per 1,000 patient treatment years, respectively (see section 4.4).

Rare post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with adalimumab (see section 4.4).

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis studies I − V. In these trials, 11.9% of patients treated with Humira and 8.1% of placebo and active control − treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at Week 24. Two patients out of 3,441 treated with Humira in all rheumatoid arthritis and psoriatic arthritis studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms.

Hepato-biliary events

In controlled Phase 3 trials of Humira in patients with rheumatoid arthritis and psoriatic arthritis with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.7% of Humira-treated patients and 1.6% of control-treated patients.

In controlled Phase 3 trials of Humira in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations ≥ 3 x ULN occurred in 6.1% of Humira-treated patients and 1.3% of control-treated patients. Most ALT elevations occurred with concomitant methotrexate use. No ALT elevations ≥ 3 x ULN occurred in

the Phase 3 trial of Humira in patients with polyarticular juvenile idiopathic arthritis who were 2 to < 4 years.

In controlled Phase 3 trials of Humira in patients with Crohn's disease and ulcerative colitis with a control period ranging from 4 to 52 weeks. ALT elevations ≥ 3 x ULN occurred in 0.9% of Humira-treated patients and 0.9% of controlled-treated patients.

In the Phase 3 trial of Humira in patients with paediatric Crohn's disease which evaluated efficacy and safety of two body weight adjusted maintenance dose regimens following body weight adjusted induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients of whom 4 were receiving concomitant immunosuppressants at baseline.

In controlled Phase 3 trials of Humira in patients with plaque Psoriasis with a control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of Humira-treated patients and 1.8% of control-treated patients.

No ALT elevations ≥ 3 X ULN occurred in the Phase 3 trial of Humira in paediatric patients with plaque psoriasis.

In controlled trials of Humira (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in patients with hidradenitis suppurativa with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of Humira-treated patients and 0.6% of control-treated patients.

In controlled trials of Humira (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis up to 80 weeks with a median exposure of 166.5 days and 105.0 days in Humira-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of Humira-treated patients and 2.4% of control-treated patients.

Across all indications in clinical trials patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have also been post-marketing reports of liver failure as well as less severe liver disorders that may precede liver failure, such as hepatitis including autoimmune hepatitis in patients receiving adalimumab.

Concurrent treatment with azathioprine/6-mercaptopurine

In adult Crohn's disease studies, higher incidences of malignant and serious infection-related adverse events were seen with the combination of Humira and azathioprine/6-mercaptopurine compared with Humira alone.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No dose-limiting toxicity was observed during clinical trials. The highest dose level evaluated has been multiple intravenous doses of 10 mg/kg, which is approximately 15 times the recommended dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors.
ATC code: L04AB04

Mechanism of action

Adalimumab binds specifically to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of0.1-0.2 nM).

Pharmacodynamic effects

After treatment with Humira, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL-6) was observed, compared to baseline in patients with rheumatoid arthritis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after Humira administration. Patients treated with Humira usually experienced improvement in haematological signs of chronic inflammation.

A rapid decrease in CRP levels was also observed in patients with polyarticular juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis and hidradenitis suppurativa after treatment with Humira. In patients with Crohn's disease, a reduction of the number of cells expressing inflammatory markers in the colon including a significant reduction of expression of TNFα was seen. Endoscopic studies in intestinal mucosa have shown evidence of mucosal healing in adalimumab treated patients.

Clinical efficacy and safety

Rheumatoid arthritis

Humira was evaluated in over 3000 patients in all rheumatoid arthritis clinical trials. The efficacy and safety of Humira were assessed in five randomised, double-blind and well-controlled studies. Some patients were treated for up to 120 months duration. Injection site pain of Humira 40 mg/0.4 ml was assessed in two randomised, active control, single-blind, two-period crossover studies.

RA study I evaluated 271 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had failed therapy with at least one disease-modifying, anti rheumatic drug and had insufficient efficacy with methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 10 to 25 mg every week. Doses of 20, 40 or 80 mg of Humira or placebo were given every other week for 24 weeks.

RA study II evaluated 544 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old and had failed therapy with at least one disease-modifying, anti-rheumatic drugs. Doses of 20 or 40 mg of Humira were given by subcutaneous injection every other week with placebo on alternative weeks or every week for 26 weeks; placebo was given every week for the same duration. No other disease-modifying anti-rheumatic drugs were allowed.

RA study III evaluated 619 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, and who had an ineffective response to methotrexate at doses of 12.5 to 25 mg or have been intolerant to 10 mg of methotrexate every week. There were three groups in this study. The first received placebo injections every week for 52 weeks. The second received 20 mg of Humira every week for 52 weeks. The third group received 40 mg of Humira every other week with placebo injections on alternate weeks. Upon completion of the first 52 weeks, 457 patients enrolled in an

open-label extension phase in which 40 mg of Humira/MTX was administered every other week up to 10 years.

RA study IV primarily assessed safety in 636 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old. Patients were permitted to be either disease-modifying, anti-rheumatic drug-naïve or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. These therapies include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine and/or gold salts. Patients were randomised to 40 mg of Humira or placebo every other week for 24 weeks.

RA study V evaluated 799 methotrexate-naïve, adult patients with moderate to severely active early rheumatoid arthritis (mean disease duration less than 9 months). This study evaluated the efficacy of Humira 40 mg every other week/methotrexate combination therapy, Humira 40 mg every other week monotherapy and methotrexate monotherapy in reducing the signs and symptoms and rate of progression of joint damage in rheumatoid arthritis for 104 weeks. Upon completion of the first 104 weeks, 497 patients enrolled in an open-label extension phase in which 40 mg of Humira was administered every other week up to 10 years.

RA studies VI and VII each evaluated 60 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old. Enrolled patients were either current users of Humira 40 mg/0.8 ml and rated their average injection site pain as at least 3 cm (on a 0-10 cm VAS) or were biologic-naïve subjects who were starting Humira 40 mg/0.8 ml. Patients were randomised to receive a single dose of Humira 40 mg/0.8 ml or Humira 40 mg/0.4 ml, followed by a single injection of the opposite treatment at their next dose.

The primary end point in RA studies I, II and III and the secondary endpoint in RA study IV was the percent of patients who achieved an ACR 20 response at Week 24 or 26. The primary endpoint in RA study V was the percent of patients who achieved an ACR 50 response at Week 52. RA studies III and V had an additional primary endpoint at 52 weeks of retardation of disease progression (as detected by X-ray results). RA study III also had a primary endpoint of changes in quality of life. The primary endpoint in RA studies VI and VII was injection site pain immediately after injection as measured by a 0-10 cm VAS.

ACR response

The percent of Humira-treated patients achieving ACR 20, 50 and 70 responses was consistent across RA studies I, II and III. The results for the 40 mg every other week dose are summarised in Table 2.

Table 2
ACR Responses in Placebo-Controlled Trials
(Percent of Patients)

Response	RA Study I[a]**		RA Study II[a]**		RA Study III[a]**	
	Placebo/ MTX[c] n=60	Humira[b]/ MTX[c] n=63	Placebo n=110	Humira[b] n=113	Placebo/ MTX[c] n=200	Humira[b]/ MTX[c] n=207
ACR 20						
6 months	13.3%	65.1%	19.1%	46.0%	29.5%	63.3%
12 months	NA	NA	NA	NA	24.0%	58.9%
ACR 50						
6 months	6.7%	52.4%	8.2%	22.1%	9.5%	39.1%
12 months	NA	NA	NA	NA	9.5%	41.5%
ACR 70						
6 months	3.3%	23.8%	1.8%	12.4%	2.5%	20.8%
12 months	NA	NA	NA	NA	4.5%	23.2%

[a] RA study I at 24 weeks, RA study II at 26 weeks , and RA study III at 24 and 52 weeks
[b] 40 mg Humira administered every other week
[c] MTX = methotrexate
**p < 0.01, Humira *versus* placebo

In RA studies I-IV, all individual components of the ACR response criteria (number of tender and swollen joints, physician and patient assessment of disease activity and pain, disability index (HAQ) scores and CRP (mg/dl) values) improved at 24 or 26 weeks compared to placebo. In RA study III, these improvements were maintained throughout 52 weeks.

In the open-label extension for RA study III, most patients who were ACR responders maintained response when followed for up to 10 years. Of 207 patients who were randomised to Humira 40 mg every other week, 114 patients continued on Humira 40 mg every other week for 5 years. Among those, 86 patients (75.4%) had ACR 20 responses; 72 patients (63.2%) had ACR 50 responses; and 41 patients (36%) had ACR 70 responses. Of 207 patients, 81 patients continued on Humira 40 mg every other week for 10 years. Among those, 64 patients (79.0%) had ACR 20 responses; 56 patients (69.1%) had ACR 50 responses; and 43 patients (53.1%) had ACR 70 responses.

In RA study IV, the ACR 20 response of patients treated with Humira plus standard of care was statistically significantly better than patients treated with placebo plus standard of care ($p < 0.001$).

In RA studies I-IV, Humira-treated patients achieved statistically significant ACR 20 and 50 responses compared to placebo as early as one to two weeks after initiation of treatment.

In RA study V with early rheumatoid arthritis patients who were methotrexate naïve, combination therapy with Humira and methotrexate led to faster and significantly greater ACR responses than methotrexate monotherapy and Humira monotherapy at Week 52 and responses were sustained at Week 104 (see Table 3).

Table 3
ACR Responses in RA Study V
(percent of patients)

Response	MTX n=257	Humira n=274	Humira/MTX n=268	p-value[a]	p-value[b]	p-value[c]
ACR 20						
Week 52	62.6%	54.4%	72.8%	0.013	< 0.001	0.043
Week 104	56.0%	49.3%	69.4%	0.002	< 0.001	0.140
ACR 50						
Week 52	45.9%	41.2%	61.6%	< 0.001	< 0.001	0.317
Week 104	42.8%	36.9%	59.0%	< 0.001	< 0.001	0.162
ACR 70						
Week 52	27.2%	25.9%	45.5%	< 0.001	< 0.001	0.656
Week 104	28.4%	28.1%	46.6%	< 0.001	< 0.001	0.864

a. p-value is from the pairwise comparison of methotrexate monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test.
b. p-value is from the pairwise comparison of Humira monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test
c. p-value is from the pairwise comparison of Humira monotherapy and methotrexate monotherapy using the Mann-Whitney U test

In the open-label extension for RA study V, ACR response rates were maintained when followed for up to 10 years. Of 542 patients who were randomised to Humira 40 mg every other week, 170 patients continued on Humira 40 mg every other week for 10 years. Among those, 154 patients (90.6%) had ACR 20 responses; 127 patients (74.7%) had ACR 50 responses; and 102 patients (60.0%) had ACR 70 responses.

At Week 52, 42.9% of patients who received Humira/methotrexate combination therapy achieved clinical remission (DAS28 (CRP) < 2.6) compared to 20.6% of patients receiving methotrexate monotherapy and 23.4% of patients receiving Humira monotherapy. Humira/methotrexate combination therapy was clinically and statistically superior to methotrexate ($p < 0.001$) and Humira monotherapy ($p < 0.001$) in achieving a low disease state in patients with recently diagnosed moderate to severe rheumatoid arthritis. The response for the two monotherapy arms was similar ($p = 0.447$). Of 342 subjects originally randomized to Humira monotherapy or Humira/methotrexate combination therapy who entered the open-label extension study, 171 subjects completed 10 years of Humira treatment. Among those, 109 subjects (63.7%) were reported to be in remission at 10 years.

Radiographic response

In RA study III, where Humira treated patients had a mean duration of rheumatoid arthritis of approximately 11 years, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score. Humira/methotrexate patients demonstrated significantly less radiographic progression than patients receiving methotrexate alone at 6 and 12 months (see Table 4).

In the open-label extension of RA Study III, the reduction in rate of progression of structural damage is maintained for 8 and 10 years in a subset of patients. At 8 years, 81 of 207 patients originally

treated with 40 mg Humira every other week were evaluated radiographically. Among those, 48 patients showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less. At 10 years, 79 of 207 patients originally treated with 40 mg Humira every other week were evaluated radiographically. Among those, 40 patients showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less.

Table 4
Radiographic Mean Changes Over 12 Months in RA Study III

	Placebo/ MTX[a]	Humira/MTX 40 mg every other week	Placebo/MTX-Humira/MTX (95% Confidence Interval[b])	p-value
Total Sharp Score	2.7	0.1	2.6 (1.4, 3.8)	< 0.001[c]
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	< 0.001
JSN[d] score	1.0	0.1	0.9 (0.3, 1.4)	0.002

[a]methotrexate
[b]95% confidence intervals for the differences in change scores between methotrexate and Humira.
[c]Based on rank analysis
[d]Joint Space Narrowing

In RA study V, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (see Table 5).

Table 5
Radiographic Mean Changes at Week 52 in RA Study V

	MTX n=257 (95% confidence interval)	Humira n=274 (95% confidence interval)	Humira/MTX n=268 (95% confidence interval)	p-value[a]	p-value[b]	p-value[c]
Total Sharp Score	5.7 (4.2-7.3)	3.0 (1.7-4.3)	1.3 (0.5-2.1)	< 0.001	0.0020	< 0.001
Erosion score	3.7 (2.7-4.7)	1.7 (1.0-2.4)	0.8 (0.4-1.2)	< 0.001	0.0082	< 0.001
JSN score	2.0 (1.2-2.8)	1.3 (0.5-2.1)	0.5 (0-1.0)	< 0.001	0.0037	0.151

[a] p-value is from the pairwise comparison of methotrexate monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test.
[b] p-value is from the pairwise comparison of Humira monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test
[c] p-value is from the pairwise comparison of Humira monotherapy and methotrexate monotherapy using the Mann-Whitney U test

Following 52 weeks and 104 weeks of treatment, the percentage of patients without progression (change from baseline in modified Total Sharp Score ≤ 0.5) was significantly higher with Humira/methotrexate combination therapy (63.8% and 61.2% respectively) compared to methotrexate monotherapy (37.4% and 33.5% respectively, $p < 0.001$) and Humira monotherapy (50.7%, $p < 0.002$ and 44.5%, $p < 0.001$ respectively).

In the open-label extension of RA study V, the mean change from baseline at Year 10 in the modified Total Sharp Score was 10.8, 9.2 and 3.9 in patients originally randomized to methotrexate monotherapy, Humira monotherapy and Humira/methotrexate combination therapy, respectively. The corresponding proportions of patients with no radiographic progression were 31.3%, 23.7% and 36.7% respectively.

Quality of life and physical function

Health-related quality of life and physical function were assessed using the disability index of the Health Assessment Questionnaire (HAQ) in the four original adequate and well-controlled trials, which was a pre-specified primary endpoint at Week 52 in RA study III. All doses/schedules of Humira in all four studies showed statistically significantly greater improvement in the disability index of the HAQ from baseline to Month 6 compared to placebo and in RA study III the same was seen at Week 52. Results from the Short Form Health Survey (SF 36) for all doses/schedules of Humira in all four studies support these findings, with statistically significant physical component summary (PCS) scores, as well as statistically significant pain and vitality domain scores for the 40 mg every other week dose. A statistically significant decrease in fatigue as measured by functional assessment of chronic illness therapy (FACIT) scores was seen in all three studies in which it was assessed (RA studies I, III, IV).

In RA study III, most subjects who achieved improvement in physical function and continued treatment maintained improvement through Week 520 (120 months) of open-label treatment. Improvement in quality of life was measured up to Week 156 (36 months) and improvement was maintained through that time.

In RA study V, the improvement in the HAQ disability index and the physical component of the SF 36 showed greater improvement ($p < 0.001$) for Humira/methotrexate combination therapy *versus* methotrexate monotherapy and Humira monotherapy at Week 52, which was maintained through Week 104. Among the 250 subjects who completed the open-label extension study, improvements in physical function were maintained through 10 years of treatment.

Injection site pain

For the pooled crossover RA studies VI and VII, a statistically significant difference for injection site pain immediately after dosing was observed between Humira 40 mg/0.8 ml and Humira 40 mg/0.4 ml (mean VAS of 3.7 cm versus 1.2 cm, scale of 0-10 cm, $P < 0.001$). This represented an 84% median reduction in injection site pain.

Juvenile idiopathic arthritis (JIA)

Polyarticular juvenile idiopathic arthritis (pJIA)

The safety and efficacy of Humira was assessed in two studies (pJIA I and II) in children with active polyarticular or polyarticular course juvenile idiopathic arthritis, who had a variety of JIA onset types (most frequently rheumatoid-factor negative or positive polyarthritis and extended oligoarthritis).

pJIA I

The safety and efficacy of Humira were assessed in a multicentre, randomised, double-blind, parallel − group study in 171 children (4-17 years old) with polyarticular JIA. In the open-label lead in phase (OL LI) patients were stratified into two groups, MTX (methotrexate)-treated or non-MTX-treated. Patients who were in the non-MTX stratum were either naïve to or had been withdrawn from MTX at least two weeks prior to study drug administration. Patients remained on stable doses of NSAIDs and or prednisone (≤ 0.2 mg/kg/day or 10 mg/day maximum). In the OL LI phase all patients received 24 mg/m^2 up to a maximum of 40 mg Humira every other week for 16 weeks. The distribution of patients by age and minimum, median and maximum dose received during the OL LI phase is presented in Table 6.

Table 6
Distribution of patients by age and adalimumab dose received during the OL LI phase

Age Group	Number of patients at Baseline n (%)	Minimum, median and maximum dose
4 to 7 years	31 (18.1)	10, 20 and 25 mg
8 to 12 years	71 (41.5)	20, 25 and 40 mg
13 to 17 years	69 (40.4)	25, 40 and 40 mg

Patients demonstrating a Pediatric ACR 30 response at Week 16 were eligible to be randomised into the double blind (DB) phase and received either Humira 24 mg/m^2 up to a maximum of 40 mg, or placebo every other week for an additional 32 weeks or until disease flare. Disease flare criteria were defined as a worsening of ≥ 30% from baseline in ≥ 3 of 6 Pediatric ACR core criteria, ≥ 2 active joints, and improvement of > 30% in no more than 1 of the 6 criteria. After 32 weeks or at disease flare, patients were eligible to enrol into the open label extension phase.

Table 7
Ped ACR 30 Responses in the JIA study

Stratum	MTX		Without MTX	
Phase				
OL-LI 16 weeks				
Ped ACR 30 response (n/N)	94.1% (80/85)		74.4% (64/86)	
Efficacy Outcomes				
Double Blind 32 weeks	Humira /MTX (N = 38)	Placebo / MTX (N = 37)	Humira (N = 30)	Placebo (N = 28)
Disease flares at the end of 32 weeks[a] (n/N)	36.8% (14/38)	64.9% (24/37)[b]	43.3% (13/30)	71.4% (20/28)[c]
Median time to disease flare	>32 weeks	20 weeks	>32 weeks	14 weeks

[a] Ped ACR 30/50/70 responses Week 48 significantly greater than those of placebo treated patients
[b] p = 0.015
[c] p = 0.031

Amongst those who responded at Week 16 (n=144), the Pediatric ACR 30/50/70/90 responses were maintained for up to six years in the OLE phase in patients who received Humira throughout the study. Over all 19 subjects, of which 11 of the baseline age group 4 to 12 and 8 of the baseline age group 13 to 17 years were treated 6 years or longer.

Overall responses were generally better and, fewer patients developed antibodies when treated with the combination of Humira and MTX compared to Humira alone. Taking these results into consideration, Humira is recommended for use in combination with MTX and for use as monotherapy in patients for whom MTX use is not appropriate (see section 4.2).

pJIA II

The safety and efficacy of Humira was assessed in an open-label, multicentre study in 32 children (2 - < 4 years old or aged 4 and above weighing < 15 kg) with moderately to severely active polyarticular JIA. The patients received 24 mg/m^2 body surface area (BSA) of Humira up to a maximum of 20 mg every other week as a single dose via SC injection for at least 24 weeks. During the study, most subjects used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs.

At Week 12 and Week 24, PedACR30 response was 93.5% and 90.0%, respectively, using the observed data approach. The proportions of subjects with PedACR50/70/90 at Week 12 and Week 24 were 90.3%/61.3%/38.7% and 83.3%/73.3%/36.7%, respectively. Amongst those who responded (Pediatric ACR 30) at Week 24 (n=27 out of 30 patients), the Pediatric ACR 30 responses were maintained for up to 60 weeks in the OLE phase in patients who received Humira throughout this time period. Overall, 20 subjects were treated for 60 weeks or longer.

Enthesitis-related arthritis

The safety and efficacy of Humira were assessed in a multicentre, randomised, double-blind study in 46 paediatric patients (6 to 17 years old) with moderate enthesitis-related arthritis. Patients were randomised to receive either 24 mg/m^2 body surface area (BSA) of Humira up to a maximum of 40 mg, or placebo every other week for 12 weeks. The double-blind period is followed by an open-label (OL) period during which patients received 24 mg/m^2 BSA of Humira up to a maximum of 40 mg every other week subcutaneously for up to an additional 192 weeks. The primary endpoint was the percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with loss of motion plus pain and/or tenderness), which was achieved with mean percent decrease of -62.6% (median percent change -88.9%) in patients in the Humira group compared to -11.6% (median percent change -50.0%) in patients in the placebo group. Improvement in number of active joints with arthritis was maintained during the OL period through Week 156 for the 26 of 31 (84%) patients in the Humira group who remained in the study. Although not statistically significant, the majority of patients demonstrated clinical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count (TJC), swollen joint count (SJC), Pediatric ACR 50 response, and Pediatric ACR 70 response.

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Humira 40 mg every other week was assessed in 393 patients in two randomised, 24 week double − blind, placebo − controlled studies in patients with active ankylosing spondylitis (mean baseline score of disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] was 6.3 in all groups) who have had an inadequate response to conventional therapy. Seventy-nine (20.1%) patients were treated concomitantly with disease modifying anti − rheumatic drugs, and 37 (9.4%) patients with glucocorticoids. The blinded period was followed by an open − label period during which patients received Humira 40 mg every other week subcutaneously for up to an additional 28 weeks. Subjects (n=215, 54.7%) who failed to achieve ASAS 20 at Weeks 12, or 16 or 20 received early escape open-label adalimumab 40 mg every other week subcutaneously and were subsequently treated as non-responders in the double-blind statistical analyses.

In the larger AS study I with 315 patients, results showed statistically significant improvement of the signs and symptoms of ankylosing spondylitis in patients treated with Humira compared to placebo. Significant response was first observed at Week 2 and maintained through 24 weeks (Table 8).

Table 8
Efficacy Responses in Placebo-Controlled AS Study – Study I
Reduction of Signs and Symptoms

Response	**Placebo N=107**	**Humira N=208**
ASAS[a] 20		
Week 2	16%	42%***
Week 12	21%	58%***
Week 24	19%	51%***
ASAS 50		

Week 2	3%	16%***
Week 12	10%	38%***
Week 24	11%	35%***
ASAS 70		
Week 2	0%	7%**
Week 12	5%	23%***
Week 24	8%	24%***
BASDAI[b] 50		
Week 2	4%	20%***
Week 12	16%	45%***
Week 24	15%	42%***

***,** Statistically significant at $p < 0.001$, < 0.01 for all comparisons between Humira and placebo at Weeks 2, 12 and 24

[a] Assessments in Ankylosing Spondylitis

[b] Bath Ankylosing Spondylitis Disease Activity Index

Humira treated patients had significantly greater improvement at Week 12 which was maintained through Week 24 in both the SF36 and Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL).

Similar trends (not all statistically significant) were seen in the smaller randomised, double − blind, placebo controlled AS study II of 82 adult patients with active ankylosing spondylitis.

Axial spondyloarthritis without radiographic evidence of AS

Humira 40 mg every other week was assessed in 185 patients in one randomised, 12 week double - blind, placebo - controlled study in patients with active non-radiographic axial spondyloarthitis (mean baseline score of disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] was 6.4 for patients treated with Humira and 6.5 for those on placebo) who have had an inadequate response to or intolerance to ≥ 1 NSAIDs, or a contraindication for NSAIDs.

Thirty-three (18%) of patients were treated concomitantly with disease modifying anti-rheumatic drugs, and 146 (79%) patients with NSAIDs at baseline. The double-blind period was followed by an open-label period during which patients receive Humira 40 mg every other week subcutaneously for up to an additional 144 weeks. Week 12 results showed statistically significant improvement of the signs and symptoms of active non-radiographic axial spondyloarthritis in patients treated with Humira compared to placebo (Table 9).

Table 9
Efficacy Response in Placebo-Controlled Axial SpA Study

Double-Blind **Response at Week 12**	**Placebo** **N=94**	**Humira** **N=91**
ASAS[a] 40	15%	36%***
ASAS 20	31%	52%**
ASAS 5/6	6%	31%***
ASAS Partial Remission	5%	16%*
BASDAI[b] 50	15%	35%**
ASDAS[c,d,e]	-0.3	-1.0***
ASDAS Inactive Disease	4%	24%***
hs-CRP[d,f,g]	-0.3	-4.7***
SPARCC[h] MRI Sacroiliac Joints[d,i]	-0.6	-3.2**
SPARCC MRI Spine[d,j]	-0.2	-1.8**

[a] Assessment of Spondyloarthritis International Society

[b] Bath Ankylosing Spondylitis Disease Activity Index
[c] Ankylosing Spondylitis Disease Activity Score
[d] mean change from baseline
[e] n=91 placebo and n=87 Humira
[f] high sensitivity C-Reactive Protein (mg/L)
[g] n=73 placebo and n=70 Humira
[h] Spondyloarthritis Research Consortium of Canada
[i] n=84 placebo and Humira
[j] n=82 placebo and n=85 Humira
***, **, * Statistically significant at p < 0.001, < 0.01, and
< 0.05, respectively, for all comparisons between Humira and placebo.

In the open-label extension, improvement in the signs and symptoms was maintained with Humira therapy through Week 156.

Inhibition of inflammation

Significant improvement of signs of inflammation as measured by hs-CRP and MRI of both Sacroiliac Joints and the Spine was maintained in Humira-treated patients through Week 156 and Week 104, respectively.

Quality of life and physical function

Health-related quality of life and physical function were assessed using the HAQ-S and the SF-36 questionnaires. Humira showed statistically significantly greater improvement in the HAQ-S total score and the SF-36 Physical Component Score (PCS) from baseline to Week 12 compared to placebo. Improvement in health-related quality of life and physical function was maintained during the open-label extension through Week 156.

Psoriatic arthritis

Humira, 40 mg every other week, was studied in patients with moderately to severely active psoriatic arthritis in two placebo-controlled studies, PsA studies I and II. PsA study I with 24 week duration, treated 313 adult patients who had an inadequate response to non-steroidal anti-inflammatory drug therapy and of these, approximately 50% were taking methotrexate. PsA study II with 12-week duration, treated 100 patients who had an inadequate response to DMARD therapy. Upon completion of both studies, 383 patients enrolled in an open-label extension study, in which 40 mg Humira was administered every other week.

There is insufficient evidence of the efficacy of Humira in patients with ankylosing spondylitis-like psoriatic arthropathy due to the small number of patients studied.

Table 10
ACR Response in Placebo-Controlled Psoriatic Arthritis Studies
(Percent of Patients)

	PsA Study I		PsA Study II	
Response	Placebo N=162	Humira N=151	Placebo N=49	Humira N=51
ACR 20				
Week 12	14%	58%***	16%	39%*
Week 24	15%	57%***	N/A	N/A
ACR 50				
Week 12	4%	36%***	2%	25%***
Week 24	6%	39%***	N/A	N/A
ACR 70				

Week 12	1%	20%***	0%	14%*
Week 24	1%	23%***	N/A	N/A

*** $p < 0.001$ for all comparisons between Humira and placebo
* $p < 0.05$ for all comparisons between Humira and placebo
N/A not applicable

ACR responses in PsA study I were similar with and without concomitant methotrexate therapy. ACR responses were maintained in the open-label extension study for up to 136 weeks.

Radiographic changes were assessed in the psoriatic arthritis studies. Radiographs of hands, wrists, and feet were obtained at baseline and Week 24 during the double-blind period when patients were on Humira or placebo and at Week 48 when all patients were on open-label Humira. A modified Total Sharp Score (mTSS), which included distal interphalangeal joints (i.e. not identical to the TSS used for rheumatoid arthritis), was used.

Humira treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment as measured by change from baseline in mTSS (mean ± SD) 0.8 ± 2.5 in the placebo group (at Week 24) compared with 0.0 ± 1.9; ($p< 0.001$) in the Humira group (at Week 48).

In subjects treated with Humira with no radiographic progression from baseline to Week 48 (n=102), 84% continued to show no radiographic progression through 144 weeks of treatment.
Humira treated patients demonstrated statistically significant improvement in physical function as assessed by HAQ and Short Form Health Survey (SF 36) compared to placebo at Week 24. Improved physical function continued during the open label extension up to Week 136.

Psoriasis

The safety and efficacy of Humira were studied in adult patients with chronic plaque psoriasis (≥ 10% BSA involvement and Psoriasis Area and Severity Index (PASI) ≥ 12 or ≥ 10) who were candidates for systemic therapy or phototherapy in randomised, double-blind studies. 73% of patients enrolled in Psoriasis Studies I and II had received prior systemic therapy or phototherapy. The safety and efficacy of Humira were also studied in adult patients with moderate to severe chronic plaque psoriasis with concomitant hand and/or foot psoriasis who were candidates for systemic therapy in a randomised double-blind study (Psoriasis Study III).

Psoriasis Study I (REVEAL) evaluated 1,212 patients within three treatment periods. In period A, patients received placebo or Humira at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. After 16 weeks of therapy, patients who achieved at least a PASI 75 response (PASI score improvement of at least 75% relative to baseline), entered period B and received open-label 40 mg Humira every other week. Patients who maintained ≥PASI 75 response at Week 33 and were originally randomised to active therapy in Period A, were re-randomised in period C to receive 40 mg Humira every other week or placebo for an additional 19 weeks. Across all treatment groups, the mean baseline PASI score was 18.9 and the baseline Physician's Global Assessment (PGA) score ranged from "moderate" (53% of subjects included) to "severe" (41%) to "very severe" (6%).

Psoriasis Study II (CHAMPION) compared the efficacy and safety of Humira *versus* methotrexate and placebo in 271 patients. Patients received placebo, an initial dose of MTX 7.5 mg and thereafter dose increases up to Week 12, with a maximum dose of 25 mg or an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) for 16 weeks. There are no data available comparing Humira and MTX beyond 16 weeks of therapy. Patients receiving MTX who achieved a ≥PASI 50 response at Week 8 and/or 12 did not receive further dose increases. Across all treatment groups, the mean baseline PASI score was 19.7 and the baseline PGA score ranged from "mild" (<1%) to "moderate" (48%) to "severe" (46%) to "very severe" (6%).

Patients participating in all Phase 2 and Phase 3 psoriasis studies were eligible to enrol into an open-label extension trial, where Humira was given for at least an additional 108 weeks.

In Psoriasis Studies I and II, a primary endpoint was the proportion of patients who achieved a PASI 75 response from baseline at Week 16 (see Tables 11 and 12).

Table 11
Ps Study I (REVEAL) - Efficacy Results at 16 Weeks

	Placebo N=398 n (%)	**Humira 40 mg eow N=814 n (%)**
≥ PASI 75[a]	26 (6.5)	578 (70.9)[b]
PASI 100	3 (0.8)	163 (20.0)[b]
PGA: Clear/minimal	17 (4.3)	506 (62.2)[b]
[a] Percent of patients achieving PASI75 response was calculated as centre-adjusted rate [b] $p < 0.001$, Humira vs. placebo		

Table 12
Ps Study II (CHAMPION) Efficacy Results at 16 Weeks

	Placebo N=53 n (%)	**MTX N=110 n (%)**	**Humira 40 mg eow N=108 n (%)**
≥ PASI 75	10 (18.9)	39 (35.5)	86 (79.6) [a, b]
PASI 100	1 (1.9)	8 (7.3)	18 (16.7) [c, d]
PGA: Clear/minimal	6 (11.3)	33 (30.0)	79 (73.1) [a, b]
[a] $p < 0.001$ Humira vs. placebo [b] $p < 0.001$ Humira vs. methotrexate [c] $p < 0.01$ Humira vs. placebo [d] $p < 0.05$ Humira vs. methotrexate			

In Psoriasis Study I, 28% of patients who were PASI 75 responders and were re-randomised to placebo at Week 33 compared to 5% continuing on Humira, $p < 0.001$, experienced “loss of adequate response” (PASI score after Week 33 and on or before Week 52 that resulted in a <PASI 50 response relative to baseline with a minimum of a 6-point increase in PASI score relative to Week 33). Of the patients who lost adequate response after re-randomisation to placebo who then enrolled into the open-label extension trial, 38% (25/66) and 55% (36/66) regained PASI 75 response after 12 and 24 weeks of re-treatment, respectively.

A total of 233 PASI 75 responders at Week 16 and Week 33 received continuous Humira therapy for 52 weeks in Psoriasis Study I, and continued Humira in the open-label extension trial. PASI 75 and PGA of clear or minimal response rates in these patients were 74.7% and 59.0%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks). In an analysis in which all patients who dropped out of the study for adverse events or lack of efficacy, or who dose-escalated, were considered non-responders, PASI 75 and PGA of clear or minimal response rates in these patients were 69.6% and 55.7%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. During the withdrawal period, symptoms of psoriasis returned over time with a median time to relapse (decline to PGA “moderate” or worse) of approximately 5 months. None of these patients experienced rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the retreatment period had a response of PGA “clear” or “minimal” after

16 weeks of retreatment, irrespective of whether they relapsed during withdrawal (69.1%[123/178] and 88.8% [95/107] for patients who relapsed and who did not relapse during the withdrawal period, respectively). A similar safety profile was observed during retreatment as before withdrawal.

Significant improvements at Week 16 from baseline compared to placebo (Studies I and II) and MTX (Study II) were demonstrated in the DLQI (Dermatology Life Quality Index). In Study I, improvements in the physical and mental component summary scores of the SF-36 were also significant compared to placebo.

In an open-label extension study, for patients who dose escalated from 40 mg every other week to 40 mg weekly due to a PASI response below 50%, 26.4% (92/349) and 37.8% (132/349) of patients achieved PASI 75 response at Week 12 and 24, respectively.

Psoriasis Study III (REACH) compared the efficacy and safety of Humira *versus* placebo in 72 patients with moderate to severe chronic plaque psoriasis and hand and/or foot psoriasis. Patients received an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) or placebo for 16 weeks. At Week 16, a statistically significantly greater proportion of patients who received Humira achieved PGA of 'clear' or 'almost clear' for the hands and/or feet compared to patients who received placebo (30.6% versus 4.3%, respectively [P = 0.014]).

Psoriasis Study IV compared efficacy and safety of Humira versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open-label Humira treatment for an additional 26 weeks. Nail psoriasis assessments included the Modified Nail Psoriasis Severity Index (mNAPSI), the Physician's Global Assessment of Fingernail Psoriasis (PGA-F) and the Nail Psoriasis Severity Index (NAPSI) (see Table 13). Humira demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement (BSA≥10% (60% of patients) and BSA<10% and ≥5% (40% of patients)).

Table 13
Ps Study IV Efficacy Results at 16, 26 and 52 Weeks

Endpoint	Week 16 Placebo-Controlled		Week 26 Placebo-Controlled		Week 52 Open-label
	Placebo N=108	Humira 40 mg eow N=109	Placebo N=108	Humira 40 mg eow N=109	Humira 40 mg eow N=80
≥ mNAPSI 75 (%)	2.9	26.0[a]	3.4	46.6[a]	65.0
PGA-F clear/minimal and ≥2-grade improvement (%)	2.9	29.7[a]	6.9	48.9[a]	61.3
Percent Change in Total Fingernail NAPSI (%)	-7.8	-44.2 [a]	-11.5	-56.2[a]	-72.2
[a] p<0.001, Humira *vs.* placebo					

Humira treated patients showed statistically significant improvements at Week 26 compared with placebo in the DLQI.

Paediatric plaque psoriasis

The efficacy of Humira was assessed in a randomised, double-blind, controlled study of 114 paediatric patients from 4 years of age with severe chronic plaque psoriasis (as defined by a PGA ≥ 4 or > 20% BSA involvement or > 10% BSA involvement with very thick lesions or PASI ≥ 20 or ≥ 10 with clinically relevant facial, genital, or hand/ foot involvement) who were inadequately controlled with topical therapy and heliotherapy or phototherapy.

Patients received Humira 0.8 mg/kg eow (up to 40 mg), 0.4 mg/kg eow (up to 20 mg), or methotrexate 0.1- 0.4 mg/kg weekly (up to 25 mg). At Week 16, more patients randomised to Humira 0.8 mg/kg had positive efficacy responses (e.g., PASI 75) than those randomised to 0.4 mg/kg eow or MTX.

Table 14: Paediatric Plaque Psoriasis Efficacy Results at 16 Weeks

	MTX[a] N=37	Humira 0.8mg/kg eow N=38
PASI 75[b]	12 (32.4%)	22 (57.9%)
PGA: Clear/minimal[c]	15 (40.5%)	23 (60.5%)
[a] MTX = methotrexate [b] P=0.027, Humira 0.8 mg/kg versus MTX [c] P=0.083, Humira 0.8 mg/kg versus MTX		

Patients who achieved PASI 75 and PGA clear or minimal were withdrawn from treatment for up to 36 weeks and monitored for loss of disease control (i.e. a worsening of PGA by at least 2 grades). Patients were then re-treated with adalimumab 0.8 mg/kg eow for an additional 16 weeks and response rates observed during retreatment were similar to the previous double-blind period: PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects).

In the open label period of the study, PASI 75 and PGA clear or minimal responses were maintained for up to an additional 52 weeks with no new safety findings.

Hidradenitis suppurativa

The safety and efficacy of Humira were assessed in randomised, double-blind, placebo-controlled studies and an open-label extension study in adult patients with moderate to severe hidradenitis suppurativa (HS) who were intolerant, had a contraindication or an inadequate response to at least a 3-month trial of systemic antibiotic therapy. The patients in HS-I and HS-II had Hurley Stage II or III disease with at least 3 abscesses or inflammatory nodules.

Study HS-I (PIONEER I) evaluated 307 patients with 2 treatment periods. In Period A, patients received placebo or Humira at an initial dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every week starting at Week 4 to Week 11. Concomitant antibiotic use was not allowed during the study. After 12 weeks of therapy, patients who had received Humira in Period A were re-randomised in Period B to 1 of 3 treatment groups (Humira 40 mg every week, Humira 40 mg every other week, or placebo from Week 12 to Week 35). Patients who had been randomised to placebo in Period A were assigned to receive Humira 40 mg every week in Period B.

Study HS-II (PIONEER II) evaluated 326 patients with 2 treatment periods. In Period A, patients received placebo or Humira at an initial dose of 160 mg at Week 0 and 80 mg at Week 2 and 40 mg every week starting at Week 4 to Week 11. 19.3% of patients had continued baseline oral antibiotic therapy during the study. After 12 weeks of therapy, patients who had received Humira in Period A were re-randomised in Period B to 1 of 3 treatment groups (Humira 40 mg every week, Humira 40 mg every other week, or placebo from Week 12 to Week 35). Patients who had been randomised to placebo in Period A were assigned to receive placebo in Period B.

Patients participating in Studies HS-I and HS-II were eligible to enrol into an open-label extension study in which Humira 40mg was administered every week. Mean exposure in all adalimumab population was 762 days. Throughout all 3 studies patients used topical antiseptic wash daily.

Clinical Response

Reduction of inflammatory lesions and prevention of worsening of abscesses and draining fistulas was assessed using Hidradenitis Suppurativa Clinical Response (HiSCR; at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count relative to Baseline). Reduction in HS-related skin pain was assessed using a Numeric Rating Scale in patients who entered the study with an initial baseline score of 3 or greater on a 11 point scale.

At Week 12, a significantly higher proportion of patients treated with Humira versus placebo achieved HiSCR. At Week 12, a significantly higher proportion of patients in Study HS-II experienced a clinically relevant decrease in HS-related skin pain (see Table 15). Patients treated with Humira had significantly reduced risk of disease flare during the initial 12 weeks of treatment.

Table 15: Efficacy Results at 12 Weeks, HS Studies I and II

	HS Study I		**HS Study II**	
	Placebo	**Humira 40 mg Weekly**	**Placebo**	**Humira 40 mg Weekly**
Hidradenitis Suppurativa Clinical Response (HiSCR)[a]	N = 154 40 (26.0%)	N = 153 64 (41.8%) *	N=163 45 (27.6%)	N=163 96 (58.9%) ***
≥30% Reduction in Skin Pain[b]	N = 109 27 (24.8%)	N = 122 34 (27.9%)	N=111 23 (20.7%)	N=105 48 (45.7%) ***

* $P < 0.05$, *** $P < 0.001$, Humira versus placebo

[a] Among all randomised patients.

[b] Among patients with baseline HS-related skin pain assessment ≥ 3, based on Numeric Rating Scale 0 – 10; 0 = no skin pain, 10 = skin pain as bad as you can imagine.

Treatment with Humira 40 mg every week significantly reduced the risk of worsening of abscesses and draining fistulas. Approximately twice the proportion of patients in the placebo group in the first 12 weeks of Studies HS-I and HS-II, compared with those in the Humira group experienced worsening of abscesses (23.0% vs 11.4%, respectively) and draining fistulas (30.0% vs 13.9%, respectively).

Greater improvements at Week 12 from baseline compared to placebo were demonstrated in skin-specific health-related quality of life, as measured by the Dermatology Life Quality Index (DLQI; Studies HS-I and HS-II), patient global satisfaction with medication treatment as measured by the Treatment Satisfaction Questionnaire - medication (TSQM; Studies HS-I and HS-II), and physical health as measured by the physical component summary score of the SF-36 (Study HS-I).

In patients with at least a partial response to Humira 40 mg weekly at Week 12, the HiSCR rate at Week 36 was higher in patients who continued weekly Humira than in patients in whom dosing frequency was reduced to every other week, or in whom treatment was withdrawn (see Table 16).

Table 16: Proportion of Patients[a] Achieving HiSCR[b] at Weeks 24 and 36 After Treatment Reassignment from Weekly Humira at Week 12

	Placebo (treatment withdrawal) N = 73	Humira 40 mg every other week N = 70	Humira 40 mg weekly N = 70
Week 24	24 (32.9%)	36 (51.4%)	40 (57.1%)
Week 36	22 (30.1%)	28 (40.0%)	39 (55.7%)

[a] Patients with at least a partial response to Humira 40 mg weekly after 12 weeks of treatment.

[b] Patients meeting protocol-specified criteria for loss of response or no improvement were required to discontinue from the studies and were counted as nonresponders.

Among patients who were at least partial responders at Week 12, and who received continuous weekly Humira therapy, the HiSCR rate at Week 48 was 68.3% and at Week 96 was 65.1%. Longer term treatment with Humira 40 mg weekly for 96 weeks identified no new safety findings.

Among patients whose Humira treatment was withdrawn at Week 12 in Studies HS-I and HS-II, the HiSCR rate 12 weeks after re-introduction of Humira 40 mg weekly returned to levels similar to that observed before withdrawal (56.0 %).

Adolescent hidradenitis suppurativa

There are no clinical trials with Humira in adolescent patients with HS. Efficacy of adalimumab for the treatment of adolescent patients with HS is predicted based on the demonstrated efficacy and exposure-response relationship in adult HS patients and the likelihood that the disease course, pathophysiology, and drug effects are substantially similar to that of adults at the same exposure levels. Safety of the recommended adalimumab dose in the adolescent HS population is based on cross-indication safety profile of adalimumab in both adults and paediatric patients at similar or more frequent doses (see section 5.2).

Crohn's disease

The safety and efficacy of Humira were assessed in over 1500 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomised, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 80% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies, CD Study I (CLASSIC I) and CD Study II (GAIN). In CD Study I, 299 TNF-antagonist naive patients were randomised to one of four treatment groups; placebo at Weeks 0 and 2, 160 mg Humira at Week 0 and 80 mg at Week 2, 80 mg at Week 0 and 40 mg at Week 2, and 40 mg at Week 0 and 20 mg at Week 2. In CD Study II, 325 patients who had lost response or were intolerant to infliximab were randomised to receive either 160 mg Humira at Week 0 and 80 mg at Week 2 or placebo at Weeks 0 and 2. The primary non-responders were excluded from the studies and therefore these patients were not further evaluated.

Maintenance of clinical remission was evaluated in CD study III (CHARM). In CD Study III, 854 patients received open-label 80 mg at Week 0 and 40 mg at Week 2. At Week 4 patients were randomised to 40 mg every other week, 40 mg every week, or placebo with a total study duration of 56 weeks. Patients in clinical response (decrease in CDAI ≥ 70) at Week 4 were stratified and

analysed separately from those not in clinical response at Week 4. Corticosteroid taper was permitted after Week 8.

CD study I and CD study II induction of remission and response rates are presented in Table 17.

Table 17
Induction of Clinical Remission and Response
(Percent of Patients)

	CD Study I: Infliximab Naive Patients			**CD Study II: Infliximab Experienced Patients**	
	Placebo N=74	**Humira 80/40 mg N = 75**	**Humira 160/80 mg N=76**	**Placebo N=166**	**Humira 160/80 mg N=159**
Week 4					
Clinical remission	12%	24%	36%*	7%	21%*
Clinical response (CR-100)	24%	37%	49%**	25%	38%**

All p-values are pairwise comparisons of proportions for Humira *versus* placebo

* $p < 0.001$

** $p < 0.01$

Similar remission rates were observed for the 160/80 mg and 80/40 mg induction regimens by Week 8 and adverse events were more frequently noted in the 160/80 mg group.

In CD Study III, at Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. Of those in clinical response at Week 4, 48% had been previously exposed to other TNF-antagonists. Maintenance of remission and response rates are presented in Table 18. Clinical remission results remained relatively constant irrespective of previous TNF-antagonist exposure.

Disease-related hospitalisations and surgeries were statistically significantly reduced with adalimumab compared with placebo at Week 56.

Table 18
Maintenance of Clinical Remission and Response
(Percent of Patients)

	Placebo	**40 mg Humira every other week**	**40 mg Humira every week**
Week 26	**N=170**	**N=172**	**N=157**
Clinical remission	17%	40%*	47%*
Clinical response (CR-100)	27%	52%*	52%*
Patients in steroid-free remission for >=90 days[a]	3% (2/66)	19% (11/58)**	15% (11/74)**
Week 56	**N=170**	**N=172**	**N=157**
Clinical remission	12%	36%*	41%*
Clinical response (CR-100)	17%	41%*	48%*
Patients in steroid-free remission for > = 90 days[a]	5% (3/66)	29% (17/58)*	20% (15/74)**

* $p < 0.001$ for Humira *versus* placebo pairwise comparisons of proportions

** $p < 0.02$ for Humira *versus* placebo pairwise comparisons of proportions

[a] Of those receiving corticosteroids at baseline

Among patients who were not in response at Week 4, 43% of Humira maintenance patients responded by Week 12 compared to 30% of placebo maintenance patients. These results suggest that some patients who have not responded by Week 4 benefit from continued maintenance therapy through Week 12. Therapy continued beyond 12 weeks did not result in significantly more responses (see section 4.2).

117/276 patients from CD study I and 272/777 patients from CD studies II and III were followed through at least 3 years of open-label adalimumab therapy. 88 and 189 patients, respectively, continued to be in clinical remission. Clinical response (CR-100) was maintained in 102 and 233 patients, respectively.

Quality of life

In CD Study I and CD Study II, statistically significant improvement in the disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at Week 4 in patients randomised to Humira 80/40 mg and 160/80 mg compared to placebo and was seen at Weeks 26 and 56 in CD Study III as well among the adalimumab treatment groups compared to the placebo group.

Paediatric Crohn's disease

Humira was assessed in a multicentre, randomised, double-blind clinical trial designed to evaluate the efficacy and safety of induction and maintenance treatment with doses dependent on body weight (< 40 kg or ≥ 40 kg) in 192 paediatric subjects between the ages of 6 and 17 (inclusive) years, with moderate to severe Crohn´s disease (CD) defined as Paediatric Crohn's Disease Activity Index (PCDAI) score > 30. Subjects had to have failed conventional therapy (including a corticosteroid and/or an immunomodulator) for CD. Subjects may also have previously lost response or been intolerant to infliximab.

All subjects received open-label induction therapy at a dose based on their Baseline body weight: 160 mg at Week 0 and 80 mg at Week 2 for subjects ≥ 40 kg, and 80 mg and 40 mg, respectively, for subjects < 40 kg.

At Week 4, subjects were randomised 1:1 based on their body weight at the time to either the Low Dose or Standard Dose maintenance regimens as shown in Table 19.

Table 19
Maintenance regimen

Patient Weight	**Low dose**	**Standard dose**
< 40 kg	10 mg eow	20 mg eow
≥ 40 kg	20 mg eow	40 mg eow

Efficacy results

The primary endpoint of the study was clinical remission at Week 26, defined as PCDAI score ≤ 10.

Clinical remission and clinical response (defined as reduction in PCDAI score of at least 15 points from Baseline) rates are presented in Table 20. Rates of discontinuation of corticosteroids or immunomodulators are presented in Table 21.

Table 20 Paediatric CD Study PCDAI Clinical Remission and Response			
	Standard Dose 40/20 mg eow N = 93	**Low Dose 20/10 mg eow N = 95**	**P value***
Week 26			
Clinical remission	38.7%	28.4%	0.075
Clinical response	59.1%	48.4%	0.073
Week 52			
Clinical remission	33.3%	23.2%	0.100
Clinical response	41.9%	28.4%	0.038
* p value for Standard Dose *versus* Low Dose comparison.			

Table 21 Paediatric CD Study Discontinuation of Corticosteroids or Immunomodulators and Fistula Remission			
	Standard Dose 40/20 mg eow	**Low Dose 20/10 mg eow**	**P value[1]**
Discontinued corticosteroids	**N= 33**	**N=38**	
Week 26	84.8%	65.8%	0.066
Week 52	69.7%	60.5%	0.420
Discontinuation of Immunomodulators[2]	**N=60**	**N=57**	
Week 52	30.0%	29.8%	0.983
Fistula remission[3]	**N=15**	**N=21**	
Week 26	46.7%	38.1%	0.608
Week 52	40.0%	23.8%	0.303

[1] p value for Standard Dose *versus* Low Dose comparison.
[2] Immunosuppressant therapy could only be discontinued at or after Week 26 at the investigator's discretion if the subject met the clinical response criterion
[3] defined as a closure of all fistulas that were draining at Baseline for at least 2 consecutive post-Baseline visits

Statistically significant increases (improvement) from Baseline to Week 26 and 52 in Body Mass Index and height velocity were observed for both treatment groups.

Statistically and clinically significant improvements from Baseline were also observed in both treatment groups for quality of life parameters (including IMPACT III).

One hundred patients (n=100) from the Paediatric CD Study continued in an open-label long-term extension study. After 5 years of adalimumab therapy, 74.0% (37/50) of the 50 patients remaining in the study continued to be in clinical remission, and 92.0% (46/50) of patients continued to be in clinical response per PCDAI.

Ulcerative colitis

The safety and efficacy of multiple doses of Humira were assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopy subscore of 2 to 3) in randomised, double-blind, placebo-controlled studies.

In study UC-I, 390 TNF-antagonist naïve patients were randomised to receive either placebo at Weeks 0 and 2, 160 mg Humira at Week 0 followed by 80 mg at Week 2, or 80 mg Humira at Week 0 followed by 40 mg at Week 2. After Week 2, patients in both adalimumab arms received 40 mg eow. Clinical remission (defined as Mayo score ≤ 2 with no subscore > 1) was assessed at Week 8.

In study UC-II, 248 patients received 160 mg of Humira at Week 0, 80 mg at Week 2 and 40 mg eow thereafter, and 246 patients received placebo. Clinical results were assessed for induction of remission at Week 8 and for maintenance of remission at Week 52.

Patients induced with 160/80 mg Humira achieved clinical remission versus placebo at Week 8 in statistically significantly greater percentages in study UC-I (18% vs. 9% respectively, p=0.031) and study UC-II (17% vs. 9% respectively, p=0.019). In study UC-II, among those treated with Humira who were in remission at Week 8, 21/41 (51%) were in remission at Week 52.

Results from the overall UC-II study population are shown in Table 22.

Table 22

Response, Remission and Mucosal Healing in Study UC-II

(Percent of Patients)

	Placebo	**Humira 40 mg eow**
Week 52	**N=246**	**N=248**
Clinical Response	18%	30%*
Clinical Remission	9%	17%*
Mucosal Healing	15%	25%*
Steroid-free remission for ≥ 90 days [a]	6% (N=140)	13% * (N=150)
Week 8 and 52		
Sustained Response	12%	24%**
Sustained Remission	4%	8%*
Sustained Mucosal Healing	11%	19%*

Clinical remission is Mayo score ≤ 2 with no subscore > 1;
Clinical response is decrease from baseline in Mayo score ≥ 3 points and ≥ 30% plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1;
* p < 0.05 for Humira *vs.* placebo pairwise comparison of proportions
**p < 0.001 for Humira *vs.* placebo pairwise comparison of proportions
[a] Of those receiving corticosteroids at baseline

Of those patients who had a response at Week 8, 47% were in response, 29% were in remission, 41% had mucosal healing, and 20% were in steroid-free remission for ≥ 90 days at Week 52.

Approximately 40% of patients in study UC-II had failed prior anti-TNF treatment with infliximab. The efficacy of adalimumab in those patients was reduced compared to that in anti-TNF naïve patients. Among patients who had failed prior anti-TNF treatment, Week 52 remission was achieved by 3% on placebo and 10% on adalimumab.

Patients from studies UC-I and UC-II had the option to roll over into an open-label long-term extension study (UC III). Following 3 years of adalimumab therapy, 75% (301/402) continued to be in clinical remission per partial Mayo score.

Hospitalisation rates

During 52 weeks of studies UC-I and UC-II, lower rates of all-cause hospitalisations and UC-related hospitalisations were observed for the adalimumab-treated arm compared to the placebo arm. The number of all cause hospitalisations in the adalimumab treatment group was 0.18 per patient year *vs*.

0.26 per patient year in the placebo group and the corresponding figures for UC-related hospitalisations were 0.12 per patient year *vs.* 0.22 per patient year.

Quality of life

In study UC-II, treatment with adalimumab resulted in improvements in the Inflammatory Bowel Disease Questionnaire (IBDQ) score.

Uveitis

The safety and efficacy of Humira were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis, excluding patients with isolated anterior uveitis, in two randomised, double-masked, placebo-controlled studies (UV I and II). Patients received placebo or Humira at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. Concomitant stable doses of one non-biologic immunosuppressant were permitted.

Study UV I evaluated 217 patients with active uveitis despite treatment with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). All patients received a 2-week standardised dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by Week 15.

Study UV II evaluated 226 patients with inactive uveitis requiring chronic corticosteroid treatment (oral prednisone 10 to 35 mg/day) at baseline to control their disease. Patients subsequently underwent a mandatory taper schedule, with complete corticosteroid discontinuation by Week 19.

The primary efficacy endpoint in both studies was ´time to treatment failure´. Treatment failure was defined by a multi-component outcome based on inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber (AC) cell grade, vitreous haze (VH) grade and best corrected visual acuity (BCVA).

Clinical Response

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with Humira versus patients receiving placebo (See Table 23). Both studies demonstrated an early and sustained effect of Humira on the treatment failure rate versus placebo (see Figure 1).

Table 23
Time to Treatment Failure in Studies UV I and UV II

Analysis Treatment	**N**	**Failure N (%)**	**Median Time to Failure (months)**	**HR[a]**	**CI 95% for HR[a]**	***P* Value[b]**
Time to Treatment Failure At or After Week 6 in Study UV I						
Primary analysis (ITT)						
Placebo	107	84 (78.5)	3.0	--	--	--
Adalimumab	110	60 (54.5)	5.6	0.50	0.36, 0.70	< 0.001
Time to Treatment Failure At or After Week 2 in Study UV II						
Primary analysis (ITT)						
Placebo	111	61 (55.0)	8.3	--	--	--
Adalimumab	115	45 (39.1)	NE[c]	0.57	0.39, 0.84	0.004

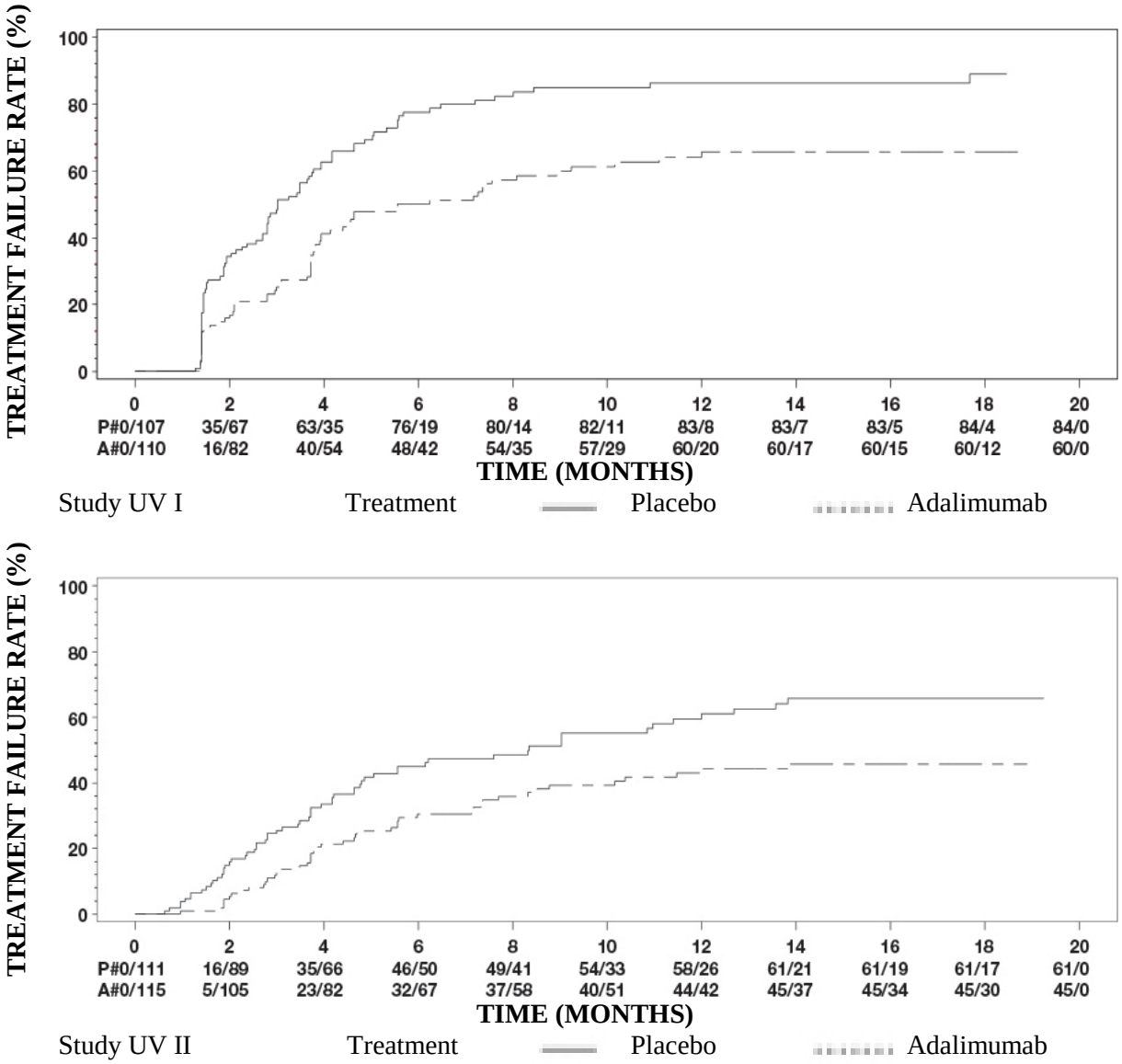
Note: Treatment failure at or after Week 6 (Study UV I), or at or after Week 2 (Study UV II), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

[a] HR of adalimumab vs placebo from proportional hazards regression with treatment as factor.

[b] 2-sided *P* value from log rank test.

[c] NE = not estimable. Fewer than half of at-risk subjects had an event.

Figure 1: Kaplan-Meier Curves Summarizing Time to Treatment Failure on or after Week 6 (Study UV I) or Week 2 (Study UV II)



Note: P# = Placebo (Number of Events/Number at Risk); A# = HUMIRA (Number of Events/Number at Risk).

In Study UV I statistically significant differences in favour of adalimumab versus placebo were observed for each component of treatment failure. In Study UV II, statistically significant differences were observed for visual acuity only, but the other components were numerically in favour of adalimumab.

Quality of Life

Patient reported outcomes regarding vision-related functioning were measured in both clinical studies, using the NEI VFQ-25. Humira was numerically favoured for the majority of subscores with statistically significant mean differences for general vision, ocular pain, near vision, mental health, and total score in Study UV I, and for general vision and mental health in Study UV II. Vision related effects were not numerically in favour of Humira for colour vision in Study UVI and for colour vision, peripheral vision and near vision in Study UV II.

Paediatric Uveitis

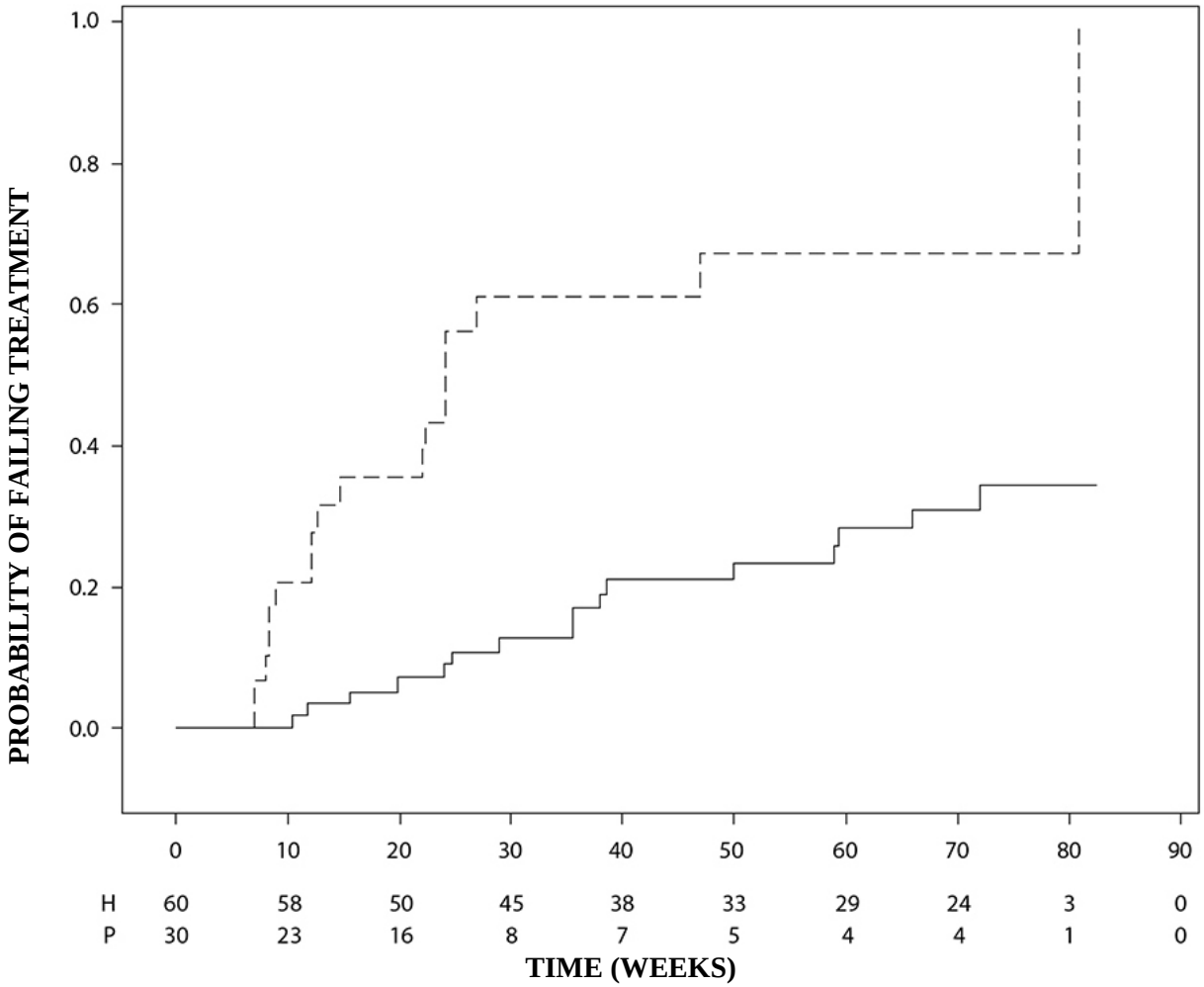
The safety and efficacy of Humira was assessed in a randomized, double-masked, controlled study of 90 paediatric patients from 2 to < 18 years of age with active JIA-associated noninfectious anterior uveitis who were refractory to at least 12 weeks of methotrexate treatment. Patients received either placebo or 20 mg adalimumab (if < 30 kg) or 40 mg adalimumab (if ≥ 30 kg) every other week in combination with their baseline dose of methotrexate.

The primary endpoint was 'time to treatment failure'. The criteria determining treatment failure were worsening or sustained non-improvement in ocular inflammation, partial improvement with development of sustained ocular co-morbidities or worsening of ocular co-morbidities, non-permitted use of concomitant medications, and suspension of treatment for an extended period of time.

Clinical Response

Adalimumab significantly delayed the time to treatment failure, as compared to placebo (See Figure 2, $P < 0.0001$ from log rank test).The median time to treatment failure was 24.1 weeks for subjects treated with placebo, whereas the median time to treatment failure was not estimable for subjects treated with adalimumab because less than one-half of these subjects experienced treatment failure. Adalimumab significantly decreased the risk of treatment failure by 75% relative to placebo, as shown by the hazard ratio (HR = 0.25 [95% CI: 0.12, 0.49]).

Figure 2: Kaplan-Meier Curves Summarizing Time to Treatment Failure in the Paediatric Uveitis Study



Note: P = Placebo (Number at Risk); H = HUMIRA (Number at Risk).

Immunogenicity

Formation of anti-adalimumab antibodies is associated with increased clearance and reduced efficacy of adalimumab. There is no apparent correlation between the presence of anti-adalimumab antibodies and the occurrence of adverse events.

Patients in rheumatoid arthritis studies I, II and III were tested at multiple time points for anti-adalimumab antibodies during the 6 to 12 month period. In the pivotal trials, anti-adalimumab antibodies were identified in 5.5% (58/1053) of patients treated with adalimumab, compared to 0.5% (2/370) on placebo. In patients not given concomitant methotrexate, the incidence was 12.4%, compared to 0.6% when adalimumab was used as add-on to methotrexate.

In patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years, anti-adalimumab antibodies were identified in 15.8% (27/171) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 25.6% (22/86) compared to 5.9% (5/85) when adalimumab was used as add-on to methotrexate.

In patients with enthesitis-related arthritis, anti-adalimumab antibodies were identified in 10.9% (5/46) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 13.6% (3/22), compared to 8.3% (2/24) when adalimumab was used as add-on to methotrexate.

In patients with psoriatic arthritis, anti-adalimumab antibodies were identified in 38/376 subjects (10%) treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 13.5% (24/178 subjects), compared to 7% (14 of 198 subjects) when adalimumab was used as add-on to methotrexate.

In patients with ankylosing spondylitis anti-adalimumab antibodies were identified in 17/204 subjects (8.3%) treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 16/185 (8.6%), compared to 1/19 (5.3%) when adalimumab was used as add-on to methotrexate.

In patients with Crohn's disease, anti-adalimumab antibodies were identified in 7/269 subjects (2.6%) and in 19/487 subjects (3.9%) with ulcerative colitis.

In adult patients with psoriasis, anti-adalimumab antibodies were identified in 77/920 subjects (8.4%) treated with adalimumab monotherapy.

In adult plaque psoriasis patients on long term adalimumab monotherapy who participated in a withdrawal and retreatment study, the rate of antibodies to adalimumab after retreatment (11 of 482 subjects, 2.3%) was similar to the rate observed prior to withdrawal (11 of 590 subjects, 1.9%).

In patients with paediatric psoriasis, anti-adalimumab antibodies were identified in 5/38 subjects (13%) treated with 0.8mg/kg adalimumab monotherapy.

In patients with moderate to severe hidradenitis suppurativa, anti-adalimumab antibodies were identified in 10/99 subjects (10.1%) treated with adalimumab.

In patients with moderately to severely active paediatric Crohn's disease, the rate of anti-adalimumab antibody development in patients receiving adalimumab was 3.3%.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab.

Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of the studies with Humira in one or more subsets of the paediatric population in ulcerative colitis, see section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption and distribution

After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. After single intravenous doses ranging from 0.25 to 10 mg/kg, concentrations were dose proportional. After doses of 0.5 mg/kg (~40 mg), clearances ranged from 11 to 15 ml/hour, the distribution volume (V_{ss}) ranged from 5 to 6 litres and the mean terminal phase half-life was approximately two weeks. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31-96% of those in serum.

Following subcutaneous administration of 40 mg of adalimumab every other week in adult rheumatoid arthritis (RA) patients the mean steady-state trough concentrations were approximately

5 μg/ml (without concomitant methotrexate) and 8 to 9 μg/ml (with concomitant methotrexate), respectively. The serum adalimumab trough levels at steady-state increased roughly proportionally with dose following 20, 40 and 80 mg subcutaneous dosing every other week and every week.

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with polyarticular juvenile idiopathic arthritis (JIA) who were 4 to 17 years the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5.6 ± 5.6 μg/ml (102% CV) for adalimumab without concomitant methotrexate and 10.9 ± 5.2 μg/ml (47.7% CV) with concomitant methotrexate.

In patients with polyarticular JIA who were 2 to < 4 years old or aged 4 and above weighing < 15 kg dosed with adalimumab 24 mg/m^2 , the mean trough steady-state serum adalimumab concentrations was 6.0 ± 6.1 μg/ml (101% CV) for adalimumab without concomitant methotrexate and 7.9 ± 5.6 μg/ml (71.2% CV) with concomitant methotrexate.

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with enthesitis-related arthritis who were 6 to 17 years, the mean trough steady-state (values measured at Week 24) serum adalimumab concentrations were 8.8 ± 6.6 μg/ml for adalimumab without concomitant methotrexate and 11.8 ± 4.3 μg/ml with concomitant methotrexate.

In adult patients with psoriasis, the mean steady-state trough concentration was 5 μg/ml during adalimumab 40 mg every other week monotherapy treatment.

Following the administration of 0.8 mg/kg (up to a maximum of 40 mg) subcutaneously every other week to paediatric patients with chronic plaque psoriasis, the mean ± SD steady-state adalimumab trough concentration was approximately 7.4 ± 5.8 μg/ml (79% CV).

In adult patients with hidradenitis suppurativa, a dose of 160 mg Humira on Week 0 followed by 80 mg on Week 2 achieved serum adalimumab trough concentrations of approximately 7 to 8 μg/ml at Week 2 and Week 4. The mean steady-state trough concentration at Week 12 through Week 36 were approximately 8 to 10 μg/ml during adalimumab 40 mg every week treatment.

Adalimumab exposure in adolescent HS patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent HS dosing schedule is 40 mg every other week. Since exposure to adalimumab can be affected by body size, adolescents with higher body weight and inadequate response may benefit from receiving the recommended adult dose of 40 mg every week.

In patients with Crohn's disease, the loading dose of 80 mg Humira on Week 0 followed by 40 mg Humira on Week 2 achieves serum adalimumab trough concentrations of approximately 5.5 μg/ml during the induction period. A loading dose of 160 mg Humira on Week 0 followed by 80 mg Humira on Week 2 achieves serum adalimumab trough concentrations of approximately 12 μg/ml during the induction period. Mean steady-state trough levels of approximately 7 μg/ml were observed in Crohn's disease patients who received a maintenance dose of 40 mg Humira every other week.

In paediatric patients with moderate to severe CD, the open-label adalimumab induction dose was 160/80 mg or 80/40 mg at Weeks 0 and 2, respectively, dependent on a body weight cut-off of 40 kg. At Week 4, patients were randomised 1:1 to either the Standard Dose (40/20 mg eow) or Low Dose (20/10 mg eow) maintenance treatment groups based on their body weight. The mean (±SD) serum adalimumab trough concentrations achieved at Week 4 were 15.7 ± 6.6 μg/ml for patients ≥ 40 kg (160/80 mg) and 10.6 ± 6.1 μg/ml for patients < 40 kg (80/40 mg).

For patients who stayed on their randomised therapy, the mean (±SD) adalimumab trough concentrations at Week 52 were 9.5 ± 5.6 μg/ml for the Standard Dose group and 3.5 ± 2.2 μg/ml for

the Low Dose group. The mean trough concentrations were maintained in patients who continued to receive adalimumab treatment eow for 52 weeks. For patients who dose escalated from eow to weekly regimen, the mean (±SD) serum concentrations of adalimumab at Week 52 were 15.3 ± 11.4 μg/ml (40/20 mg, weekly) and 6.7 ± 3.5 μg/ml (20/10 mg, weekly).

In patients with ulcerative colitis, a loading dose of 160 mg Humira on Week 0 followed by 80 mg Humira on Week 2 achieves serum adalimumab trough concentrations of approximately 12 μg/ml during the induction period. Mean steady-state trough levels of approximately 8 μg/ml were observed in ulcerative colitis patients who received a maintenance dose of 40 mg Humira every other week.

In patients with uveitis, a loading dose of 80 mg adalimumab on Week 0 followed by 40 mg adalimumab every other week starting at Week 1, resulted in mean steady-state concentrations of approximately 8 to 10 μg/mL.

Adalimumab exposure in paediatric uveitis patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). No clinical exposure data are available on the use of a loading dose in children < 6 years. The predicted exposures indicate that in the absence of methotrexate, a loading dose may lead to an initial increase in systemic exposure.

Elimination

Population pharmacokinetic analyses with data from over 1,300 RA patients revealed a trend toward higher apparent clearance of adalimumab with increasing body weight. After adjustment for weight differences, gender and age appeared to have a minimal effect on adalimumab clearance. The serum levels of free adalimumab (not bound to anti-adalimumab antibodies, AAA) were observed to be lower in patients with measurable AAA.

Hepatic or renal impairment

Humira has not been studied in patients with hepatic or renal impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity.

An embryo-foetal developmental toxicity/perinatal developmental study has been performed in cynomologous monkeys at 0, 30 and 100 mg/kg (9-17 monkeys/group) and has revealed no evidence of harm to the foetuses due to adalimumab. Neither carcinogenicity studies, nor a standard assessment of fertility and postnatal toxicity, were performed with adalimumab due to the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and to the development of neutralising antibodies in rodents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the pre-filled syringe or pre-filled pen in its outer carton in order to protect from light.

A single Humira pre-filled syringe or pre-filled pen may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. The syringe or pen must be protected from light, and discarded if not used within the 14 -day period.

6.5 Nature and contents of container

Humira 40 mg solution for injection in pre-filled syringe
Humira 40 mg solution for injection in single-use pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

Packs of:
- 1 pre-filled syringe (0.4 ml sterile solution) with 1 alcohol pad in a blister.
- 2 pre-filled syringes (0.4 ml sterile solution), each with 1 alcohol pad, in a blister.
- 4 pre-filled syringes (0.4 ml sterile solution), each with 1 alcohol pad, in a blister.
- 6 pre-filled syringes (0.4 ml sterile solution), each with 1 alcohol pad, in a blister.

Humira 40 mg solution for injection in pre-filled pen
Humira 40 mg solution for injection in single-use pre-filled pen for patient use containing a pre-filled syringe. The syringe inside the pen is made from type 1 glass with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

Packs of:
- 1 pre-filled pen (0.4 ml sterile solution), with 2 alcohol pads in a blister.
- 2 pre-filled pens (0.4 ml sterile solution), each with 1 alcohol pad, in a blister.
- 4 pre-filled pens (0.4 ml sterile solution), each with 1 alcohol pad, in a blister.
- 6 pre-filled pens (0.4 ml sterile solution), each with 1 alcohol pad, in a blister.

Not all presentations or pack sizes may be marketed.

6.6 Special precautions for disposal

Humira does not contain preservatives. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

Humira 40 mg solution for injection in pre-filled syringe
EU/1/03/256/012
EU/1/03/256/013
EU/1/03/256/014
EU/1/03/256/015

Humira 40 mg solution for injection in pre-filled pen
EU/1/03/256/016
EU/1/03/256/017
EU/1/03/256/018
EU/1/03/256/019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 September 2003
Date of latest renewal: 08 September 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Humira 80 mg solution for injection in pre-filled syringe
Humira 80 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Humira 80 mg solution for injection in pre-filled syringe
Each 0.8 ml single dose pre-filled syringe contains 80 mg of adalimumab.

Humira 80 mg solution for injection in pre-filled pen
Each 0.8 ml single dose pre-filled pen contains 80 mg of adalimumab.

Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Psoriasis

Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Hidradenitis suppurativa (HS)

Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy (see sections 5.1 and 5.2).

Crohn’s disease

Humira is indicated for treatment of moderately to severely active Crohn’s disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's disease

Humira is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

Humira is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Uveitis

Humira is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Paediatric Uveitis

Humira is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

4.2 Posology and method of administration

Humira treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which Humira is indicated. Ophthalmologists are advised to consult with an appropriate specialist before initiation of treatment with Humira (see section 4.4). Patients treated with Humira should be given the special alert card.

After proper training in injection technique, patients may self-inject with Humira if their physician determines that it is appropriate and with medical follow-up as necessary.

During treatment with Humira, other concomitant therapies (e.g., corticosteroids and/or immunomodulatory agents) should be optimised.

Posology

Psoriasis

The recommended dose of Humira for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose. Humira 40 mg solution for injection in pre-filled syringe and/or pre-filled pen is available for the maintenance dose.

Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.

Beyond 16 weeks, patients with inadequate response may benefit from an increase in dosing frequency to 40 mg every week. The benefits and risks of continued weekly Humira therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosing frequency (see section 5.1). If adequate response is achieved with an increased dosing frequency, the dose may subsequently be reduced to 40 mg every other week.

Hidradenitis suppurativa

The recommended Humira dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at Day 1 (given as two 80 mg injections in one day or as one 80 mg injection per day for two consecutive days), followed by 80 mg two weeks later at Day 15. Two weeks later (Day 29) continue with a dose of 40 mg every week. Antibiotics may be continued during treatment with

Humira if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Humira. Humira 40 mg solution for injection in pre-filled syringe and/or pre-filled pen is available for the maintenance dose.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

Should treatment be interrupted, Humira 40 mg every week may be re-introduced (see section 5.1).

The benefit and risk of continued long-term treatment should be periodically evaluated (see section 5.1).

Crohn's disease

The recommended Humira induction dose regimen for adult patients with moderately to severely active Crohn's disease is 80 mg at Week 0 followed by 40 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at Week 0 (given as two 80 mg injections in one day or as one 80 mg injection per day for two consecutive days), 80 mg at Week 2, can be used with the awareness that the risk for adverse events is higher during induction.

After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Alternatively, if a patient has stopped Humira and signs and symptoms of disease recur, Humira may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose. Humira 40 mg solution for injection in pre-filled syringe and/or pre-filled pen is available for the maintenance dose.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg Humira every week.

Some patients who have not responded by Week 4 may benefit from continued maintenance therapy through Week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Ulcerative colitis

The recommended Humira induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at Week 0 (given as two 80 mg injections in one day or as one 80 mg injection per day for two consecutive days) and 80 mg at Week 2. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Humira 40 mg solution for injection in pre-filled syringe and/or pre-filled pen is available for the maintenance dose.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg Humira every week.

Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment. Humira therapy should not be continued in patients failing to respond within this time period.

Uveitis

The recommended dose of Humira for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. Humira 40 mg solution for injection in pre-filled syringe and/or pre-filled pen is available for the maintenance dose. There is limited experience in the initiation of treatment with Humira alone. Treatment with Humira can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with Humira.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis (see section 5.1).

Elderly

No dose adjustment is required.

Renal and/or hepatic impairment

Humira has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population

Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)

There are no clinical trials with Humira in adolescent patients with HS. The posology of Humira in these patients has been determined from pharmacokinetic modelling and simulation (see section 5.2).

The recommended Humira dose is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via subcutaneous injection.

In adolescent patients with inadequate response to Humira 40 mg every other week, an increase in dosing frequency to 40 mg every week may be considered.

Antibiotics may be continued during treatment with Humira if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Humira.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

Should treatment be interrupted, Humira may be re-introduced as appropriate.

The benefit and risk of continued long-term treatment should be periodically evaluated (see adult data in section 5.1)

There is no relevant use of Humira in children aged less than 12 years in this indication.

Paediatric Crohn's disease

Paediatric Crohn's disease patients < 40 kg:

The recommended Humira induction dose regimen for paediatric subjects with moderately to severely active Crohn's disease is 40 mg at Week 0 followed by 20 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 80 mg at Week 0, 40 mg at Week 2 can be used, with the awareness that the risk for adverse events may be higher with use of the higher induction dose. Humira 40 mg solution for injection in pre-filled syringe and/or pre-filled pen is available.

After induction treatment, the recommended dose is 20 mg every other week via subcutaneous injection. Some subjects who experience insufficient response may benefit from an increase in dosing frequency to 20 mg Humira every week. Humira 40 mg/0.8 ml solution for injection for paediatric use (vial) is available for the maintenance dose.

Paediatric Crohn's disease patients ≥ 40 kg:

The recommended Humira induction dose regimen for paediatric subjects with moderately to severely active Crohn's disease is 80 mg at Week 0 followed by 40 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at Week 0 (given as two 80 mg injections in one day or as one 80 mg injection per day for two consecutive days), 80 mg at Week 2 can be used, with the awareness that the risk for adverse events may be higher with use of the higher induction dose.

After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Some subjects who experience insufficient response may benefit from an increase in dosing frequency to 40 mg Humira every week. Humira 40 mg solution for injection in pre-filled syringe and/or pre-filled pen is available for the maintenance dose.

Continued therapy should be carefully considered in a subject not responding by Week 12.

There is no relevant use of Humira in children aged below 6 years for this indication.

Paediatric Uveitis

In paediatric uveitis, there is no experience in the treatment with Humira without concomitant treatment with methotrexate.

Paediatric uveitis patients < 30 kg:

The recommended dose of Humira is 20 mg every other week in combination with methotrexate.

When Humira therapy is initiated, a loading dose of 40 mg may be administered one week prior to the start of maintenance therapy. No clinical data are available on the use of a Humira loading dose in children < 6 years of age (see section 5.2).

Paediatric uveitis patients ≥ 30 kg:

The recommended dose of Humira is 40 mg every other week in combination with methotrexate.

When Humira therapy is initiated, a loading dose of 80 mg may be administered one week prior to the start of maintenance therapy.

There is no relevant use of Humira in children aged less than 2 years in this indication.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis (see section 5.1).

Paediatric plaque psoriasis

The safety and efficacy of Humira in children aged 4-17 years have been established for plaque psoriasis. The recommended Humira dose is up to a maximum of 40 mg per dose. Humira 40 mg/0.8 ml solution for injection for paediatric use (vial), Humira 40 mg solution for injection in pre-filled syringe and/or Humira 40 mg solution for injection in pre-filled pen is available.

Paediatric ulcerative colitis

The safety and efficacy of Humira in children aged 4-17 years have not yet been established. No data are available. There is no relevant use of Humira in children aged < 4 years for this indication.

Method of administration

Humira is administered by subcutaneous injection. Full instructions for use are provided in the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active tuberculosis or other severe infections such as sepsis, and opportunistic infections (see section 4.4).

Moderate to severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections

Patients taking TNF-antagonists are more susceptible to serious infections. Impaired lung function may increase the risk for developing infections. Patients must therefore be monitored closely for infections, including tuberculosis, before, during and after treatment with Humira. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period.

Treatment with Humira should not be initiated in patients with active infections including chronic or localised infections until infections are controlled. In patients who have been exposed to tuberculosis and patients who have travelled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with Humira should be considered prior to initiating therapy (see *Other opportunistic infections*).

Patients who develop a new infection while undergoing treatment with Humira, should be monitored closely and undergo a complete diagnostic evaluation. Administration of Humira should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of Humira in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications.

Serious infections

Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis have been reported in patients receiving Humira.

Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia. Hospitalisation or fatal outcomes associated with infections have been reported.

Tuberculosis

Tuberculosis, including reactivation and new onset of tuberculosis, has been reported in patients receiving Humira. Reports included cases of pulmonary and extra-pulmonary (i.e. disseminated) tuberculosis.

Before initiation of therapy with Humira, all patients must be evaluated for both active or inactive ("latent") tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients (local recommendations may apply). It is recommended that the conduct and results of these tests are recorded in the patient alert card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Humira therapy must not be initiated (see section 4.3).

In all situations described below, the benefit/risk balance of therapy should be very carefully considered.

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted.

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylaxis treatment before the initiation of Humira, and in accordance with local recommendations.

Use of anti-tuberculosis prophylaxis treatment should also be considered before the initiation of Humira in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with Humira. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with Humira.

Patients should be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (e.g., persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with Humira.

Other opportunistic infections

Opportunistic infections, including invasive fungal infections have been observed in patients receiving Humira. These infections have not consistently been recognised in patients taking TNF-antagonists and this has resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.

For patients who develop the signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock an invasive fungal infection should be suspected and administration of Humira should be promptly discontinued. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections.

Hepatitis B reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including Humira, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had a fatal outcome. Patients should be tested for HBV infection before initiating treatment with Humira. For patients who test positive for hepatitis B infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Carriers of HBV who require treatment with Humira should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data from treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, Humira should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurological events

TNF-antagonists including Humira have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of Humira in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of Humira should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of Humira therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Allergic reactions

Serious allergic reactions associated with Humira were rare during clinical trials. Non-serious allergic reactions associated with Humira were uncommon during clinical trials. Reports of serious allergic reactions including anaphylaxis have been received following Humira administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Humira should be discontinued immediately and appropriate therapy initiated.

Immunosuppression

In a study of 64 patients with rheumatoid arthritis that were treated with Humira, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T-, B, - NK-cells, monocyte/macrophages, and neutrophils.

Malignancies and lymphoproliferative disorders

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare. In the post marketing setting, cases of leukaemia have been reported in patients treated with a TNF-antagonist. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active,

inflammatory disease, which complicates the risk estimation. With the current knowledge, a possible risk for the development of lymphomas, leukaemia, and other malignancies in patients treated with a TNF-antagonist cannot be excluded.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including adalimumab in the post marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Rare postmarketing cases of hepatosplenic T-cell lymphoma have been identified in patients treated with adalimumab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Some of these hepatosplenic T-cell lymphomas with Humira have occurred in young adult patients on concomitant treatment with azathioprine or 6-mercaptopurine used for inflammatory bowel disease. The potential risk with the combination of azathioprine or 6-mercaptopurine and Humira should be carefully considered. A risk for the development of hepatosplenic T-cell lymphoma in patients treated with Humira cannot be excluded (see section 4.8).

No studies have been conducted that include patients with a history of malignancy or in whom treatment with Humira is continued following development of malignancy. Thus additional caution should be exercised in considering Humira treatment of these patients (see section 4.8).

All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with Humira. Melanoma and Merkel cell carcinoma have also been reported in patients treated with TNF-antagonists including adalimumab (see section 4.8).

In an exploratory clinical trial evaluating the use of another TNF-antagonist, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking.

With current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.

Haematologic reactions

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF-antagonists. Adverse events of the haematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been reported with Humira. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor) while on Humira. Discontinuation of Humira therapy should be considered in patients with confirmed significant haematologic abnormalities.

Vaccinations

Similar antibody responses to the standard 23-valent pneumococcal vaccine and the influenza trivalent virus vaccination were observed in a study in 226 adult subjects with rheumatoid arthritis

who were treated with adalimumab or placebo. No data are available on the secondary transmission of infection by live vaccines in patients receiving Humira.

It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy.

Patients on Humira may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Congestive heart failure

In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving Humira. Humira should be used with caution in patients with mild heart failure (NYHA class I/II). Humira is contraindicated in moderate to severe heart failure (see section 4.3). Treatment with Humira must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes

Treatment with Humira may result in the formation of autoimmune antibodies. The impact of long-term treatment with Humira on the development of autoimmune diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Humira and is positive for antibodies against double-stranded DNA, further treatment with Humira should not be given (see section 4.8).

Concurrent administration of biologic DMARDS or TNF-antagonists

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-antagonist, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF-antagonists. Therefore, the combination of adalimumab and anakinra is not recommended. (See section 4.5).

Concomitant administration of adalimumab with other biologic DMARDS (e.g, anakinra and abatacept) or other TNF-antagonists is not recommended based upon the possible increased risk for infections, including serious infections and other potential pharmacological interactions. (See section 4.5).

Surgery

There is limited safety experience of surgical procedures in patients treated with Humira. The long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Humira should be closely monitored for infections, and appropriate actions should be taken. There is limited safety experience in patients undergoing arthroplasty while receiving Humira.

Small bowel obstruction

Failure to respond to treatment for Crohn's disease may indicate the presence of fixed fibrotic stricture that may require surgical treatment. Available data suggest that Humira does not worsen or cause strictures.

Elderly

The frequency of serious infections among Humira treated subjects over 65 years of age (3.7%) was higher than for those under 65 years of age (1.5%). Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly.

Paediatric population

See Vaccinations above.

4.5 Interaction with other medicinal products and other forms of interaction

Humira has been studied in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis patients taking Humira as monotherapy and those taking concomitant methotrexate. Antibody formation was lower when Humira was given together with methotrexate in comparison with use as monotherapy. Administration of Humira without methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab (see section 5.1).

The combination of Humira and anakinra is not recommended (see section 4.4 “Concurrent administration of biologic DMARDS or TNF-antagonists”).

The combination of Humira and abatacept is not recommended (see section 4.4 “Concurrent administration of biologic DMARDS or TNF-antagonists”).

4.6 Fertility, pregnancy and lactation

Women of child bearing potential/Contraception in males and females

Women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and continue its use for at least five months after the last Humira treatment.

Pregnancy

For Humira, limited clinical data on exposed pregnancies are available

In a developmental toxicity study conducted in monkeys, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. Preclinical data on postnatal toxicity of adalimumab are not available (see section 5.3).

Due to its inhibition of TNFα, adalimumab administered during pregnancy could affect normal immune responses in the newborn. Administration of adalimumab is not recommended during pregnancy.

Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother’s last adalimumab injection during pregnancy.

Breast feeding

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion.

However, because human immunoglobulins are excreted in milk, women must not breast-feed for at least five months after the last Humira treatment.

Fertility

Preclinical data on fertility effects of adalimumab are not available.

4.7 Effects on ability to drive and use machines

Humira may have a minor influence on the ability to drive and use machines. Vertigo and visual impairment may occur following administration of Humira (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Humira was studied in 9,506 patients in pivotal controlled and open label trials for up to 60 months or more. These trials included rheumatoid arthritis patients with short term and long standing disease, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis) as well as axial spondyloarthritis (ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients. The pivotal controlled studies involved 6,089 patients receiving Humira and 3,801 patients receiving placebo or active comparator during the controlled period.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of pivotal studies was 5.9% for patients taking Humira and 5.4% for control treated patients.

The most commonly reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain.

Serious adverse reactions have been reported for Humira. TNF-antagonists, such as Humira affect the immune system and their use may affect the body's defence against infection and cancer.
Fatal and life-threatening infections (including sepsis, opportunistic infections and TB), HBV reactivation and various malignancies (including leukaemia, lymphoma and HSTCL) have also been reported with use of Humira.

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia, aplastic anaemia, central and peripheral demyelinating events and reports of lupus, lupus-related conditions and Stevens-Johnson syndrome.

Paediatric population

Undesirable effects in paediatric patients

In general, the adverse events in paediatric patients were similar in frequency and type to those seen in adult patients.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience and are displayed by system organ class and frequency in Table 1 below: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The highest frequency seen among the various indications has been included. An asterisk (*) appears in the SOC column if further information is found elsewhere in sections 4.3, 4.4 and 4.8.

Table 1
Undesirable Effects

System Organ Class	Frequency	Adverse Reaction
Infections and infestations*	Very common	respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections, joint infections
	Uncommon	neurological infections (including viral meningitis), opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), bacterial infections, eye infections, diverticulitis[1)]
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Common	skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma), benign neoplasm
	Uncommon	lymphoma**, solid organ neoplasm (including breast cancer,

System Organ Class	Frequency	Adverse Reaction
		lung neoplasm and thyroid neoplasm), melanoma**
	Rare	leukaemia[1)]
	Not known	hepatosplenic T-cell lymphoma[1)] Merkel cell carcinoma (neuroendocrine carcinoma of the skin)[1)]
Blood and the lymphatic system disorders*	Very common	leukopenia (including neutropenia and agranulocytosis), anaemia
	Common	leucocytosis, thrombocytopenia
	Uncommon	idiopathic thrombocytopenic purpura
	Rare	pancytopenia
Immune system disorders*	Common	hypersensitivity, allergies (including seasonal allergy)
	Uncommon	sarcoidosis[1)], vasculitis
	Rare	anaphylaxis[1)]
Metabolism and nutrition disorders	Very common	lipids increased
	Common	hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia, hyperglycaemia, hypophosphatemia, dehydration
Psychiatric disorders	Common	mood alterations (including depression), anxiety, insomnia
Nervous system disorders*	Very common	headache
	Common	paraesthesias (including hypoesthesia),

System Organ Class	Frequency	Adverse Reaction
		migraine, nerve root compression
	Uncommon	cerebrovascular accident[1)], tremor, neuropathy
	Rare	multiple sclerosis, demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome) [1)]
Eye disorders	Common	visual impairment, conjunctivitis, blepharitis, eye swelling
	Uncommon	diplopia
Ear and labyrinth disorders	Common	vertigo
	Uncommon	deafness, tinnitus
Cardiac disorders*	Common	tachycardia
	Uncommon	myocardial infarction[1)], arrhythmia, congestive heart failure
	Rare	cardiac arrest
Vascular disorders	Common	hypertension, flushing, haematoma
	Uncommon	aortic aneurysm, vascular arterial occlusion, thrombophlebitis
Respiratory, thoracic and mediastinal disorders*	Common	asthma, dyspnoea, cough
	Uncommon	pulmonary embolism[1)], interstitial lung disease, chronic obstructive pulmonary disease, pneumonitis,

System Organ Class	Frequency	Adverse Reaction
		pleural effusion[1)]
	Rare	pulmonary fibrosis[1)]
Gastrointestinal disorders	Very common	abdominal pain, nausea and vomiting
	Common	GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	pancreatitis, dysphagia, face oedema
	Rare	intestinal perforation[1)]
Hepato-biliary disorders*	Very Common	elevated liver enzymes
	Uncommon	cholecystitis and cholelithiasis, hepatic steatosis, bilirubin increased
	Rare	hepatitis reactivation of hepatitis B[1)] autoimmune hepatitis[1)]
	Not known	liver failure[1)]
Skin and subcutaneous tissue disorders	Very Common	rash (including exfoliative rash)
	Common	worsening or new onset of psoriasis (including palmoplantar pustular psoriasis)[1)], urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis, hyperhidrosis, alopecia[1)], pruritus
	Uncommon	night sweats, scar
	Rare	erythema multiforme[1)], Stevens-Johnson syndrome[1)], angioedema[1)], cutaneous vasculitis[1)]

System Organ Class	Frequency	Adverse Reaction
	Not known	worsening of symptoms of dermatomyositis[1)]
Musculoskeletal and connective tissue disorders	Very common	musculoskeletal pain
	Common	muscle spasms (including blood creatine phosphokinase increased)
	Uncommon	rhabdomyolysis, systemic lupus erythematosus
	Rare	lupus-like syndrome[1)]
Renal and urinary disorders	Common	renal impairment, haematuria
	Uncommon	nocturia
Reproductive system and breast disorders	Uncommon	erectile dysfunction
General disorders and administration site conditions*	Very Common	injection site reaction (including injection site erythema)
	Common	chest pain, oedema, pyrexia[1)]
	Uncommon	inflammation
Investigations*	Common	coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), autoantibody test positive (including double stranded DNA antibody), blood lactate dehydrogenase increased
Injury, poisoning and procedural complications	Common	impaired healing

* further information is found elsewhere in sections 4.3, 4.4 and 4.8
** including open label extension studies
[1)] including spontaneous reporting data

Hidradenitis suppurativa

The safety profile for patients with HS treated with Humira weekly was consistent with the known safety profile of Humira.

Uveitis

The safety profile for patients with uveitis treated with Humira every other week was consistent with the known safety profile of Humira.

Description of selected adverse reactions

Injection site reactions

In the pivotal controlled trials in adults and children, 12.9% of patients treated with Humira developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 7.2% of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Infections

In the pivotal controlled trials in adults and children, the rate of infection was 1.51 per patient year in the Humira treated patients and 1.46 per patient year in the placebo and active control-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, and sinusitis. Most patients continued on Humira after the infection resolved.

The incidence of serious infections was 0.04 per patient year in Humira treated patients and 0.03 per patient year in placebo and active control − treated patients.

In controlled and open label adult and paediatric studies with Humira, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extra-pulmonary locations) and invasive opportunistic infections (e.g. disseminated or extrapulmonary histoplasmosis, blastomycosis, coccidioidomycosis, pneumocystis, candidiasis, aspergillosis and listeriosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

Malignancies and lymphoproliferative disorders

No malignancies were observed in 249 paediatric patients with an exposure of 655.6 patient years during Humira trials in patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis). In addition, no malignancies were observed in 192 paediatric patients with an exposure of 498.1 patient years during Humira trials in paediatric patients with Crohn's disease. No malignancies were observed in 77 paediatric patients with an exposure of 80.0 patient years during a Humira trial in paediatric patients with chronic plaque psoriasis. No malignancies were observed in 60 paediatric patients with an exposure of 58.4 patient years during a Humira trial in paediatric patients with uveitis.

During the controlled portions of pivotal Humira trials in adults of at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.8 (4.4, 10.5) per 1,000 patient-years among 5,291 Humira treated patients *versus* a rate of 6.3 (3.4, 11.8) per 1,000 patient-years among 3,444 control patients (median duration of treatment was 4.0 months for Humira and 3.8 months for control-treated patients). The rate (95% confidence interval) of non-melanoma skin cancers was 8.8 (6.0, 13.0) per 1,000 patient-years among Humira-treated patients and 3.2 (1.3, 7.6) per 1,000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) of 2.7 (1.4, 5.4) per 1,000 patient-years among Humira-

treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients. The rate (95% confidence interval) of lymphomas was 0.7 (0.2, 2.7) per 1,000 patient-years among Humira-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients.

When combining controlled portions of these trials and ongoing and completed open label extension studies with a median duration of approximately 3.3 years including 6,427 patients and over 26,439 patient-years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 8.5 per 1,000 patient years. The observed rate of non-melanoma skin cancers is approximately 9.6 per 1,000 patient years, and the observed rate of lymphomas is approximately 1.3 per 1,000 patient years.

In post-marketing experience from January 2003 to December 2010, predominantly in patients with rheumatoid arthritis, the reported rate of malignancies is approximately 2.7 per 1,000 patient treatment years. The reported rates for non-melanoma skin cancers and lymphomas are approximately 0.2 and 0.3 per 1,000 patient treatment years, respectively (see section 4.4).

Rare post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with adalimumab (see section 4.4).

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis studies I − V. In these trials, 11.9% of patients treated with Humira and 8.1% of placebo and active control − treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at Week 24. Two patients out of 3,441 treated with Humira in all rheumatoid arthritis and psoriatic arthritis studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms.

Hepato-biliary events

In controlled Phase 3 trials of Humira in patients with rheumatoid arthritis and psoriatic arthritis with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.7% of Humira-treated patients and 1.6% of control-treated patients.

In controlled Phase 3 trials of Humira in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations ≥ 3 x ULN occurred in 6.1% of Humira-treated patients and 1.3% of control-treated patients. Most ALT elevations occurred with concomitant methotrexate use. No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial of Humira in patients with polyarticular juvenile idiopathic arthritis who were 2 to < 4 years.

In controlled Phase 3 trials of Humira in patients with Crohn's disease and ulcerative colitis with a control period ranging from 4 to 52 weeks. ALT elevations ≥ 3 x ULN occurred in 0.9% of Humira-treated patients and 0.9% of controlled-treated patients.

In the Phase 3 trial of Humira in patients with paediatric Crohn's disease which evaluated efficacy and safety of two body weight adjusted maintenance dose regimens following body weight adjusted induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients of whom 4 were receiving concomitant immunosuppressants at baseline.

In controlled Phase 3 trials of Humira in patients with plaque Psoriasis with a control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of Humira-treated patients and 1.8% of control-treated patients.

No ALT elevations ≥ 3 X ULN occurred in the Phase 3 trial of Humira in paediatric patients with plaque psoriasis.

In controlled trials of Humira (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in patients with hidradenitis suppurativa with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of Humira-treated patients and 0.6% of control-treated patients.

In controlled trials of Humira (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis up to 80 weeks with a median exposure of 166.5 days and 105.0 days in Humira-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of Humira-treated patients and 2.4% of control-treated patients.

Across all indications in clinical trials patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have also been post-marketing reports of liver failure as well as less severe liver disorders that may precede liver failure, such as hepatitis including autoimmune hepatitis in patients receiving adalimumab.

Concurrent treatment with azathioprine/6-mercaptopurine

In adult Crohn's disease studies, higher incidences of malignant and serious infection-related adverse events were seen with the combination of Humira and azathioprine/6-mercaptopurine compared with Humira alone.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No dose-limiting toxicity was observed during clinical trials. The highest dose level evaluated has been multiple intravenous doses of 10 mg/kg, which is approximately 15 times the recommended dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors. ATC code: L04AB04

Mechanism of action

Adalimumab binds specifically to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of0.1-0.2 nM).

Pharmacodynamic effects

After treatment with Humira, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL-6) was observed, compared to baseline in patients with rheumatoid arthritis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after Humira administration. Patients treated with Humira usually experienced improvement in haematological signs of chronic inflammation.

A rapid decrease in CRP levels was also observed in patients with polyarticular juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis and hidradenitis suppurativa after treatment with Humira. In patients with Crohn's disease, a reduction of the number of cells expressing inflammatory markers in the colon including a significant reduction of expression of TNFα was seen. Endoscopic studies in intestinal mucosa have shown evidence of mucosal healing in adalimumab treated patients.

Clinical efficacy and safety

Psoriasis

The safety and efficacy of Humira were studied in adult patients with chronic plaque psoriasis (≥ 10% BSA involvement and Psoriasis Area and Severity Index (PASI) ≥ 12 or ≥ 10) who were candidates for systemic therapy or phototherapy in randomised, double-blind studies. 73% of patients enrolled in Psoriasis Studies I and II had received prior systemic therapy or phototherapy. The safety and efficacy of Humira were also studied in adult patients with moderate to severe chronic plaque psoriasis with concomitant hand and/or foot psoriasis who were candidates for systemic therapy in a randomised double-blind study (Psoriasis Study III).

Psoriasis Study I (REVEAL) evaluated 1,212 patients within three treatment periods. In period A, patients received placebo or Humira at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. After 16 weeks of therapy, patients who achieved at least a PASI 75 response (PASI score improvement of at least 75% relative to baseline), entered period B and received open-label 40 mg Humira every other week. Patients who maintained ≥PASI 75 response at Week 33 and were originally randomised to active therapy in Period A, were re-randomised in period C to receive 40 mg Humira every other week or placebo for an additional 19 weeks. Across all treatment groups, the mean baseline PASI score was 18.9 and the baseline Physician's Global Assessment (PGA) score ranged from "moderate" (53% of subjects included) to "severe" (41%) to "very severe" (6%).

Psoriasis Study II (CHAMPION) compared the efficacy and safety of Humira *versus* methotrexate and placebo in 271 patients. Patients received placebo, an initial dose of MTX 7.5 mg and thereafter dose increases up to Week 12, with a maximum dose of 25 mg or an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) for 16 weeks. There are no data available comparing Humira and MTX beyond 16 weeks of therapy. Patients receiving MTX who achieved a ≥PASI 50 response at Week 8 and/or 12 did not receive further dose increases. Across all treatment groups, the mean baseline PASI score was 19.7 and the baseline PGA score ranged from "mild" (<1%) to "moderate" (48%) to "severe" (46%) to "very severe" (6%).

Patients participating in all Phase 2 and Phase 3 psoriasis studies were eligible to enrol into an open-label extension trial, where Humira was given for at least an additional 108 weeks.

In Psoriasis Studies I and II, a primary endpoint was the proportion of patients who achieved a PASI 75 response from baseline at Week 16 (see Tables 2 and 3).

Table 2
Ps Study I (REVEAL) - Efficacy Results at 16 Weeks

	Placebo N=398 n (%)	**Humira 40 mg eow N=814 n (%)**
≥ PASI 75[a]	26 (6.5)	578 (70.9)[b]
PASI 100	3 (0.8)	163 (20.0)[b]
PGA: Clear/minimal	17 (4.3)	506 (62.2)[b]

[a] Percent of patients achieving PASI75 response was calculated as centre-adjusted rate
[b] $p < 0.001$, Humira vs. placebo

Table 3
Ps Study II (CHAMPION) Efficacy Results at 16 Weeks

	Placebo N=53 n (%)	**MTX N=110 n (%)**	**Humira 40 mg eow N=108 n (%)**
≥ PASI 75	10 (18.9)	39 (35.5)	86 (79.6) [a, b]
PASI 100	1 (1.9)	8 (7.3)	18 (16.7) [c, d]
PGA: Clear/minimal	6 (11.3)	33 (30.0)	79 (73.1) [a, b]

[a] $p < 0.001$ Humira vs. placebo
[b] $p < 0.001$ Humira vs. methotrexate
[c] $p < 0.01$ Humira vs. placebo
[d] $p < 0.05$ Humira vs. methotrexate

In Psoriasis Study I, 28% of patients who were PASI 75 responders and were re-randomised to placebo at Week 33 compared to 5% continuing on Humira, $p < 0.001$, experienced "loss of adequate response" (PASI score after Week 33 and on or before Week 52 that resulted in a <PASI 50 response relative to baseline with a minimum of a 6-point increase in PASI score relative to Week 33). Of the patients who lost adequate response after re-randomisation to placebo who then enrolled into the open-label extension trial, 38% (25/66) and 55% (36/66) regained PASI 75 response after 12 and 24 weeks of re-treatment, respectively.

A total of 233 PASI 75 responders at Week 16 and Week 33 received continuous Humira therapy for 52 weeks in Psoriasis Study I, and continued Humira in the open-label extension trial. PASI 75 and PGA of clear or minimal response rates in these patients were 74.7% and 59.0%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks). In an analysis in which all patients who dropped out of the study for adverse events or lack of efficacy, or who dose-escalated, were considered non-responders, PASI 75 and PGA of clear or minimal response rates in these patients were 69.6% and 55.7%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. During the withdrawal period, symptoms of psoriasis returned over time with a median time to relapse (decline to PGA "moderate" or worse) of approximately 5 months. None of these patients experienced rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the retreatment period had a response of PGA "clear" or "minimal" after 16 weeks of retreatment, irrespective of whether they relapsed during withdrawal (69.1%[123/178] and 88.8% [95/107] for patients who relapsed and who did not relapse during the withdrawal period, respectively). A similar safety profile was observed during retreatment as before withdrawal.

Significant improvements at Week 16 from baseline compared to placebo (Studies I and II) and MTX (Study II) were demonstrated in the DLQI (Dermatology Life Quality Index). In Study I, improvements in the physical and mental component summary scores of the SF-36 were also significant compared to placebo.

In an open-label extension study, for patients who dose escalated from 40 mg every other week to 40 mg weekly due to a PASI response below 50%, 26.4% (92/349) and 37.8% (132/349) of patients achieved PASI 75 response at Week 12 and 24, respectively.

Psoriasis Study III (REACH) compared the efficacy and safety of Humira *versus* placebo in 72 patients with moderate to severe chronic plaque psoriasis and hand and/or foot psoriasis. Patients received an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) or placebo for 16 weeks. At Week 16, a statistically significantly greater proportion of patients who received Humira achieved PGA of 'clear' or 'almost clear' for the hands and/or feet compared to patients who received placebo (30.6% versus 4.3%, respectively [P = 0.014]).

Psoriasis Study IV compared efficacy and safety of Humira versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open-label Humira treatment for an additional 26 weeks. Nail psoriasis assessments included the Modified Nail Psoriasis Severity Index (mNAPSI), the Physician's Global Assessment of Fingernail Psoriasis (PGA-F) and the Nail Psoriasis Severity Index (NAPSI) (see Table 4). Humira demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement (BSA≥10% (60% of patients) and BSA<10% and ≥5% (40% of patients)).

Table 4
Ps Study IV Efficacy Results at 16, 26 and 52 Weeks

Endpoint	Week 16 Placebo-Controlled		Week 26 Placebo-Controlled		Week 52 Open-label
	Placebo N=108	Humira 40 mg eow N=109	Placebo N=108	Humira 40 mg eow N=109	Humira 40 mg eow N=80
≥ mNAPSI 75 (%)	2.9	26.0[a]	3.4	46.6[a]	65.0
PGA-F clear/minimal and ≥2-grade improvement (%)	2.9	29.7[a]	6.9	48.9[a]	61.3
Percent Change in Total Fingernail NAPSI (%)	-7.8	-44.2 [a]	-11.5	-56.2[a]	-72.2
[a] p<0.001, Humira *vs.* placebo					

Humira treated patients showed statistically significant improvements at Week 26 compared with placebo in the DLQI.

Hidradenitis suppurativa

The safety and efficacy of Humira were assessed in randomised, double-blind, placebo-controlled studies and an open-label extension study in adult patients with moderate to severe hidradenitis suppurativa (HS) who were intolerant, had a contraindication or an inadequate response to at least a 3-month trial of systemic antibiotic therapy. The patients in HS-I and HS-II had Hurley Stage II or III disease with at least 3 abscesses or inflammatory nodules.

Study HS-I (PIONEER I) evaluated 307 patients with 2 treatment periods. In Period A, patients received placebo or Humira at an initial dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every week starting at Week 4 to Week 11. Concomitant antibiotic use was not allowed during the study. After 12 weeks of therapy, patients who had received Humira in Period A were re-randomised in Period B to 1 of 3 treatment groups (Humira 40 mg every week, Humira 40 mg every other week,

or placebo from Week 12 to Week 35). Patients who had been randomised to placebo in Period A were assigned to receive Humira 40 mg every week in Period B.

Study HS-II (PIONEER II) evaluated 326 patients with 2 treatment periods. In Period A, patients received placebo or Humira at an initial dose of 160 mg at Week 0 and 80 mg at Week 2 and 40 mg every week starting at Week 4 to Week 11. 19.3% of patients had continued baseline oral antibiotic therapy during the study. After 12 weeks of therapy, patients who had received Humira in Period A were re-randomised in Period B to 1 of 3 treatment groups (Humira 40 mg every week, Humira 40 mg every other week, or placebo from Week 12 to Week 35). Patients who had been randomised to placebo in Period A were assigned to receive placebo in Period B.

Patients participating in Studies HS-I and HS-II were eligible to enrol into an open-label extension study in which Humira 40mg was administered every week. Mean exposure in all adalimumab population was 762 days. Throughout all 3 studies patients used topical antiseptic wash daily.

Clinical Response

Reduction of inflammatory lesions and prevention of worsening of abscesses and draining fistulas was assessed using Hidradenitis Suppurativa Clinical Response (HiSCR; at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count relative to Baseline). Reduction in HS-related skin pain was assessed using a Numeric Rating Scale in patients who entered the study with an initial baseline score of 3 or greater on a 11 point scale.

At Week 12, a significantly higher proportion of patients treated with Humira versus placebo achieved HiSCR. At Week 12, a significantly higher proportion of patients in Study HS-II experienced a clinically relevant decrease in HS-related skin pain (see Table 5). Patients treated with Humira had significantly reduced risk of disease flare during the initial 12 weeks of treatment.

Table 5: Efficacy Results at 12 Weeks, HS Studies I and II

	HS Study I		**HS Study II**	
	Placebo	**Humira 40 mg Weekly**	**Placebo**	**Humira 40 mg Weekly**
Hidradenitis Suppurativa Clinical Response (HiSCR)[a]	N = 154 40 (26.0%)	N = 153 64 (41.8%) *	N=163 45 (27.6%)	N=163 96 (58.9%) ***
≥30% Reduction in Skin Pain[b]	N = 109 27 (24.8%)	N = 122 34 (27.9%)	N=111 23 (20.7%)	N=105 48 (45.7%) ***
* $P < 0.05$, ***$P < 0.001$, Humira versus placebo [c] Among all randomised patients. [d] Among patients with baseline HS-related skin pain assessment ≥ 3, based on Numeric Rating Scale 0 – 10; 0 = no skin pain, 10 = skin pain as bad as you can imagine.				

Treatment with Humira 40 mg every week significantly reduced the risk of worsening of abscesses and draining fistulas. Approximately twice the proportion of patients in the placebo group in the first 12 weeks of Studies HS-I and HS-II, compared with those in the Humira group experienced worsening of abscesses (23.0% vs 11.4%, respectively) and draining fistulas (30.0% vs 13.9%, respectively).

Greater improvements at Week 12 from baseline compared to placebo were demonstrated in skin-specific health-related quality of life, as measured by the Dermatology Life Quality Index (DLQI; Studies HS-I and HS-II), patient global satisfaction with medication treatment as measured by the Treatment Satisfaction Questionnaire - medication (TSQM; Studies HS-I and HS-II), and physical health as measured by the physical component summary score of the SF-36 (Study HS-I).

In patients with at least a partial response to Humira 40 mg weekly at Week 12, the HiSCR rate at Week 36 was higher in patients who continued weekly Humira than in patients in whom dosing frequency was reduced to every other week, or in whom treatment was withdrawn (see Table 6).

Table 6: Proportion of Patients[a] Achieving HiSCR[b] at Weeks 24 and 36 After Treatment Reassignment from Weekly Humira at Week 12

	Placebo (treatment withdrawal) N = 73	**Humira 40 mg every other week N = 70**	**Humira 40 mg weekly N = 70**
Week 24	24 (32.9%)	36 (51.4%)	40 (57.1%)
Week 36	22 (30.1%)	28 (40.0%)	39 (55.7%)

[c] Patients with at least a partial response to Humira 40 mg weekly after 12 weeks of treatment.

[d] Patients meeting protocol-specified criteria for loss of response or no improvement were required to discontinue from the studies and were counted as nonresponders.

Among patients who were at least partial responders at Week 12, and who received continuous weekly Humira therapy, the HiSCR rate at Week 48 was 68.3% and at Week 96 was 65.1%. Longer term treatment with Humira 40 mg weekly for 96 weeks identified no new safety findings.

Among patients whose Humira treatment was withdrawn at Week 12 in Studies HS-I and HS-II, the HiSCR rate 12 weeks after re-introduction of Humira 40 mg weekly returned to levels similar to that observed before withdrawal (56.0 %).

Adolescent hidradenitis suppurativa

There are no clinical trials with Humira in adolescent patients with HS. Efficacy of adalimumab for the treatment of adolescent patients with HS is predicted based on the demonstrated efficacy and exposure-response relationship in adult HS patients and the likelihood that the disease course, pathophysiology, and drug effects are substantially similar to that of adults at the same exposure levels. Safety of the recommended adalimumab dose in the adolescent HS population is based on cross-indication safety profile of adalimumab in both adults and paediatric patients at similar or more frequent doses (see section 5.2).

Crohn's disease

The safety and efficacy of Humira were assessed in over 1500 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomised, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 80% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies, CD Study I (CLASSIC I) and CD Study II (GAIN). In CD Study I, 299 TNF-antagonist naive patients were randomised to one of four treatment groups; placebo at Weeks 0 and 2, 160 mg Humira at Week 0 and 80 mg at Week 2, 80 mg at Week 0 and 40 mg at Week 2, and 40 mg at Week 0 and 20 mg at Week 2. In CD Study II, 325 patients who had lost response or were intolerant to infliximab were randomised to receive either 160 mg Humira at Week 0 and 80 mg at Week 2 or placebo at Weeks 0 and 2. The primary non-responders were excluded from the studies and therefore these patients were not further evaluated.

Maintenance of clinical remission was evaluated in CD study III (CHARM). In CD Study III, 854 patients received open-label 80 mg at Week 0 and 40 mg at Week 2. At Week 4 patients were

randomised to 40 mg every other week, 40 mg every week, or placebo with a total study duration of 56 weeks. Patients in clinical response (decrease in CDAI ≥ 70) at Week 4 were stratified and analysed separately from those not in clinical response at Week 4. Corticosteroid taper was permitted after Week 8.

CD study I and CD study II induction of remission and response rates are presented in Table 7.

Table 7
Induction of Clinical Remission and Response
(Percent of Patients)

	CDStudy I: Infliximab Naive Patients			**CD Study II: Infliximab Experienced Patients**	
	Placebo N=74	**Humira 80/40 mg N = 75**	**Humira 160/80 mg N=76**	**Placebo N=166**	**Humira 160/80 mg N=159**
Week 4					
Clinical remission	12%	24%	36%*	7%	21%*
Clinical response (CR-100)	24%	37%	49%**	25%	38%**

All p-values are pairwise comparisons of proportions for Humira *versus* placebo

* $p < 0.001$

** $p < 0.01$

Similar remission rates were observed for the 160/80 mg and 80/40 mg induction regimens by Week 8 and adverse events were more frequently noted in the 160/80 mg group.

In CD Study III, at Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. Of those in clinical response at Week 4, 48% had been previously exposed to other TNF-antagonists. Maintenance of remission and response rates are presented in Table 8. Clinical remission results remained relatively constant irrespective of previous TNF-antagonist exposure.

Disease-related hospitalisations and surgeries were statistically significantly reduced with adalimumab compared with placebo at Week 56.

Table 8
Maintenance of Clinical Remission and Response
(Percent of Patients)

	Placebo	40 mg Humira every other week	40 mg Humira every week
Week 26	**N=170**	**N=172**	**N=157**
Clinical remission	17%	40%*	47%*
Clinical response (CR-100)	27%	52%*	52%*
Patients in steroid-free remission for >=90 days[a]	3% (2/66)	19% (11/58)**	15% (11/74)**
Week 56	**N=170**	**N=172**	**N=157**
Clinical remission	12%	36%*	41%*
Clinical response (CR-100)	17%	41%*	48%*
Patients in steroid-free remission for > = 90 days[a]	5% (3/66)	29% (17/58)*	20% (15/74)**

* $p < 0.001$ for Humira *versus* placebo pairwise comparisons of proportions

** $p < 0.02$ for Humira *versus* placebo pairwise comparisons of proportions

[a] Of those receiving corticosteroids at baseline

Among patients who were not in response at Week 4, 43% of Humira maintenance patients responded by Week 12 compared to 30% of placebo maintenance patients. These results suggest that some patients who have not responded by Week 4 benefit from continued maintenance therapy through Week 12. Therapy continued beyond 12 weeks did not result in significantly more responses (see section 4.2).

117/276 patients from CD study I and 272/777 patients from CD studies II and III were followed through at least 3 years of open-label adalimumab therapy. 88 and 189 patients, respectively, continued to be in clinical remission. Clinical response (CR-100) was maintained in 102 and 233 patients, respectively.

Quality of life

In CD Study I and CD Study II, statistically significant improvement in the disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at Week 4 in patients randomised to Humira 80/40 mg and 160/80 mg compared to placebo and was seen at Weeks 26 and 56 in CD Study III as well among the adalimumab treatment groups compared to the placebo group.

Paediatric Crohn's disease

Humira was assessed in a multicentre, randomised, double-blind clinical trial designed to evaluate the efficacy and safety of induction and maintenance treatment with doses dependent on body weight (< 40 kg or ≥ 40 kg) in 192 paediatric subjects between the ages of 6 and 17 (inclusive) years, with moderate to severe Crohn´s disease (CD) defined as Paediatric Crohn's Disease Activity Index (PCDAI) score > 30. Subjects had to have failed conventional therapy (including a corticosteroid and/or an immunomodulator) for CD. Subjects may also have previously lost response or been intolerant to infliximab.

All subjects received open-label induction therapy at a dose based on their Baseline body weight: 160 mg at Week 0 and 80 mg at Week 2 for subjects ≥ 40 kg, and 80 mg and 40 mg, respectively, for subjects < 40 kg.

At Week 4, subjects were randomised 1:1 based on their body weight at the time to either the Low Dose or Standard Dose maintenance regimens as shown in Table 9.

Table 9
Maintenance regimen

Patient Weight	**Low dose**	**Standard dose**
< 40 kg	10 mg eow	20 mg eow
≥ 40 kg	20 mg eow	40 mg eow

Efficacy results

The primary endpoint of the study was clinical remission at Week 26, defined as PCDAI score ≤ 10.

Clinical remission and clinical response (defined as reduction in PCDAI score of at least 15 points from Baseline) rates are presented in Table 10. Rates of discontinuation of corticosteroids or immunomodulators are presented in Table 11.

Table 10
Paediatric CD Study
PCDAI Clinical Remission and Response

	Standard Dose 40/20 mg eow N = 93	**Low Dose 20/10 mg eow N = 95**	**P value***
Week 26			
Clinical remission	38.7%	28.4%	0.075
Clinical response	59.1%	48.4%	0.073
Week 52			
Clinical remission	33.3%	23.2%	0.100
Clinical response	41.9%	28.4%	0.038
* p value for Standard Dose *versus* Low Dose comparison.			

Table 11
Paediatric CD Study
Discontinuation of Corticosteroids or Immunomodulators and Fistula Remission

	Standard Dose 40/20 mg eow	**Low Dose 20/10 mg eow**	**P value[1]**
Discontinued corticosteroids	**N= 33**	**N=38**	
Week 26	84.8%	65.8%	0.066
Week 52	69.7%	60.5%	0.420
Discontinuation of Immunomodulators[2]	**N=60**	**N=57**	
Week 52	30.0%	29.8%	0.983
Fistula remission[3]	**N=15**	**N=21**	
Week 26	46.7%	38.1%	0.608
Week 52	40.0%	23.8%	0.303

[1] p value for Standard Dose *versus* Low Dose comparison.
[2] Immunosuppressant therapy could only be discontinued at or after Week 26 at the investigator's discretion if the subject met the clinical response criterion
[3] defined as a closure of all fistulas that were draining at Baseline for at least 2 consecutive post-Baseline visits

Statistically significant increases (improvement) from Baseline to Week 26 and 52 in Body Mass Index and height velocity were observed for both treatment groups.

Statistically and clinically significant improvements from Baseline were also observed in both treatment groups for quality of life parameters (including IMPACT III).

One hundred patients (n=100) from the Paediatric CD Study continued in an open-label long-term extension study. After 5 years of adalimumab therapy, 74.0% (37/50) of the 50 patients remaining in the study continued to be in clinical remission, and 92.0% (46/50) of patients continued to be in clinical response per PCDAI.

Ulcerative colitis

The safety and efficacy of multiple doses of Humira were assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopy subscore of 2 to 3) in randomised, double-blind, placebo-controlled studies.

In study UC-I, 390 TNF-antagonist naïve patients were randomised to receive either placebo at Weeks 0 and 2, 160 mg Humira at Week 0 followed by 80 mg at Week 2, or 80 mg Humira at Week 0 followed by 40 mg at Week 2. After Week 2, patients in both adalimumab arms received 40 mg eow. Clinical remission (defined as Mayo score ≤ 2 with no subscore > 1) was assessed at Week 8.

In study UC-II, 248 patients received 160 mg of Humira at Week 0, 80 mg at Week 2 and 40 mg eow thereafter, and 246 patients received placebo. Clinical results were assessed for induction of remission at Week 8 and for maintenance of remission at Week 52.

Patients induced with 160/80 mg Humira achieved clinical remission versus placebo at Week 8 in statistically significantly greater percentages in study UC-I (18% vs. 9% respectively, p=0.031) and study UC-II (17% vs. 9% respectively, p=0.019). In study UC-II, among those treated with Humira who were in remission at Week 8, 21/41 (51%) were in remission at Week 52.

Results from the overall UC-II study population are shown in Table 12.

Table 12

Response, Remission and Mucosal Healing in Study UC-II

(Percent of Patients)

	Placebo	**Humira 40 mg eow**
Week 52	**N=246**	**N=248**
Clinical Response	18%	30%*
Clinical Remission	9%	17%*
Mucosal Healing	15%	25%*
Steroid-free remission for ≥ 90 days [a]	6% (N=140)	13% * (N=150)
Week 8 and 52		
Sustained Response	12%	24%**
Sustained Remission	4%	8%*
Sustained Mucosal Healing	11%	19%*

Clinical remission is Mayo score ≤ 2 with no subscore > 1;
Clinical response is decrease from baseline in Mayo score ≥ 3 points and ≥ 30% plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1;
* $p < 0.05$ for Humira *vs.* placebo pairwise comparison of proportions
** $p < 0.001$ for Humira *vs.* placebo pairwise comparison of proportions
[a] Of those receiving corticosteroids at baseline

Of those patients who had a response at Week 8, 47% were in response, 29% were in remission, 41% had mucosal healing, and 20% were in steroid-free remission for ≥ 90 days at Week 52.

Approximately 40% of patients in study UC-II had failed prior anti-TNF treatment with infliximab. The efficacy of adalimumab in those patients was reduced compared to that in anti-TNF naïve patients. Among patients who had failed prior anti-TNF treatment, Week 52 remission was achieved by 3% on placebo and 10% on adalimumab.

Patients from studies UC-I and UC-II had the option to roll over into an open-label long-term extension study (UC III). Following 3 years of adalimumab therapy, 75% (301/402) continued to be in clinical remission per partial Mayo score.

Hospitalisation rates

During 52 weeks of studies UC-I and UC-II, lower rates of all-cause hospitalisations and UC-related hospitalisations were observed for the adalimumab-treated arm compared to the placebo arm. The number of all cause hospitalisations in the adalimumab treatment group was 0.18 per patient year *vs*. 0.26 per patient year in the placebo group and the corresponding figures for UC-related hospitalisations were 0.12 per patient year *vs.* 0.22 per patient year.

Quality of life

In study UC-II, treatment with adalimumab resulted in improvements in the Inflammatory Bowel Disease Questionnaire (IBDQ) score.

Uveitis

The safety and efficacy of Humira were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis, excluding patients with isolated anterior uveitis, in two randomised, double-masked, placebo-controlled studies (UV I and II). Patients received placebo or Humira at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. Concomitant stable doses of one non-biologic immunosuppressant were permitted.

Study UV I evaluated 217 patients with active uveitis despite treatment with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). All patients received a 2-week standardised dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by Week 15.

Study UV II evaluated 226 patients with inactive uveitis requiring chronic corticosteroid treatment (oral prednisone 10 to 35 mg/day) at baseline to control their disease. Patients subsequently underwent a mandatory taper schedule, with complete corticosteroid discontinuation by Week 19.

The primary efficacy endpoint in both studies was ´time to treatment failure´. Treatment failure was defined by a multi-component outcome based on inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber (AC) cell grade, vitreous haze (VH) grade and best corrected visual acuity (BCVA).

Clinical Response

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with Humira versus patients receiving placebo (See Table 13). Both studies demonstrated an early and sustained effect of Humira on the treatment failure rate versus placebo (see Figure 1).

Table 13
Time to Treatment Failure in Studies UV I and UV II

Analysis Treatment	N	Failure N (%)	Median Time to Failure (months)	HR[a]	CI 95% for HR[a]	*P* Value[b]
Time to Treatment Failure At or After Week 6 in Study UV I						
Primary analysis (ITT)						
Placebo	107	84 (78.5)	3.0	--	--	--
Adalimumab	110	60 (54.5)	5.6	0.50	0.36, 0.70	< 0.001
Time to Treatment Failure At or After Week 2 in Study UV II						
Primary analysis (ITT)						
Placebo	111	61 (55.0)	8.3	--	--	--
Adalimumab	115	45 (39.1)	NE[c]	0.57	0.39, 0.84	0.004

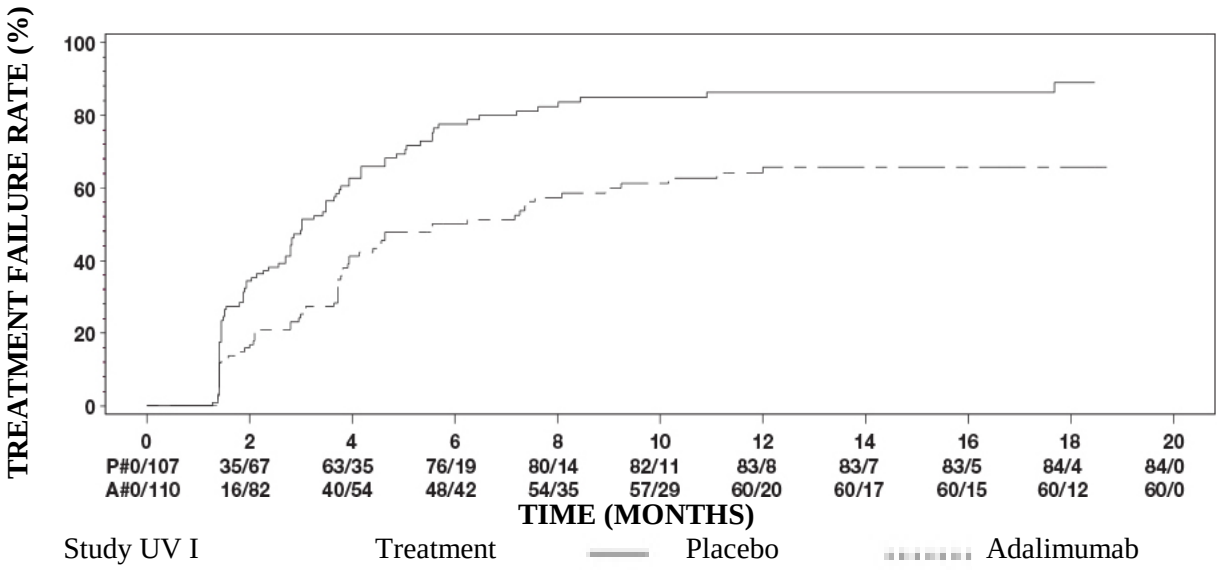
Note: Treatment failure at or after Week 6 (Study UV I), or at or after Week 2 (Study UV II), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

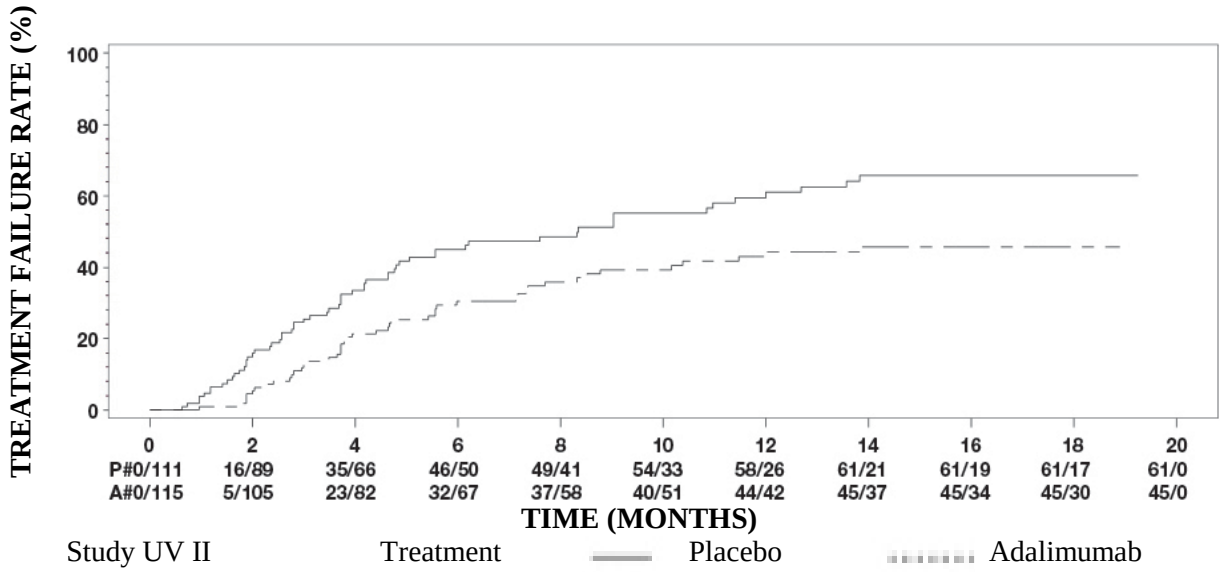
[a] HR of adalimumab vs placebo from proportional hazards regression with treatment as factor.

[b] 2-sided *P* value from log rank test.

[c] NE = not estimable. Fewer than half of at-risk subjects had an event.

Figure 1: Kaplan-Meier Curves Summarizing Time to Treatment Failure on or after Week 6 (Study UV I) or Week 2 (Study UV II)





Note: P# = Placebo (Number of Events/Number at Risk); A# = HUMIRA (Number of Events/Number at Risk).

In Study UV I statistically significant differences in favour of adalimumab versus placebo were observed for each component of treatment failure. In Study UV II, statistically significant differences were observed for visual acuity only, but the other components were numerically in favour of adalimumab.

Quality of Life

Patient reported outcomes regarding vision-related functioning were measured in both clinical studies, using the NEI VFQ-25. Humira was numerically favoured for the majority of subscores with statistically significant mean differences for general vision, ocular pain, near vision, mental health, and total score in Study UV I, and for general vision and mental health in Study UV II. Vision related effects were not numerically in favour of Humira for colour vision in Study UVI and for colour vision, peripheral vision and near vision in Study UV II.

Paediatric Uveitis

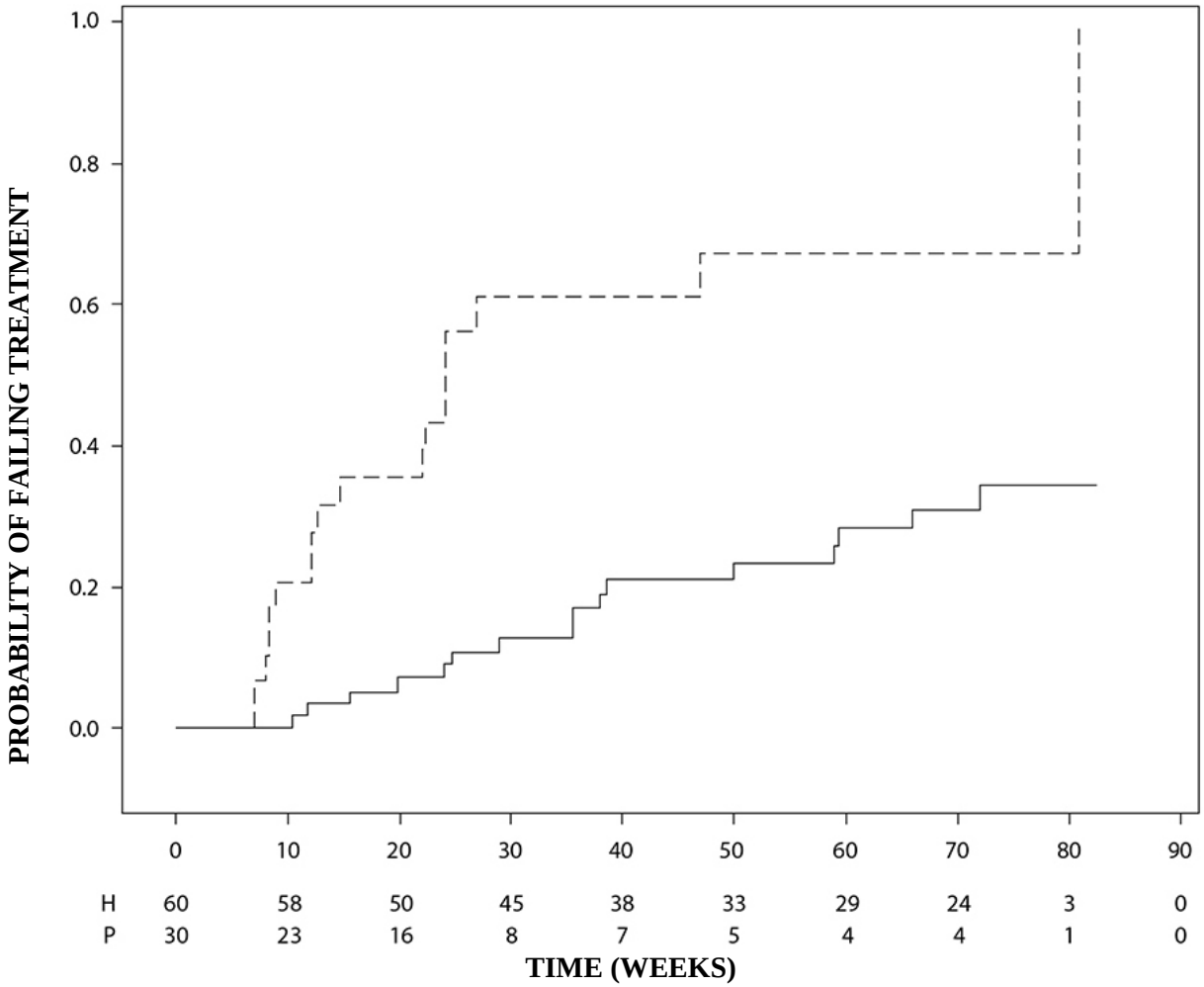
The safety and efficacy of Humira was assessed in a randomized, double-masked, controlled study of 90 paediatric patients from 2 to < 18 years of age with active JIA-associated noninfectious anterior uveitis who were refractory to at least 12 weeks of methotrexate treatment. Patients received either placebo or 20 mg adalimumab (if < 30 kg) or 40 mg adalimumab (if ≥ 30 kg) every other week in combination with their baseline dose of methotrexate.

The primary endpoint was 'time to treatment failure'. The criteria determining treatment failure were worsening or sustained non-improvement in ocular inflammation, partial improvement with development of sustained ocular co-morbidities or worsening of ocular co-morbidities, non-permitted use of concomitant medications, and suspension of treatment for an extended period of time.

Clinical Response

Adalimumab significantly delayed the time to treatment failure, as compared to placebo (See Figure 2, P < 0.0001 from log rank test).The median time to treatment failure was 24.1 weeks for subjects treated with placebo, whereas the median time to treatment failure was not estimable for subjects treated with adalimumab because less than one-half of these subjects experienced treatment failure. Adalimumab significantly decreased the risk of treatment failure by 75% relative to placebo, as shown by the hazard ratio (HR = 0.25 [95% CI: 0.12, 0.49]).

Figure 2: Kaplan-Meier Curves Summarizing Time to Treatment Failure in the Paediatric Uveitis Study



Note: P = Placebo (Number at Risk); H = HUMIRA (Number at Risk).

Immunogenicity

Formation of anti-adalimumab antibodies is associated with increased clearance and reduced efficacy of adalimumab. There is no apparent correlation between the presence of anti-adalimumab antibodies and the occurrence of adverse events.

In patients with Crohn's disease, anti-adalimumab antibodies were identified in 7/269 subjects (2.6%) and in 19/487 subjects (3.9%) with ulcerative colitis.

In adult patients with psoriasis, anti-adalimumab antibodies were identified in 77/920 subjects (8.4%) treated with adalimumab monotherapy.

In adult plaque psoriasis patients on long term adalimumab monotherapy who participated in a withdrawal and retreatment study, the rate of antibodies to adalimumab after retreatment (11 of 482 subjects, 2.3%) was similar to the rate observed prior to withdrawal (11 of 590 subjects, 1.9%).

In patients with moderate to severe hidradenitis suppurativa, anti-adalimumab antibodies were identified in 10/99 subjects (10.1%) treated with adalimumab.

In patients with moderately to severely active paediatric Crohn's disease, the rate of anti-adalimumab antibody development in patients receiving adalimumab was 3.3%.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab.

Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of the studies with Humira in one or more subsets of the paediatric population in ulcerative colitis, see section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption and distribution

After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. After single intravenous doses ranging from 0.25 to 10 mg/kg, concentrations were dose proportional. After doses of 0.5 mg/kg (~40 mg), clearances ranged from 11 to 15 ml/hour, the distribution volume (V_{ss}) ranged from 5 to 6 litres and the mean terminal phase half-life was approximately two weeks. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31-96% of those in serum.

In adult patients with psoriasis, the mean steady-state trough concentration was 5 μg/ml during adalimumab 40 mg every other week monotherapy treatment.

In adult patients with hidradenitis suppurativa, a dose of 160 mg Humira on Week 0 followed by 80 mg on Week 2 achieved serum adalimumab trough concentrations of approximately 7 to 8 μg/ml at Week 2 and Week 4. The mean steady-state trough concentration at Week 12 through Week 36 were approximately 8 to 10 μg/ml during adalimumab 40 mg every week treatment.

Adalimumab exposure in adolescent HS patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent HS dosing schedule is 40 mg every other week. Since exposure to adalimumab can be affected by body size, adolescents with higher body weight and inadequate response may benefit from receiving the recommended adult dose of 40 mg every week.

In patients with Crohn's disease, the loading dose of 80 mg Humira on Week 0 followed by 40 mg Humira on Week 2 achieves serum adalimumab trough concentrations of approximately 5.5 μg/ml during the induction period. A loading dose of 160 mg Humira on Week 0 followed by 80 mg Humira on Week 2 achieves serum adalimumab trough concentrations of approximately 12 μg/ml during the induction period. Mean steady-state trough levels of approximately 7 μg/ml were observed in Crohn's disease patients who received a maintenance dose of 40 mg Humira every other week.

In paediatric patients with moderate to severe CD, the open-label adalimumab induction dose was 160/80 mg or 80/40 mg at Weeks 0 and 2, respectively, dependent on a body weight cut-off of 40 kg. At Week 4, patients were randomised 1:1 to either the Standard Dose (40/20 mg eow) or Low Dose (20/10 mg eow) maintenance treatment groups based on their body weight. The mean (±SD) serum adalimumab trough concentrations achieved at Week 4 were 15.7 ± 6.6 μg/ml for patients ≥ 40 kg (160/80 mg) and 10.6 ± 6.1 μg/ml for patients < 40 kg (80/40 mg).

For patients who stayed on their randomised therapy, the mean (±SD) adalimumab trough concentrations at Week 52 were 9.5 ± 5.6 μg/ml for the Standard Dose group and 3.5 ± 2.2 μg/ml for the Low Dose group. The mean trough concentrations were maintained in patients who continued to receive adalimumab treatment eow for 52 weeks. For patients who dose escalated from eow to weekly regimen, the mean (±SD) serum concentrations of adalimumab at Week 52 were 15.3 ± 11.4 μg/ml (40/20 mg, weekly) and 6.7 ± 3.5 μg/ml (20/10 mg, weekly).

In patients with ulcerative colitis, a loading dose of 160 mg Humira on Week 0 followed by 80 mg Humira on Week 2 achieves serum adalimumab trough concentrations of approximately 12 μg/ml during the induction period. Mean steady-state trough levels of approximately 8 μg/ml were observed in ulcerative colitis patients who received a maintenance dose of 40 mg Humira every other week.

In patients with uveitis, a loading dose of 80 mg adalimumab on Week 0 followed by 40 mg adalimumab every other week starting at Week 1, resulted in mean steady-state concentrations of approximately 8 to 10 μg/mL.

Adalimumab exposure in paediatric uveitis patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). No clinical exposure data are available on the use of a loading dose in children < 6 years. The predicted exposures indicate that in the absence of methotrexate, a loading dose may lead to an initial increase in systemic exposure.

Elimination

Population pharmacokinetic analyses with data from over 1,300 RA patients revealed a trend toward higher apparent clearance of adalimumab with increasing body weight. After adjustment for weight differences, gender and age appeared to have a minimal effect on adalimumab clearance. The serum levels of free adalimumab (not bound to anti-adalimumab antibodies, AAA) were observed to be lower in patients with measurable AAA.

Hepatic or renal impairment

Humira has not been studied in patients with hepatic or renal impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity.

An embryo-foetal developmental toxicity/perinatal developmental study has been performed in cynomologous monkeys at 0, 30 and 100 mg/kg (9-17 monkeys/group) and has revealed no evidence of harm to the foetuses due to adalimumab. Neither carcinogenicity studies, nor a standard assessment of fertility and postnatal toxicity, were performed with adalimumab due to the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and to the development of neutralising antibodies in rodents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the pre-filled syringe or pre-filled pen in its outer carton in order to protect from light.

A single Humira pre-filled syringe or pre-filled pen may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. The syringe or pen must be protected from light, and discarded if not used within the 14 -day period.

6.5 Nature and contents of container

Humira 80 mg solution for injection in pre-filled syringe
Humira 80 mg solution for injection in single-use pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

Packs of:
- 1 pre-filled syringe (0.8 ml sterile solution) with 1 alcohol pad in a blister.

Humira 80 mg solution for injection in pre-filled pen
Humira 80 mg solution for injection in single-use pre-filled pen for patient use containing a pre-filled syringe. The syringe inside the pen is made from type 1 glass with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

Packs of:
- 1 pre-filled pen (0.8 ml sterile solution), with 2 alcohol pads in a blister.

Not all presentations or pack sizes may be marketed.

6.6 Special precautions for disposal

Humira does not contain preservatives. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

Humira 80 mg solution for injection in pre-filled syringe
EU/1/03/256/020

Humira 80 mg solution for injection in pre-filled pen
EU/1/03/256/021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 September 2003
Date of latest renewal: 08 September 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

AbbVie Bioresearch Center
100 Research Drive
Worcester
MA 01605
USA

and

AbbVie Biotechnology Ltd.
Road No. 2, Km. 59.2
Barceloneta
Puerto Rico 00617

and

Lonza Biologics Porriño,S.L
A Relva s/n
36400 O Porriño
Pontevedra, Spain

and

Lonza Biologics Tuas PTE Ltd
35 Tuas South Ave 6
Singapore 637377

Name and address of the manufacturers responsible for batch release

AbbVie Biotechnology GmbH
Max-Planck-Ring 2
D-65205 Wiesbaden
Germany

and

AbbVie Biotechnology GmbH
Knollstrasse
67061 Ludwigshafen
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that the Educational programme is implemented for currently authorised indications. This programme shall ensure that physicians who intend to prescribe Humira are aware of:

- the risk of serious infections, sepsis, tuberculosis and other opportunistic infections
- the risk of heart failure
- the risk of central nervous system demyelination
- the risk of malignancies
- the Patient Alert Card is to be given to patients using Humira

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR VIAL MULITPACK, COMPRISING OF 2 PACKS

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg/0.8 ml solution for injection for paediatric use
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.8 ml vial contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Contains 2 cartons each for a single injection only
Each carton contains:
1 vial containing 40 mg adalimumab for paediatric use
1 sterile injection syringe
1 sterile needle
1 sterile vial adapter
2 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg/0.8 ml solution for injection for paediatric use
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.8 ml vial contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial containing 40 mg adalimumab for paediatric use
1 sterile injection syringe
1 sterile needle
1 sterile vial adapter
2 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Each item for single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

Not applicable (multipack).

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

Not applicable (multipack).

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Humira 40 mg/0.8 ml injection
Subcutaneous use
adalimumab

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/0.8 ml

6. OTHER

For single use only

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.8 ml pre-filled syringe contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe containing 40 mg adalimumab
1 alcohol pad

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.8 ml pre-filled syringe contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 pre-filled syringes, each containing 40 mg adalimumab
2 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.8 ml pre-filled syringe contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

4 pre-filled syringes, each containing 40 mg adalimumab
4 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.8 ml pre-filled syringe contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

6 pre-filled syringes, each containing 40 mg adalimumab
6 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TRAY BACKING TEXT

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe
adalimumab

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

For storage information, see package leaflet.

For single use only

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Humira 40 mg injection
adalimumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/0.8 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe with needleguard
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.8 ml pre-filled syringe with needleguard contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe containing 40 mg adalimumab
1 alcohol pad

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TRAY BACKING TEXT

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe with needleguard
adalimumab

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

For storage information, see package leaflet.
For single use only

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Humira 40 mg injection
adalimumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/0.8 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled pen
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.8 ml pre-filled pen contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled pen, containing 40 mg adalimumab
2 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled pen
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.8 ml pre-filled pen contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 pre-filled pens, each containing 40 mg adalimumab
2 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled pen
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.8 ml pre-filled pen contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

4 pre-filled pens, each containing 40 mg adalimumab
4 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled pen
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.8 ml pre-filled pen contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

6 pre-filled pens, each containing 40 mg adalimumab
6 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TRAY BACKING TEXT

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled pen
adalimumab

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

For storage information, see package leaflet.
For single use only

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Humira 40 mg injection
adalimumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/0.8 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 1 SYRINGE PACK

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.4 ml pre-filled syringe contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, polysorbate 80, and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe containing 40 mg adalimumab
1 alcohol pad

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 2 SYRINGE PACK

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.4 ml pre-filled syringe contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, polysorbate 80, and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 pre-filled syringes, each containing 40 mg adalimumab
2 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 4 SYRINGE PACK

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.4 ml pre-filled syringe contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, polysorbate 80, and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

4 pre-filled syringes, each containing 40 mg adalimumab
4 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/014

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 6 SYRINGE PACK

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.4 ml pre-filled syringe contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, polysorbate 80, and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

6 pre-filled syringes, each containing 40 mg adalimumab
6 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TRAY BACKING TEXT

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe
adalimumab

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

For storage information, see package leaflet.

For single use only

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Humira 40 mg injection
adalimumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/0.4 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled pen
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.4 ml pre-filled pen contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, polysorbate 80 and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled pen, containing 40 mg adalimumab
2 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled pen
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.4 ml pre-filled pen contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, polysorbate 80 and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 pre-filled pens, each containing 40 mg adalimumab
2 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/017

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled pen
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.4 ml pre-filled pen contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, polysorbate 80 and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

4 pre-filled pens, each containing 40 mg adalimumab
4 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/018

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled pen
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.4 ml pre-filled pen contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, polysorbate 80 and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

6 pre-filled pens, each containing 40 mg adalimumab
6 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/019

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 40 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TRAY BACKING TEXT

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled pen
adalimumab

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

For storage information, see package leaflet.
For single use only
40 mg/0.4 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Humira 40 mg injection
adalimumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/0.4 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 80 mg solution for injection in pre-filled syringe
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.8 ml pre-filled syringe contains 80 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, polysorbate 80, and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe, containing 80 mg adalimumab
1 alcohol pad

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/020

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 80 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TRAY BACKING TEXT

1. NAME OF THE MEDICINAL PRODUCT

Humira 80 mg solution for injection in pre-filled syringe
adalimumab

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

For storage information, see package leaflet.

For single use only

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Humira 80 mg injection
adalimumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Humira 80 mg solution for injection in pre-filled pen
adalimumab

2. STATEMENT OF ACTIVE SUBSTANCE

One 0.8 ml pre-filled pen contains 80 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, polysorbate 80 and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled pen, containing 80 mg adalimumab
2 alcohol pads

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

For single use only

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC-8ºC). Do not freeze.
Refer to package leaflet for alternative storage details.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

12. MARKETING AUTHORISATION NUMBER

EU/1/03/256/021

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Humira 80 mg

17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TRAY BACKING TEXT

1. NAME OF THE MEDICINAL PRODUCT

Humira 80 mg solution for injection in pre-filled pen
adalimumab

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

For storage information, see package leaflet.
For single use only

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Humira 80 mg injection
adalimumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 mg

6. OTHER

REMINDER STICKERS TEXT (included in pack)

Humira

Mark your calendar with the stickers provided to remind you of the date for your next dose.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Humira 40 mg/0.8 ml solution for injection for paediatric use
adalimumab

Read all of this leaflet carefully before your child starts using this medicine because it contains important information.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Alert Card, which contains important safety information that you need to be aware of before your child is given Humira and during treatment with Humira. Keep this Patient Alert Card with you or your child.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as your child's.
- If your child gets any side effects, talk to your child's doctor or pharmacist. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet:

1. What Humira is and what it is used for

Humira contains the active substance adalimumab, a selective immuno suppressive agent.
Humira is intended for treatment of polyarticular juvenile idiopathic arthritis in children 2-17 years, enthesitis-related arthritis in children 6-17 years, Crohn's disease in children 6-17 years, plaque psoriasis in children from 4-17 years, hidradenitis suppurativa in adolescents from 12 years of age, and chronic non-infectious uveitis in children from 2 years of age. It is a medicine that decreases the inflammation process of these diseases. The active ingredient, adalimumab, is a human monoclonal antibody produced by cultured cells. Monoclonal antibodies are proteins that recognise and bind to other unique proteins. Adalimumab binds to a specific protein (tumour necrosis factor or TNFα), which is present at increased levels in inflammatory diseases such as polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, Crohn's disease, hidradenitis suppurativa, plaque psoriasis and uveitis.

Polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis

Polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis are inflammatory diseases.

Humira is used to treat polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis. Your child may first be given other disease-modifying medicines, such as methotrexate. If your child does not respond well enough to these medicines, he/she will be given Humira to treat the polyarticular juvenile idiopathic arthritis or enthesitis-related arthritis.

Paediatric Crohn's disease

Crohn's disease is an inflammatory disease of the digestive tract. Humira is indicated for the treatment of Crohn's disease in children aged 6 to 17 years. Your child will first be given other

medicines. If your child does not respond well enough to these medicines, he/she will be given Humira to reduce the signs and symptoms of Crohn's disease.

Paediatric plaque psoriasis

Plaque psoriasis is a skin condition that causes red, flaky, crusty patches of skin covered with silvery scales. Psoriasis is believed to be caused by a problem with the body's immune system that leads to an increased production of skin cells.

Humira is used to treat severe plaque psoriasis in children and adolescents aged 4 to 17 years in whom topical therapy and phototherapies have either not worked very well or are not suitable.

Adolescent hidradenitis suppurativa

Hidradenitis suppurativa (sometimes called acne inversa) is a chronic and often painful inflammatory skin disease. Symptoms may include tender nodules (lumps) and abscesses (boils) that may leak pus. It most commonly affects specific areas of the skin, such as under the breasts, the armpits, inner thighs, groin and buttocks. Scarring may also occur in affected areas.

Humira is used to treat hidradenitis suppurativa in adolescents from 12 years of age. Humira can reduce the number of nodules and abscesses you have, and the pain that is often associated with the disease. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Chronic non-infectious uveitis in children

Non-infectious uveitis is an inflammatory disease affecting certain parts of the eye.

Humira is used to treat children from 2 years of age with chronic non-infectious uveitis with inflammation affecting the front of the eye. This inflammation may lead to a decrease of vision and/or the presence of floaters in the eye (black dots or wispy lines that move across the field of vision). Humira works by reducing this inflammation.

2. What you need to know before your child uses Humira

Do not use Humira

- If your child is allergic to adalimumab or any of the other ingredients of this medicine (listed in section 6).

- If your child has a severe infection, including active tuberculosis (see "Warnings and precautions"). It is important that you tell your doctor if your child has symptoms of infections, e.g. fever, wounds, feeling tired, dental problems.

- If your child has moderate or severe heart failure. It is important to tell your doctor if your child has had or has a serious heart condition (see "Warnings and precautions").

Warnings and precautions

Talk to your child's doctor or pharmacist before using Humira

- If your child experiences allergic reactions with symptoms such as chest tightness, wheezing, dizziness, swelling or rash do not inject more Humira and contact your doctor immediately.

- If your child has an infection, including long-term or localized infection (for example, leg ulcer) consult your doctor before starting Humira. If you are unsure, please contact your doctor.

- Your child might get infections more easily while receiving Humira treatment. This risk may increase if his/her lung function is impaired. These infections may be serious and include tuberculosis, infections caused by viruses, fungi, parasites or bacteria, or other opportunistic infections and sepsis that may, in rare cases, be life-threatening. It is important to tell your doctor if your child gets symptoms such as fever, wounds, feeling tired or dental problems. Your doctor may recommend temporary discontinuation of Humira.

- As cases of tuberculosis have been reported in patients treated with Humira, your doctor will check your child for signs and symptoms of tuberculosis before starting Humira. This will include a thorough medical evaluation including your child's medical history and appropriate screening tests (for example chest X-ray and a tuberculin test). The conduct and results of these tests should be recorded on your child's Patient Alert Card. It is very important that you tell your doctor if your child has ever had tuberculosis, or if he/she has been in close contact with someone who has had tuberculosis. Tuberculosis can develop during therapy even if your child has received preventative treatment for tuberculosis. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy tell your doctor immediately.

- Advise your doctor if your child resides or travels in regions where fungal infections such as histoplasmosis, coccidioidomycosis or blastomycosis are endemic.

- Advise your doctor if your child has a history of recurrent infections or other conditions that increase the risk of infections.

- Advise your doctor if your child is a carrier of the hepatitis B virus (HBV), if he/she has active HBV or if you think he/she might be at risk of contracting HBV. Your child's doctor should test your child for HBV. Humira can cause reactivation of HBV in people who carry this virus. In some rare cases, especially if your child is taking other medicines that suppress the immune system, reactivation of HBV can be life-threatening.

- It is important to tell your doctor if your child gets symptoms of infections, such as fever, wounds, feeling tired or dental problems.

- If your child is about to undergo surgery or dental procedures please inform your doctor that he/she is taking Humira. Your doctor may recommend temporary discontinuation.

- If your child has or develops a demyelinating disease such as multiple sclerosis, your doctor will decide if he/she should receive or continue to receive Humira. Tell your doctor immediately if your child experiences symptoms like changes in vision, weakness in arms or legs or numbness or tingling in any part of the body.

- Certain vaccines may cause infections and should not be given while receiving Humira. Please check with your doctor before your child receives any vaccines. It is recommended that children, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy. If you received Humira while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately five months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy so they can decide when your baby should receive any vaccine.

- If your child has mild heart failure and is being treated with Humira, his/her heart failure status must be closely monitored by your doctor. It is important to tell your doctor if your child has had or has a serious heart condition. If he/she develops new or worsening symptoms of heart failure (e.g. shortness of breath, or swelling of his/her feet), you must contact your doctor immediately. Your doctor will decide if your child should receive Humira.

- In some patients the body may fail to produce enough of the blood cells that help your child's body fight infections or help him/her to stop bleeding. If your child develops a fever that does not go away, bruises or bleeds very easily or looks very pale, call your doctor right away. Your doctor may decide to stop treatment.

- There have been very rare cases of certain kinds of cancer in children and adult patients taking Humira or other TNF blockers. People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting lymphoma (a kind of cancer that affects the lymph system), and leukemia (a kind of cancer that affects the blood and bone marrow). If your child takes Humira the risk of getting lymphoma, leukemia, or other cancers may increase. On rare occasions, a specific and severe type of lymphoma, has been observed in patients taking Humira. Some of those patients were also treated with azathioprine or 6- mercaptopurine. Tell your doctor if your child is taking azathioprine or 6-mercaptopurine with Humira. In addition cases of non-melanoma skin cancer have been observed in patients taking Humira. If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.

- There have been cases of cancers other than lymphoma in patients with a specific type of lung disease called Chronic Obstructive Pulmonary Disease (COPD) treated with another TNF blocker. If your child has COPD, or is a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for your child.

Children and adolescents

Vaccinations: if possible your child should be up to date with all vaccinations before using Humira.

Do not give Humira to children with polyarticular juvenile idiopathic arthritis below the age of 2 years.

Other medicines and Humira

Tell your child’s doctor or pharmacist if your child is taking, has recently taken or might take any other medicines.

Humira can be taken together with methotrexate or certain disease-modifying anti-rheumatic agents (sulfasalazine, hydroxychloroquine, leflunomide and injectable gold preparations), steroids or pain medications including non-steroidal anti-inflammatory drugs (NSAIDs).

Your child should not take Humira with medicines containing the active substance, anakinra or abatacept. If you have questions, please ask your doctor.

Humira with food and drink

Since Humira is injected under the skin (subcutaneously), food and drink should not affect Humira.

Pregnancy and breast-feeding

The effects of Humira in pregnant women are not known and so the use of Humira in pregnant women is not recommended. Your child is advised to avoid becoming pregnant and must use adequate

contraception while using Humira and for at least 5 months after the last Humira treatment. If your child becomes pregnant, you should consult your doctor.

It is not known whether adalimumab passes into breast milk.

If your child is a breast-feeding mother, she should stop breast-feeding during Humira treatment and for at least 5 months after the last Humira treatment. If you received Humira during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy before the baby receives any vaccine (for more information see section on vaccination).

If you think your child may be pregnant or is planning to have a baby, ask your doctor or pharmacist for advice before they use this medicine.

Driving and using machines

Humira may have a minor influence on the ability to drive, cycle or use machines. Room spinning sensation and vision disturbances may occur after taking Humira.

3. How to use Humira

Always use this medicine exactly as your child's doctor or pharmacist has instructed. Check with your child's doctor or pharmacist if you are not sure about any of the instructions or if you have any questions.

Children with polyarticular juvenile idiopathic arthritis

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 2 to 12 years depends on the height and weight of your child. Your child's doctor will tell you the correct dose to use.

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 13 to 17 years, is 40 mg every other week.

Children with enthesitis-related arthritis

The recommended dose of Humira for patients with enthesitis-related arthritis, aged 6 to 17 years depends on the height and weight of the child.

Children or adolescents with Crohn's disease

Children or adolescents weighing less than 40 kg:

The usual dose regimen is 40 mg initially followed by 20 mg two weeks later. If a faster response is required, your child's doctor may prescribe an initial dose of 80 mg (as 2 injections in 1 day) followed by 40 mg two weeks later.

Thereafter, the usual dose is 20 mg every other week. Depending on your child's response, your child's doctor may increase the dose frequency to 20 mg every week.

Children or adolescents weighing 40 kg or more:

The usual dose regimen is 80 mg initially followed by 40 mg two weeks later. If a faster response is required, your child's doctor may prescribe an initial dose of 160 mg initially (as 4 injections in 1 day or as 2 injections per day for 2 consecutive days) followed by 80 mg two weeks later.

Thereafter, the usual dose is 40 mg every other week. Depending on your child's response, your child's doctor may increase the dose frequency to 40 mg every week.

For patients who are prescribed a full 40 mg dose of Humira, a 40 mg pen and a 40 mg prefilled syringe are also available for use.

Children or adolescents with psoriasis

The recommended dose of Humira for patients aged 4 to 17 years with plaque psoriasis depends on the weight of your child. Your child's doctor will tell you the correct dose to use.

Adolescents with hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)

The recommended dose of Humira is an initial dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week starting one week later. If you have an inadequate response, your doctor may increase the dose frequency to 40 mg every week.

It is recommended that you use an antiseptic wash daily on the affected areas.

A 40 mg pen and a 40 mg prefilled syringe are also available for use.

Children with chronic non-infectious uveitis from 2 years of age

Children weighing less than 30 kg:

The usual dose of Humira is 20 mg every other week with methotrexate.

Your child's doctor may also prescribe an initial dose of 40 mg which may be administered one week prior to the start of the usual dose.

Children weighing 30 kg or more:

The usual dose of Humira is 40 mg every other week with methotrexate.

Your child's doctor may also prescribe an initial dose of 80 mg which may be administered one week prior to the start of the usual dose.

Method and route of administration

Humira is administered by injection under the skin (by subcutaneous injection).

Instructions for preparing and giving an injection of Humira:

The following instructions explain how to inject Humira. Please read the instructions carefully and follow them step by step. You will be instructed by your child's doctor or his/her assistant on the technique of self-injection and the amount to give to your child. Do not attempt to give your child an injection until you are sure that you understand how to prepare and give the injection. After proper training, the injection can be self-administered or given by another person, for example a family member or friend.

Failure to perform the following steps as described may cause contamination which may lead to infection of your child.

This injection should not be mixed in the same syringe or vial with any other medicine.

1) Setting up

- Make sure you know the proper amount (volume) needed for dosing. If you don't know the amount, **STOP HERE** and contact your doctor for further instruction.

- You will need a special container for waste, such as a sharps container or as instructed by your nurse, doctor or pharmacist. Place the container on your work surface.

- Wash your hands thoroughly

- Remove one box containing, one syringe, one vial adapter, one vial, two alcohol pads and one needle from the carton. If there is a second box in the carton for a future injection, place it back in the refrigerator immediately.

- Look at the expiry date on the box to be used. DO NOT use any item after the date shown on the box.

- Set up the following items on a clean surface, DO NOT take them out of their individual packaging yet.

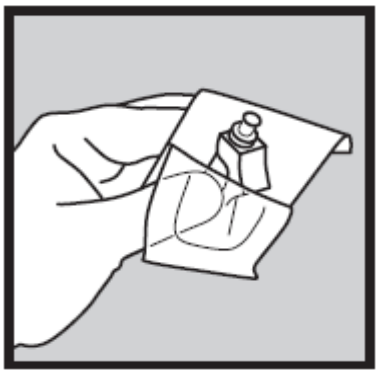
  - One 1 ml syringe (1)
  - One vial adapter (2)
  - One vial for paediatric use of Humira for injection (3)
  - Two alcohol pads (4)
  - One needle (5)

- Humira is a liquid that is clear and colourless. DO NOT use if the liquid is cloudy, discoloured or has flakes or particles in it.

2) Preparing the Humira dose for injection

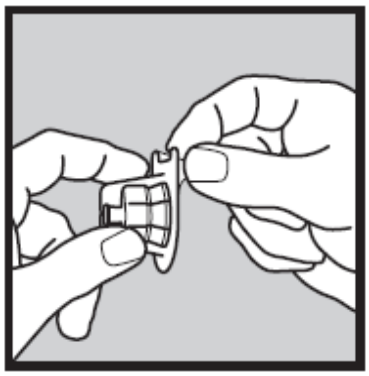
General handling: **DO NOT** dispose of any waste items until after the injection is completed.

- Prepare the needle by partially peeling the package open from the end closest to the yellow syringe connector. Peel the package just far enough to expose the yellow syringe connector. Set the package down with the clear side of the package facing up.

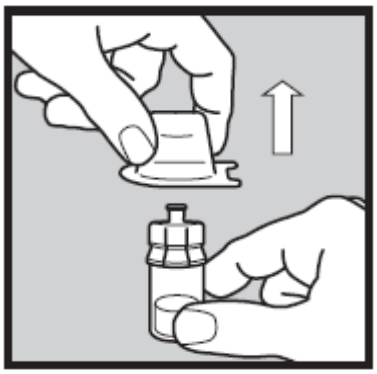


- Pop off the white plastic cap from the vial to see the top of the vial stopper.

- Use one of the alcohol pads to wipe the vial stopper. DO NOT touch the vial stopper after wiping with the alcohol pad.
- Peel the cover off the vial adapter package but do not take out the vial adapter.



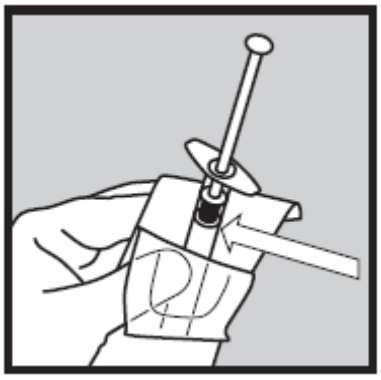
- Hold the vial with the vial stopper facing up.
- With the vial adapter still in the clear package, attach it to the vial stopper by pushing down until the vial adapter snaps in place.
- When you are sure the adapter is attached to the vial, lift off the package from the vial adapter.
- Gently set the vial with vial adapter down on your clean work surface. Be careful that it does not fall over. **DO NOT** touch the vial adapter.



- Prepare the syringe by partially peeling the package open from the end closest to white plunger rod.
- Peel the clear package just far enough to expose the white plunger rod, but do not take the syringe out of the package.
- Hold the syringe package and **SLOWLY** pull the white plunger rod out to 0.1 ml beyond the prescribed dose (For example, if the prescribed dose is 0.5 ml, pull the white plunger rod to 0.6 ml). **NEVER** pull past the 0.9 ml position regardless of prescribed dose.
- You will set the volume to the prescribed dose in a later step.
- **DO NOT** pull the white plunger rod completely out of the syringe.

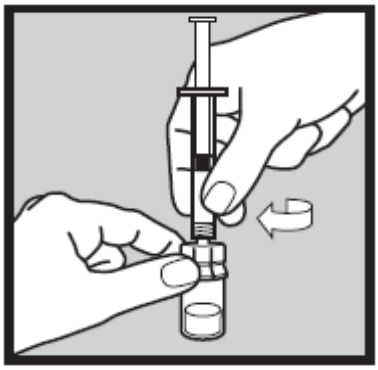
NOTE:

If the white plunger rod is pulled completely out of the syringe, discard the syringe and contact your Humira provider for a replacement. **DO NOT** try to reinsert the white plunger rod.

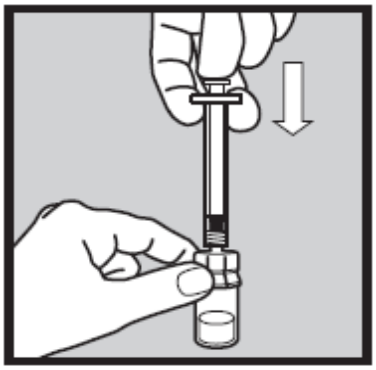


Dose + 0.1 ml

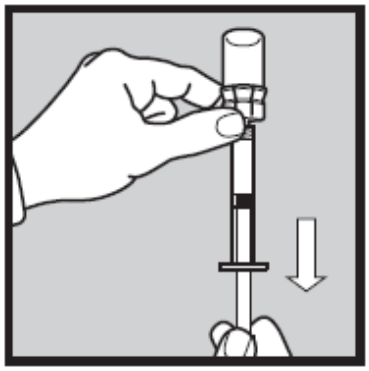
- **DO NOT** use the white plunger rod to remove the syringe from the package. Hold the syringe on the graduated area and pull the syringe from its package. **DO NOT** set the syringe down at any time.
- While holding the vial adapter firmly, insert the syringe tip into the vial adapter and twist the syringe clockwise with one hand until firm. **DO NOT** over-tighten.



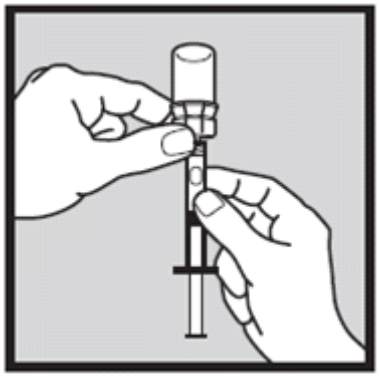
- While holding the vial, push the white plunger rod all the way down. This step is important to get the proper dose. Hold the white plunger rod in and turn the vial and syringe upside down.



- **SLOWLY** pull the white plunger rod out to 0.1 ml beyond the prescribed dose. This is important to get the proper dose. You will set the volume to the prescribed dose in step 4, Dose Preparation. If the prescribed dose is 0.5 ml, pull the white plunger rod out to 0.6 ml. You will see the liquid medication from the vial go into the syringe.



- Push the white plunger rod all the way back in to push the liquid medication back into the vial. Again, **SLOWLY** pull the white plunger rod out to 0.1 ml beyond the prescribed dose, this is important to get the proper dose and important in order to prevent air bubbles or air gaps in the liquid medication. You will set the volume to the prescribed dose in step 4, Dose Preparation.

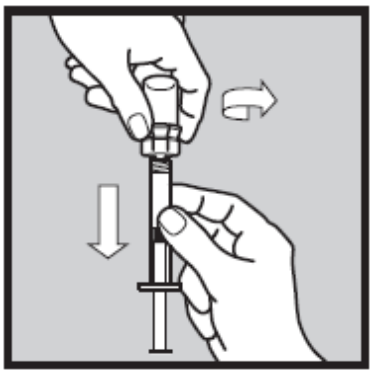


- If you see remaining air bubbles or air gaps in the liquid medication in the syringe, you may repeat this process up to 3 times. **DO NOT** shake the syringe.

NOTE:

If the white plunger rod is pulled completely out of the syringe, discard the syringe and contact your Humira provider for a replacement. **DO NOT** try to reinsert the white plunger rod.

- While still holding the syringe upright at the graduated area, remove the vial adapter with the vial by twisting the vial adapter off with the other hand. Be sure to remove the vial adapter with the vial from the syringe. **DO NOT** touch the tip of the syringe.



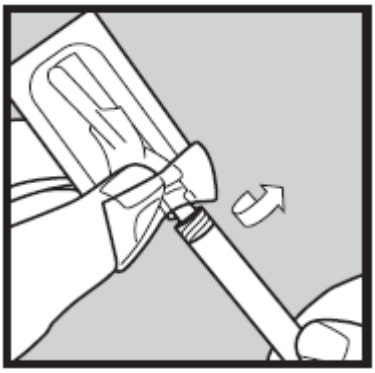
- If a large air bubble or air gap can be seen near the syringe tip, **SLOWLY** push the white plunger rod into the syringe until fluid begins to enter the syringe tip. **DO NOT** push the white plunger rod past the dose position.

- For example, if the prescribed dose is 0.5 ml, **DO NOT** push the white plunger rod past the 0.5 ml position.

- Check to see that the fluid remaining in the syringe is at least the prescribed dose volume. If the remaining volume is less than the prescribed dose volume, DO NOT use the syringe and contact your healthcare provider.

- With your free hand, pick up the needle package with the yellow syringe connector facing down.

- Keeping the syringe up, insert the syringe tip into the yellow syringe connector and twist the syringe as indicated by the arrow in the picture until firm. The needle is now attached to the syringe.

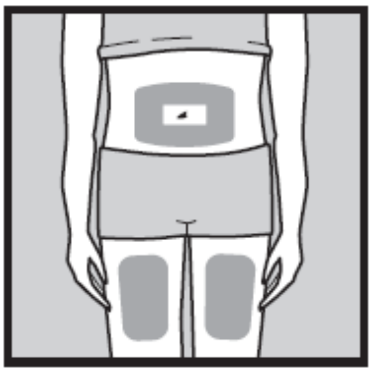


- Pull the needle package off, but **DO NOT** remove the clear needle cap.

- Place the syringe on your clean work surface. Continue with injection site and dose preparation immediately.

3) Choosing and preparing an injection site

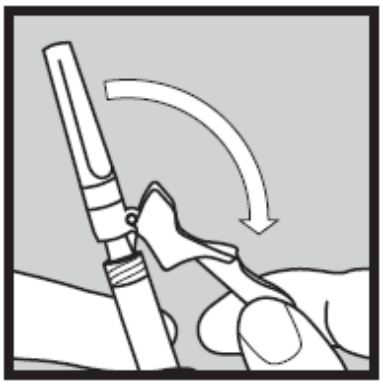
- Choose a site on your thigh or stomach. DO NOT use the same site that was used for the last injection.
- The new injection site should be given at least 3 cm from the last injection site.



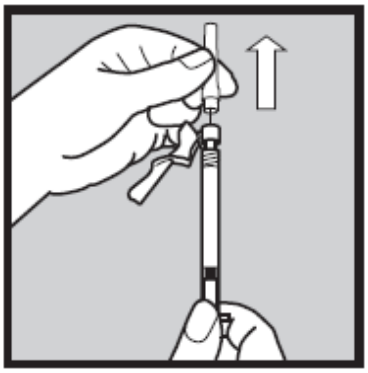
- **DO NOT** inject in an area where the skin is reddened, bruised, or hard. This may mean there is an infection and therefore you should contact your doctor.
- To reduce the chance of infection, wipe the injection site with the other alcohol pad. **DO NOT** touch the area again before injecting.

4) Dose Preparation

- Pick up the syringe with the needle pointing up.
- Use your other hand to flip the pink needle cover down toward the syringe.



- Remove the clear needle cap by pulling it straight up with your other hand.

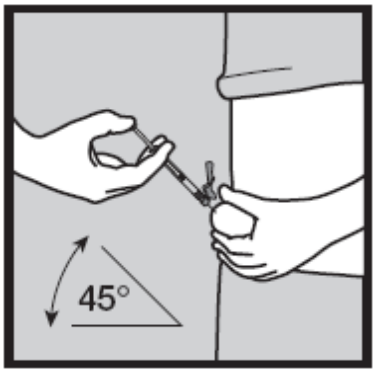


- The needle is clean.
- **DO NOT** touch the needle.
- **DO NOT** set the syringe down at any time after the clear needle cap is off.
- **DO NOT** try to put the clear needle cap back on the needle.

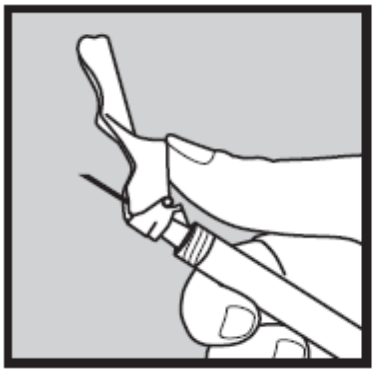
- Hold the syringe at eye-level with the needle pointing up to see the amount clearly. Be careful not to squirt the liquid medication into your eye.
- Recheck the prescribed medication amount.
- Push the white plunger rod gently into the syringe until the syringe contains the prescribed amount of liquid. Excess liquid may come out of the needle while the white plunger rod is being pushed. **DO NOT** wipe off the needle or the syringe.

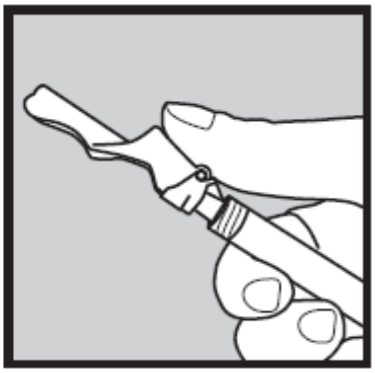
Injecting Humira

- With the free hand, gently grasp the cleaned area of skin and hold firmly.
- With the other hand, hold syringe at 45-degree angle to skin.
- With one quick, short motion, push needle all the way into skin.
- Let go of the skin in your hand.
- Push the white plunger rod to inject the liquid medication until the syringe is empty.
- When the syringe is empty, remove the needle from skin, being careful to pull it out at the same angle as when it was inserted.



- Gently flip the pink needle cover up, over the needle and snap into place, and set the syringe with needle on the work surface. DO NOT put the clear needle cap back on the needle.





- Using a piece of gauze, apply pressure over the injection site for 10 seconds. A little bleeding may occur. DO NOT rub the injection site. Use a plaster if you want to.

Throwing away supplies

- You will need a special container for waste, such as a sharps container or as instructed by your nurse, doctor or pharmacist.
- Put the syringe with needle, vial and vial adapter into a special sharps container. DO NOT put these items into regular household waste.
- The syringe, needle, vial and vial adapter MUST NEVER be reused.
- Keep the special container out of the sight and reach of children at all times.
- Throw away all other used items into your regular household waste.

If you use more Humira than you should:

If you accidentally inject a larger amount of Humira liquid, or if you inject Humira more frequently than told to by your doctor, you should call your doctor and tell him/her that your child has taken more. Always take the outer carton or the vial of the medicine with you, even if it is empty.

If you use less Humira than you should:

If you accidentally inject a smaller amount of Humira liquid, or if you inject Humira less frequently than told to by your child's doctor or pharmacist, you should call your child's doctor or pharmacist and tell him/her that your child has taken less. Always take the outer carton or the vial of the medicine with you, even if it is empty.

If you forget to use Humira:

If you forget to give your child a Humira injection, you should inject the Humira dose as soon as you remember. Then administer your child's next dose as you would have on the originally scheduled day, had you not forgotten a dose.

If your child stops using Humira:

The decision to stop using Humira should be discussed with your child's doctor. Your child's symptoms may return upon discontinuation.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 4 months after the last Humira injection.

Tell your doctor immediately if you notice any of the following:
- Severe rash, hives or other signs of allergic reaction;
- Swollen face, hands, feet;
- Trouble breathing, swallowing;
- Shortness of breath with exertion or upon lying down or swelling of the feet.

Tell your doctor as soon as possible if you notice any of the following:

Signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination;
- Feeling weak or tired;
- Coughing;
- Tingling;
- Numbness;
- Double vision;
- Arm or leg weakness;
- A bump or open sore that doesn't heal;
- Signs and symptoms suggestive of blood disorders such as persistent fever, bruising, bleeding, paleness.

The symptoms described above can be signs of the below listed side effects, which have been observed with Humira:

Very common (may affect more than 1 in 10 people):

- injection site reactions (including pain, swelling, redness or itching);
- respiratory tract infections (including cold, runny nose, sinus infection, pneumonia);
- headache;
- abdominal pain;
- nausea and vomiting;
- rash;
- musculoskeletal pain.

Common (may affect up to 1 in 10 people):

- serious infections (including blood poisoning and influenza);
- skin infections (including cellulitis and shingles);
- ear infections;
- oral infections (including tooth infections and cold sores);
- reproductive tract infections;
- urinary tract infection;
- fungal infections;
- joint infections,
- benign tumours;
- skin cancer;
- allergic reactions (including seasonal allergy);
- dehydration;
- mood swings (including depression);
- anxiety;
- difficulty sleeping;
- sensation disorders such as tingling, prickling or numbness;
- migraine;
- nerve root compression (including low back pain and leg pain);
- vision disturbances;
- eye inflammation;
- inflammation of the eye lid and eye swelling;
- vertigo;
- sensation of heart beating rapidly;
- high blood pressure;
- flushing;
- haematoma;
- cough;
- asthma;
- shortness of breath;
- gastrointestinal bleeding;
- dyspepsia (indigestion, bloating, heart burn);
- acid reflux disease;
- sicca syndrome (including dry eyes and dry mouth);
- itching;
- itchy rash;
- bruising;
- inflammation of the skin (such as eczema);
- breaking of finger nails and toe nails;
- increased sweating;
- hair loss;
- new onset or worsening of psoriasis;
- muscle spasms;
- blood in urine;
- kidney problems;
- chest pain;
- oedema;
- fever;
- reduction in blood platelets which increases risk of bleeding or bruising;
- impaired healing.

Uncommon (may affect up to 1 in 100 people):

- opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered);
- neurological infections (including viral meningitis);
- eye infections;
- bacterial infections;
- diverticulitis (inflammation and infection of the large intestine);
- cancer;
- cancer that affects the lymph system;
- melanoma;
- immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis);
- vasculitis (inflammation of blood vessels);
- tremor;
- stroke;
- neuropathy;
- double vision;
- hearing loss, buzzing;
- sensation of heart beating irregularly such as skipped beats;
- heart problems that can cause shortness of breath or ankle swelling;
- heart attack;
- a sac in the wall of a major artery, inflammation and clot of a vein; blockage of a blood vessel;
- lung diseases causing shortness of breath (including inflammation);
- pulmonary embolism (bloackage in an artery of the lung);
- pleural effusion (abnormal collection of fluid on the pleural space);
- inflammation of the pancreas which causes severe pain in the abdomen and back;
- difficulty in swallowing;
- facial oedema;
- gallbladder inflammation, gallbladder stones;
- fatty liver;
- night sweats;
- scar;
- abnormal muscle breakdown;
- systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems);
- sleep interruptions;
- impotence;
- inflammations.

Rare (may affect up to 1 in 1000 people)

- leukemia (cancer affecting the blood and bone marrow);
- severe allergic reaction with shock;
- multiple sclerosis;
- nerve disorders (such as eye nerve inflammation and Guillain-Barré syndrome that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body);
- heart stops pumping;
- pulmonary fibrosis (scarring of the lung);
- intestinal perforation;
- hepatitis;
- reactivation of hepatitis B;
- autoimmune hepatitis (inflammation of the liver caused by the body's own immune system);
- cutaneous vasculitis (inflammation of blood vessels in the skin);

- Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash);
- facial oedema associated with allergic reactions;
- erythema multiforme (inflammatory skin rash);
- lupus-like syndrome.

Not known (frequency cannot be estimated from available data):

- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal);
- Merkel cell carcinoma (a type of skin cancer);
- liver failure;
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness).

Some side effects observed with Humira may not have symptoms and may only be discovered through blood tests. These include:

Very common (may affect more than 1 in 10 people):

- low blood measurements for white blood cells;
- low blood measurements for red blood cells;
- increased lipids in the blood;
- elevated liver enzymes.

Common (may affect up to 1 in 10 people):

- high blood measurements for white blood cells;
- low blood measurements for platelets;
- increased uric acid in the blood;
- abnormal blood measurements for sodium;
- low blood measurements for calcium;
- low blood measurements for phosphate;
- high blood sugar;
- high blood measurements for lactate dehydrogenase;
- autoantibodies present in the blood.

Rare (may affect up to 1 in 1,000 people):

- low blood measurements for white blood cells, red blood cells and platelet count.

Not known (frequency cannot be estimated from available data):

- liver failure.

Reporting of side effects

If your child gets any side effects, talk to your child’s doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Humira

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label/blister/carton after EXP.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Humira contains

The active substance is adalimumab.
The other ingredients are mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections.
This medicinal product contains less than 1 mmol of sodium (23 mg) per 0.8 ml dose, i.e. essentially 'sodium-free' and does not contain preservatives.

What the Humira vial looks like and contents of the pack

Humira 40 mg solution for injection in vials is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.8 ml solution.

The Humira vial is a glass vial containing a solution of adalimumab. One pack contains 2 boxes, each containing 1 vial, 1 empty sterile syringe, 1 needle, 1 vial adapter and 2 alcohol pads.

Humira is also available as a pre-filled syringe or a pre-filled pen.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

Package leaflet: Information for the patient

Humira 40 mg solution for injection in pre-filled syringe
adalimumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Alert Card, which contains important safety information that you need to be aware of before you are given Humira and during treatment with Humira. Keep this Patient Alert Card with you.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet:

1. What Humira is and what it is used for

Humira contains the active substance adalimumab, a selective immuno suppressive agent.
Humira is intended for treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and non-infectious uveitis. It is a medicine that decreases the inflammation process of these diseases. The active ingredient, adalimumab, is a human monoclonal antibody produced by cultured cells. Monoclonal antibodies are proteins that recognise and bind to other unique proteins. Adalimumab binds to a specific protein (tumour necrosis factor or TNFα), which is present at increased levels in inflammatory diseases such as rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and non-infectious uveitis.

Rheumatoid arthritis

Rheumatoid arthritis is an inflammatory disease of the joints.

Humira is used to treat rheumatoid arthritis in adults. If you have moderate to severe active rheumatoid arthritis, you may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira to treat your rheumatoid arthritis.

Humira can also be used to treat severe, active and progressive rheumatoid arthritis without previous methotrexate treatment.

Humira has been shown to slow down the damage to the cartilage and bone of the joints caused by the disease and to improve physical function.

Usually, Humira is used with methotrexate. If your doctor determines that methotrexate is inappropriate, Humira can be given alone.

Polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis

Polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis are inflammatory diseases.

Humira is used to treat polyarticular juvenile idiopathic arthritis in children and adolescents aged 2 to 17 years and enthesitis-related arthritis in children and adolescents aged 6 to 17 years. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira to treat your polyarticular juvenile idiopathic arthritis or enthesitis-related arthritis.

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, are inflammatory diseases of the spine.

Humira is used to treat ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis in adults. If you have ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your disease.

Psoriatic arthritis

Psoriatic arthritis is an inflammation of the joints associated with psoriasis.

Humira is used to treat psoriatic arthritis in adults. Humira has been shown to slow down the damage to the cartilage and bone of the joints caused by the disease and to improve physical function.

Plaque psoriasis in adults and children

Plaque psoriasis is a skin condition that causes red, flaky, crusty patches of skin covered with silvery scales. Plaque psoriasis can also affect the nails, causing them to crumble, become thickened and lift away from the nail bed which can be painful. Psoriasis is believed to be caused by a problem with the body’s immune system that leads to an increased production of skin cells.

Humira is used to treat moderate to severe plaque psoriasis in adults. Humira is also used to treat severe plaque psoriasis in children and adolescents aged 4 to 17 years for whom topical therapy and phototherapies have either not worked very well or are not suitable.

Hidradenitis suppurativa in adults and adolescents

Hidradenitis suppurativa (sometimes called acne inversa) is a chronic and often painful inflammatory skin disease. Symptoms may include tender nodules (lumps) and abscesses (boils) that may leak pus. It most commonly affects specific areas of the skin, such as under the breasts, the armpits, inner thighs, groin and buttocks. Scarring may also occur in affected areas.

Humira is used to treat hidradenitis suppurativa in adults and adolescents from 12 years of age. Humira can reduce the number of nodules and abscesses you have, and the pain that is often

associated with the disease. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Crohn's disease in adults and children

Crohn's disease is an inflammatory disease of the digestive tract.

Humira is used to treat Crohn's disease in adults and children aged 6 to 17 years. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your Crohn's disease.

Ulcerative colitis

Ulcerative colitis is an inflammatory disease of the bowel.

Humira is used to treat ulcerative colitis in adults. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your disease.

Non-infectious uveitis in adults and children

Non-infectious uveitis is an inflammatory disease affecting certain parts of the eye.

Humira is used to treat
- Adults with non-infectious uveitis with inflammation affecting the back of the eye
- Children from 2 years of age with chronic non-infectious uveitis with inflammation affecting the front of the eye

This inflammation may lead to a decrease of vision and/or the presence of floaters in the eye (black dots or wispy lines that move across the field of vision). Humira works by reducing this inflammation.

2. What you need to know before you use Humira

Do not use Humira

- If you are allergic to adalimumab or any of the other ingredients of this medicine (listed in section 6).

- If you have a severe infection, including active tuberculosis (see Warnings and precautions"). It is important that you tell your doctor if you have symptoms of infections, e.g. fever, wounds, feeling tired, dental problems.

- If you have moderate or severe heart failure. It is important to tell your doctor if you have had or have a serious heart condition (see "Warnings and precautions").

Warnings and precautions

Talk to your doctor or pharmacist before using Humira

- If you experience allergic reactions with symptoms such as chest tightness, wheezing, dizziness, swelling or rash do not inject more Humira and contact your doctor immediately.

- If you have an infection, including long-term or localized infection (for example, leg ulcer) consult your doctor before starting Humira. If you are unsure, please contact your doctor.

- You might get infections more easily while you are receiving Humira treatment. This risk may increase if your lung function is impaired. These infections may be serious and include tuberculosis, infections caused by viruses, fungi, parasites or bacteria, or other opportunistic infections and sepsis that may, in rare cases, be life-threatening. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems. Your doctor may recommend temporary discontinuation of Humira.

- As cases of tuberculosis have been reported in patients treated with Humira, your doctor will check you for signs and symptoms of tuberculosis before starting Humira. This will include a thorough medical evaluation including your medical history and appropriate screening tests (for example chest X-ray and a tuberculin test). The conduct and results of these tests should be recorded on your Patient Alert Card. It is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. Tuberculosis can develop during therapy even if you have received preventative treatment for tuberculosis. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy tell your doctor immediately.

- Advise your doctor if you reside or travel in regions where fungal infections such as histoplasmosis, coccidioidomycosis or blastomycosis are endemic.

- Advise your doctor if you have a history of recurrent infections or other conditions that increase the risk of infections.

- Advise your doctor if you are a carrier of the hepatitis B virus (HBV), if you have active HBV or if you think you might be at risk of contracting HBV. Your doctor should test you for HBV. Humira can cause reactivation of HBV in people who carry this virus. In some rare cases, especially if you are taking other medicines that suppress the immune system, reactivation of HBV can be life-threatening.

- If you are over 65 years you may be more susceptible to infections while taking Humira. You and your doctor should pay special attention to signs of infection while you are being treated with Humira. It is important to tell your doctor if you get symptoms of infections, such as fever, wounds, feeling tired or dental problems.

- If you are about to undergo surgery or dental procedures please inform your doctor that you are taking Humira. Your doctor may recommend temporary discontinuation of Humira.

- If you have or develop demyelinating disease such as multiple sclerosis, your doctor will decide if you should receive or continue to receive Humira. Tell your doctor immediately if you experience symptoms like changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body.

- Certain vaccines may cause infections and should not be given while receiving Humira. Please check with your doctor before you receive any vaccines. It is recommended that children, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy. If you received Humira while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately five months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy so they can decide when your baby should receive any vaccine.

- If you have mild heart failure and you are being treated with Humira, your heart failure status must be closely monitored by your doctor. It is important to tell your doctor if you have had

or have a serious heart condition. If you develop new or worsening symptoms of heart failure (e.g. shortness of breath, or swelling of your feet), you must contact your doctor immediately. Your doctor will decide if you should receive Humira.

- In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that does not go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

- There have been very rare cases of certain kinds of cancer in children and adult patients taking Humira or other TNF blockers. People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting lymphoma (a kind of cancer that affects the lymph system), and leukemia (a kind of cancer that affects the blood and bone marrow). If you take Humira the risk of getting lymphoma, leukemia, or other cancers may increase. On rare occasions, a specific and severe type of lymphoma has been observed in patients taking Humira. Some of those patients were also treated with azathioprine or 6- mercaptopurine. Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Humira. In addition cases of non-melanoma skin cancer have been observed in patients taking Humira. If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.

- There have been cases of cancers other than lymphoma in patients with a specific type of lung disease called Chronic Obstructive Pulmonary Disease (COPD) treated with another TNF blocker. If you have COPD, or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.

Children and adolescents

- Vaccinations: if possible children should be up to date with all vaccinations before using Humira.
- Do not give Humira to children with polyarticular juvenile idiopathic arthritis below the age of 2 years.

Other medicines and Humira

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Humira can be taken together with methotrexate or certain disease-modifying anti-rheumatic agents (sulfasalazine, hydroxychloroquine, leflunomide and injectable gold preparations), steroids or pain medications including non-steroidal anti-inflammatory drugs (NSAIDs).

You should not take Humira with medicines containing the active substance, anakinra or abatacept. If you have questions, please ask your doctor.

Humira with food and drink

Since Humira is injected under the skin (subcutaneously), food and drink should not affect Humira.

Pregnancy and breast-feeding

The effects of Humira in pregnant women are not known and so the use of Humira in pregnant women is not recommended. You are advised to avoid becoming pregnant and must use adequate contraception while using Humira and for at least 5 months after the last Humira treatment. If you become pregnant, you should consult your doctor.

It is not known whether adalimumab passes into breast milk.

If you are a breast-feeding mother, you should stop breast-feeding during Humira treatment and for at least 5 months after the last Humira treatment. If you received Humira during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy before the baby receives any vaccine (for more information see section on vaccination).

If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Humira may have a minor influence on your ability to drive, cycle or use machines. Room spinning sensation and vision disturbances may occur after taking Humira.

3. How to use Humira

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Humira is injected under the skin (subcutaneous use). The usual dose for adults with rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, and for patients with psoriatic arthritis is 40 mg adalimumab given every other week as a single dose.

In rheumatoid arthritis, methotrexate is continued while using Humira. If your doctor determines that methotrexate is inappropriate, Humira can be given alone.

If you have rheumatoid arthritis and you do not receive methotrexate with your Humira therapy, your doctor may decide to give 40 mg adalimumab every week.

Children with polyarticular juvenile idiopathic arthritis

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 2 to 12 years depends on the height and weight of the child. Your child's doctor will tell you the correct dose to use.

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 13 to 17 years, is 40 mg every other week.

Children with enthesitis-related arthritis

The recommended dose of Humira for patients with enthesitis-related arthritis, aged 6 to 17 years depends on the height and weight of the child.

Adults with psoriasis

The usual dose for adults with psoriasis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. You should continue to inject Humira for as long as your doctor has told you. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

Children or adolescents with plaque psoriasis

The recommended dose of Humira for patients aged 4 to 17 years with plaque psoriasis depends on the weight of your child. Your child's doctor will tell you the correct dose to use.

Patients requiring a dose less than 40 mg should use the 40mg vial presentation of Humira.

Adults with hidradenitis suppurativa

The usual dose regimen for hidradenitis suppurativa is an initial dose of 160 mg (as 4 injections in one day or 2 injections per day for two consecutive days), followed by an 80 mg dose (as 2 injections on the same day) two weeks later. After two further weeks, continue with a dose of 40 mg every week. It is recommended that you use an antiseptic wash daily on the affected areas.

Adolescents with hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)

The recommended dose of Humira is an initial dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week starting one week later. If you have an inadequate response, your doctor may increase the dose frequency to 40 mg every week.

It is recommended that you use an antiseptic wash daily on the affected areas.

Adults with Crohn's disease

The usual dose regimen for Crohn's disease is 80 mg initially followed by 40 mg every other week two weeks later. If a faster response is required your doctor may prescribe an initial dose of 160 mg (as 4 injections in one day or 2 injections per day for two consecutive days), followed by 80 mg two weeks later, and thereafter as 40 mg every other week. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

Children or adolescents with Crohn's disease

Children or adolescents weighing less than 40 kg:

The usual dose regimen is 40 mg initially followed by 20 mg two weeks later. If a faster response is required, your doctor may prescribe an initial dose of 80 mg (as 2 injections in 1 day) followed by 40 mg two weeks later.

Thereafter, the usual dose is 20 mg every other week. Depending on your response, your doctor may increase the dose frequency to 20 mg every week.

Children or adolescents weighing 40 kg or more:

The usual dose regimen is 80 mg initially followed by 40 mg two weeks later. If a faster response is required, your doctor may prescribe an initial dose of 160 mg (as 4 injections in 1 day or as 2 injections per day for 2 consecutive days) followed by 80 mg two weeks later.

Thereafter, the usual dose is 40mg every other week. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

Patients requiring a dose less than 40 mg should use the 40 mg vial presentation of Humira.

Adults with ulcerative colitis

The usual Humira dose for adults with ulcerative colitis is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days) and 80 mg at Week 2, and thereafter 40 mg every other week. Depending on your response, your doctor may increase the dose to 40 mg every week.

Adults with non-infectious uveitis

The usual dose for adults with non-infectious uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. You should continue to inject Humira for as long as your doctor has told you.

In non-infectious uveitis, corticosteroids or other medicines that influence the immune system may be continued while using Humira. Humira can also be given alone.

Children with chronic non-infectious uveitis from 2 years of age

Children weighing less than 30 kg:

The usual dose of Humira is 20 mg every other week with methotrexate.

Your child's doctor may also prescribe an initial dose of 40 mg which may be administered one week prior to the start of the usual dose.

Children weighing 30 kg or more:

The usual dose of Humira is 40 mg every other week with methotrexate.

Your child's doctor may also prescribe an initial dose of 80 mg which may be administered one week prior to the start of the usual dose.

Method and route of administration

Humira is administered by injection under the skin (by subcutaneous injection).

Instructions for preparing and giving an injection of Humira:

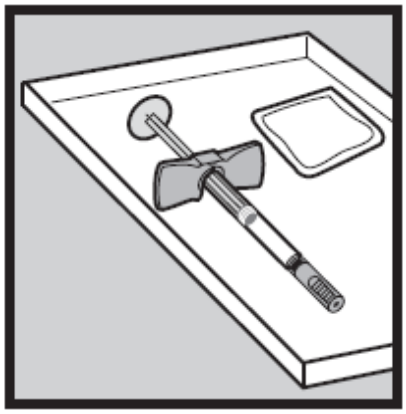
The following instructions explain how to inject Humira. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or his/her assistant on the technique of self-injection. Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection. After proper training, the injection can be self-administered or given by another person, for example a family member or friend.

This injection should not be mixed in the same syringe or vial with any other medicine.

1) Setting up

Wash your hands thoroughly
Set up the following items on a clean surface

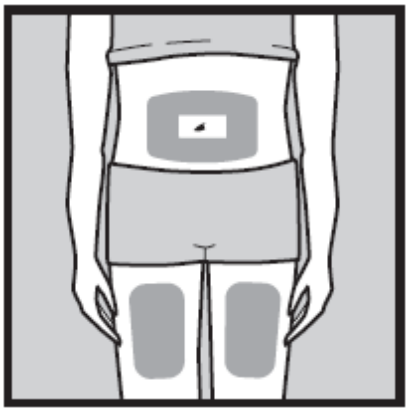
- One pre-filled syringe of Humira for injection
- One alcohol pad



Look at the expiry date on the syringe. Do not use the product after the month and year shown.

2) Choosing and preparing an injection site

Choose a site on your thigh or stomach

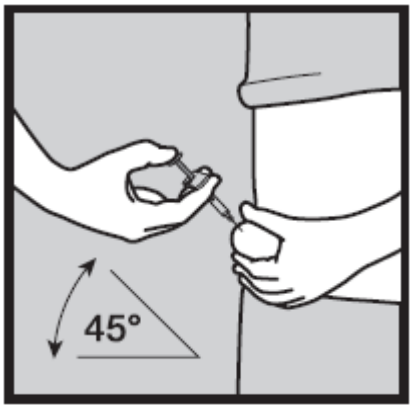


Each new injection should be given at least 3 cm from the last injection site.

- Do not inject in an area where the skin is reddened, bruised, or hard. This may mean there is an infection.
- Wipe the injection site with the enclosed alcohol pad, using a circular motion.
- Do not touch the area again before injecting.

3) Injecting Humira

- Do NOT shake the syringe.
- Remove cap from needle syringe, being careful not to touch the needle or let it touch any surface.
- With one hand, gently grasp the cleaned areas of skin and hold firmly



- With the other hand, hold syringe at 45-degree angle to skin, with the grooved side up.
- With one quick, short motion, push needle all the way into skin
- Release the skin with the first hand
- Push plunger to inject solution – it can take from 2 to 5 seconds to empty the syringe
- When the syringe is empty, remove the needle from skin, being careful to keep it at the same angle as when it was inserted
- Using your thumb or a piece of gauze, apply pressure over the injection site for 10 seconds. A little bleeding may occur. Do not rub the injection site. Use a plaster if you want to.

4) Throwing away supplies

- The Humira syringe should NEVER be reused. NEVER recap a needle.
- After injecting Humira, immediately throw away the used syringe in a special container as instructed by your doctor, nurse or pharmacist.
- Keep this container out of the sight and reach of children

If you use more Humira than you should:

If you accidentally inject Humira more frequently than told to by your doctor or pharmacist, you should call your doctor or pharmacist and tell him/her that you have taken more. Always take the outer carton of the medicine with you, even if it is empty.

If you forget to use Humira:

If you forget to give yourself an injection, you should inject the next dose of Humira as soon as you remember. Then take your next dose as you would have on your originally scheduled day, had you not forgotten a dose.

If you stop using Humira:

The decision to stop using Humira should be discussed with your doctor. Your symptoms may return upon discontinuation.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 4 months after the last Humira injection.

Tell your doctor immediately if you notice any of the following:
- Severe rash, hives or other signs of allergic reaction;
- Swollen face, hands, feet;
- Trouble breathing, swallowing;
- Shortness of breath with exertion or upon lying down or swelling of the feet.

Tell your doctor as soon as possible if you notice any of the following:
- Signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination;
- Feeling weak or tired;
- Coughing;
- Tingling;
- Numbness;
- Double vision;
- Arm or leg weakness;
- A bump or open sore that doesn't heal;
- Signs and symptoms suggestive of blood disorders such as persistent fever, bruising, bleeding, paleness

The symptoms described above can be signs of the below listed side effects, which have been observed with Humira:

Very common (may affect more than 1 in 10 people):

- injection site reactions (including pain, swelling, redness or itching);
- respiratory tract infections (including cold, runny nose, sinus infection, pneumonia);
- headache;
- abdominal pain;
- nausea and vomiting;
- rash;
- musculoskeletal pain.

Common (may affect up to 1 in 10people):

- serious infections (including blood poisoning and influenza);
- skin infections (including cellulitis and shingles);
- ear infections;
- oral infections (including tooth infections and cold sores);
- reproductive tract infections;
- urinary tract infection;
- fungal infections;
- joint infections;
- benign tumours;
- skin cancer;
- allergic reactions (including seasonal allergy);
- dehydration;
- mood swings (including depression);
- anxiety;
- difficulty sleeping;
- sensation disorders such as tingling, prickling or numbness;
- migraine;
- nerve root compression (including low back pain and leg pain);
- vision disturbances;
- eye inflammation;
- inflammation of the eye lid and eye swelling;

- vertigo;
- sensation of heart beating rapidly;
- high blood pressure;
- flushing;
- haematoma;
- cough;
- asthma;
- shortness of breath;
- gastrointestinal bleeding;
- dyspepsia (indigestion, bloating, heart burn);
- acid reflux disease;
- sicca syndrome (including dry eyes and dry mouth);
- itching;
- itchy rash;
- bruising;
- inflammation of the skin (such as eczema);
- breaking of finger nails and toe nails;
- increased sweating;
- hair loss;
- new onset or worsening of psoriasis;
- muscle spasms;
- blood in urine;
- kidney problems;
- chest pain;
- oedema;
- fever;
- reduction in blood platelets which increases risk of bleeding or bruising;
- impaired healing.

Uncommon (may affect up to 1 in 100 people):

- opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered);
- neurological infections (including viral meningitis);
- eye infections;
- bacterial infections;
- diverticulitis (inflammation and infection of the large intestine);
- cancer;
- cancer that affects the lymph system;
- melanoma;
- immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis);
- vasculitis (inflammation of blood vessels);
- tremor;
- neuropathy;
- stroke;
- double vision;
- hearing loss, buzzing;
- sensation of heart beating irregularly such as skipped beats;
- heart problems that can cause shortness of breath or ankle swelling;
- heart attack;
- a sac in the wall of a major artery, inflammation and clot of a vein; blockage of a blood vessel;
- lung diseases causing shortness of breath (including inflammation);

- pulmonary embolism (blockage in an artery of the lung);
- pleural effusion (abnormal collection of fluid in the pleural space);
- inflammation of the pancreas which causes severe pain in the abdomen and back;
- difficulty in swallowing;
- facial oedema;
- gallbladder inflammation, gallbladder stones;
- fatty liver;
- night sweats;
- scar;
- abnormal muscle breakdown;
- systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems);
- sleep interruptions;
- impotence;
- inflammations.

Rare (may affect up to 1 in 1,000 people):

- leukaemia (cancer affecting the blood and bone marrow);
- Severe allergic reaction with shock;
- multiple sclerosis;
- nerve disorders (such as eye nerve inflammation and Guillain-Barré syndrome that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body);
- heart stops pumping;
- pulmonary fibrosis (scarring of the lung);
- intestinal perforation;
- hepatitis;
- reactivation of hepatitis B;
- autoimmune hepatitis (inflammation of the liver caused by the body's own immune system);
- cutaneous vasculitis (inflammation of blood vessels in the skin);
- Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash);
- facial oedema associated with allergic reactions;
- erythema multiforme (inflammatory skin rash);
- lupus-like syndrome.

Not known (frequency cannot be estimated from available data):

- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal);
- Merkel cell carcinoma (a type of skin cancer);
- liver failure;
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness).

Some side effects observed with Humira may not have symptoms and may only be discovered through blood tests. These include:

Very common (may affect more than 1 in 10 people):

- low blood measurements for white blood cells;
- low blood measurements for red blood cells;
- increased lipids in the blood;
- elevated liver enzymes.

Common (may affect up to 1 in 10 people):

- high blood measurements for white blood cells;
- low blood measurements for platelets;
- increased uric acid in the blood;
- abnormal blood measurements for sodium;
- low blood measurements for calcium;
- low blood measurements for phosphate;
- high blood sugar;
- high blood measurements for lactate dehydrogenase;
- autoantibodies present in the blood.

Rare (may affect up to 1 in 1,000 people):

- low blood measurements for white blood cells, red blood cells and platelet count.

Not known (frequency cannot be estimated from available data):

- liver failure.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Humira

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label/blister/carton after EXP.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

Alternative Storage:

When needed (for example when you are travelling), a single Humira pre-filled syringe may be stored at room temperature (up to 25°C) for a maximum period of 14 days – be sure to protect it from light. Once removed from the refrigerator for room temperature storage, the syringe **must be used within 14 days or discarded**, even if it is returned to the refrigerator.

You should record the date when the syringe is first removed from refrigerator, and the date after which it should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Humira contains

The active substance is adalimumab.
The other ingredients are mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections.

This medicinal product contains less than 1 mmol of sodium (23 mg) per 0.8 ml dose, i.e. essentially 'sodium-free' and does not contain preservatives.

What the Humira pre-filled syringe looks like and contents of the pack

Humira 40 mg solution for injection in pre-filled syringe is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.8 ml solution.

The Humira pre-filled syringe is a glass syringe containing a solution of adalimumab. Each pack contains 1, 2, 4 or 6 pre-filled syringes for patient use with 1, 2, 4 or 6 alcohol pads, respectively. Not all pack sizes may be marketed.

Humira is available as a vial, a pre-filled syringe and a pre-filled pen.

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and

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

Package leaflet: Information for the patient

Humira 40 mg solution for injection in pre-filled syringe with needleguard
adalimumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Alert Card, which contains important safety information that you need to be aware of before you are given Humira and during treatment with Humira. Keep this Patient Alert Card with you.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet:

1. What Humira is and what it is used for

Humira contains the active substance adalimumab, a selective immunosuppressive agent. Humira is intended for treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and non-infectious uveitis. It is a medicine that decreases the inflammation process of these diseases. The active ingredient, adalimumab, is a human monoclonal antibody produced by cultured cells. Monoclonal antibodies are proteins that recognise and bind to other unique proteins. Adalimumab binds to a specific protein (tumour necrosis factor or TNFα), which is present at increased levels in inflammatory diseases such as rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and non-infectious uveitis.

<u>Rheumatoid arthritis</u>

Rheumatoid arthritis is an inflammatory disease of the joints.

Humira is used to treat rheumatoid arthritis in adults. If you have moderate to severe active rheumatoid arthritis, you may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira to treat your rheumatoid arthritis.

Humira can also be used to treat severe, active and progressive rheumatoid arthritis without previous methotrexate treatment.

Humira has been shown to slow down the damage to the cartilage and bone of the joints caused by the disease and to improve physical function.

Usually, Humira is used with methotrexate. If your doctor determines that methotrexate is inappropriate, Humira can be given alone.

Polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis

Polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis are inflammatory diseases.

Humira is used to treat polyarticular juvenile idiopathic arthritis in children and adolescents aged 2 to 17 years and enthesitis-related arthritis in children and adolescents aged 6 to 17 years. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira to treat your polyarticular juvenile idiopathic arthritis or enthesitis-related arthritis.

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, are inflammatory diseases of the spine.

Humira is used to treat ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis in adults. If you have ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your disease.

Psoriatic arthritis

Psoriatic arthritis is an inflammation of the joints associated with psoriasis.

Humira is used to treat psoriatic arthritis in adults. Humira has been shown to slow down the damage to the cartilage and bone of the joints caused by the disease and to improve physical function.

Plaque psoriasis in adults and children

Plaque psoriasis is a skin condition that causes red, flaky, crusty patches of skin covered with silvery scales. Plaque psoriasis can also affect the nails, causing them to crumble, become thickened and lift away from the nail bed which can be painful. Psoriasis is believed to be caused by a problem with the body’s immune system that leads to an increased production of skin cells.

Humira is used to treat moderate to severe plaque psoriasis in adults. Humira is also used to treat severe plaque psoriasis in children and adolescents aged 4 to 17 years for whom topical therapy and phototherapies have either not worked very well or are not suitable.

Hidradenitis suppurativa in adults and adolescents

Hidradenitis suppurativa (sometimes called acne inversa) is a chronic and often painful inflammatory skin disease. Symptoms may include tender nodules (lumps) and abscesses (boils) that may leak pus. It most commonly affects specific areas of the skin, such as under the breasts, the armpits, inner thighs, groin and buttocks. Scarring may also occur in affected areas.

Humira is used to treat hidradenitis suppurativa in adults and adolescents from 12 years of age. Humira can reduce the number of nodules and abscesses you have, and the pain that is often

associated with the disease. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Crohn's disease in adults and children

Crohn's disease is an inflammatory disease of the digestive tract.

Humira is used to treat Crohn's disease in adults and children aged 6 to 17 years. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your Crohn's disease.

Ulcerative colitis

Ulcerative colitis is an inflammatory disease of the bowel.

Humira is used to treat ulcerative colitis in adults. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your disease.

Non-infectious uveitis in adults and children

Non-infectious uveitis is an inflammatory disease affecting certain parts of the eye.

Humira is used to treat
- Adults with non-infectious uveitis with inflammation affecting the back of the eye
- Children from 2 years of age with chronic non-infectious uveitis with inflammation affecting the front of the eye

This inflammation may lead to a decrease of vision and/or the presence of floaters in the eye (black dots or wispy lines that move across the field of vision). Humira works by reducing this inflammation.

2. What you need to know before you use Humira

Do not use Humira

- If you are allergic to adalimumab or any of the other ingredients of this medicine (listed in section 6).

- If you have a severe infection, including active tuberculosis (see "Warnings and precautions"). It is important that you tell your doctor if you have symptoms of infections, e.g. fever, wounds, feeling tired, dental problems.

- If you have moderate or severe heart failure. It is important to tell your doctor if you have had or have a serious heart condition (see "Warnings and precautions").

Warnings and precautions

Talk to your doctor or pharmacist before using Humira

- If you experience allergic reactions with symptoms such as chest tightness, wheezing, dizziness, swelling or rash do not inject more Humira and contact your doctor immediately.

- If you have an infection, including long-term or localized infection (for example, leg ulcer) consult your doctor before starting Humira. If you are unsure, please contact your doctor.

- You might get infections more easily while you are receiving Humira treatment. This risk may increase if your lung function is impaired. These infections may be more serious and include tuberculosis, infections caused by viruses, fungi, parasites or bacteria, or other opportunistic infections and sepsis that may, in rare case, be life-threatening. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems. Your doctor may recommend temporary discontinuation of Humira.

- As cases of tuberculosis have been reported in patients treated with Humira, your doctor will check you for signs and symptoms of tuberculosis before starting Humira. This will include a thorough medical evaluation including your medical history and appropriate screening tests (for example chest X-ray and a tuberculin test). The conduct and results of these tests should be recorded on your Patient Alert Card. It is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. Tuberculosis can develop during therapy even if you have received preventative treatment for tuberculosis. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy tell your doctor immediately.

- Advise your doctor if you reside or travel in regions where fungal infections such as histoplasmosis, coccidioidomycosis or blastomycosis are endemic.

- Advise your doctor if you have a history of recurrent infections or other conditions that increase the risk of infections.

- Advise your doctor if you are a carrier of the hepatitis B virus (HBV), if you have active HBV or if you think you might be at risk of contracting HBV. Your doctor should test you for HBV. Humira can cause reactivation of HBV in people who carry this virus. In some rare cases, especially if you are taking other medicines that suppress the immune system, reactivation of HBV can be life-threatening.

- If you are over 65 years you may be more susceptible to infections while taking Humira. You and your doctor should pay special attention to signs of infection while you are being treated with Humira. It is important to tell your doctor if you get symptoms of infections, such as fever, wounds, feeling tired or dental problems.

- If you are about to undergo surgery or dental procedures please inform your doctor that you are taking Humira. Your doctor may recommend temporary discontinuation of Humira.

- If you have or develop demyelinating disease such as multiple sclerosis, your doctor will decide if you should receive or continue to receive Humira. Tell your doctor immediately if you experience symptoms like changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body.

- Certain vaccines may cause infections and should not be given while receiving Humira. Please check with your doctor before you receive any vaccines. It is recommended that children, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy. If you received Humira while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately five months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy so they can decide when your baby should receive any vaccine.

- If you have mild heart failure and you are being treated with Humira, your heart failure status must be closely monitored by your doctor. It is important to tell your doctor if you have had

or have a serious heart condition. If you develop new or worsening symptoms of heart failure (e.g. shortness of breath, or swelling of your feet), you must contact your doctor immediately. Your doctor will decide if you should receive Humira.

- In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that does not go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

- There have been very rare cases of certain kinds of cancer in children and adult patients taking Humira or other TNF blockers. People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting lymphoma (a kind of cancer that affects the lymph system), and leukemia (a kind of cancer that affects the blood and bone marrow). If you take Humira the risk of getting lymphoma, leukemia, or other cancers may increase. On rare occasions, a specific and severe type of lymphoma has been observed in patients taking Humira. Some of those patients were also treated with azathioprine or 6- mercaptopurine. Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Humira. In addition cases of non-melanoma skin cancer have been observed in patients taking Humira. If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.

- There have been cases of cancers, other than lymphoma, have been reported in patients with a specific type of lung disease called Chronic Obstructive Pulmonary Disease (COPD) treated with another TNF blocker. If you have COPD, or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.

Children and adolescents

- Vaccinations: if possible children should be up to date with all vaccinations before using Humira.
- Do not give Humira to children with polyarticular juvenile idiopathic arthritis below the age of 2 years.

Other medicines and Humira

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Humira can be taken together with methotrexate or certain disease-modifying anti-rheumatic agents (sulfasalazine, hydroxychloroquine, leflunomide and injectable gold preparations), steroids or pain medications including non-steroidal anti-inflammatory drugs (NSAIDs).

You should not take Humira with medicines containing the active substance, anakinra or abatacept. If you have questions, please ask your doctor.

Humira with food and drink

Since Humira is injected under the skin (subcutaneously), food and drink should not affect Humira.

Pregnancy and breast-feeding

The effects of Humira in pregnant women are not known and so the use of Humira in pregnant women is not recommended. You are advised to avoid becoming pregnant and must use adequate contraception while using Humira and for at least 5 months after the last Humira treatment. If you become pregnant, you should consult your doctor.

It is not known whether adalimumab passes into breast milk.

If you are a breast-feeding mother, you should stop breast-feeding during Humira treatment, and for at least 5 months after the last Humira treatment. If you received Humira during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy before the baby receives any vaccine (for more information see section on vaccination).

If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Humira may have a minor influence on your ability to drive, cycle or use machines. Room spinning sensation and vision disturbances may occur after taking Humira.

3. How to use Humira

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Humira is injected under the skin (subcutaneous use). The usual dose for adults with rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, and for patients with psoriatic arthritis is 40 mg adalimumab given every other week as a single dose.

In rheumatoid arthritis, methotrexate is continued while using Humira. If your doctor determines that methotrexate is inappropriate, Humira can be given alone.

If you have rheumatoid arthritis and you do not receive methotrexate with your Humira therapy, your doctor may decide to give 40 mg adalimumab every week.

Children with polyarticular juvenile idiopathic arthritis

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 2 to 12 years depends on the height and weight of the child. Your child's doctor will tell you the correct dose to use.

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 13 to 17 years, is 40 mg every other week.

Children with enthesitis-related arthritis

The recommended dose of Humira for patients with enthesitis-related arthritis, aged 6 to 17 years depends on the height and weight of the child.

Adults with psoriasis

The usual dose for adults with psoriasis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. You should continue to inject Humira for as long

as your doctor has told you. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

Children or adolescents with plaque psoriasis

The recommended dose of Humira for patients aged 4 to 17 years with plaque psoriasis depends on the weight of your child. Your child's doctor will tell you the correct dose to use.

Patients requiring a dose less than 40 mg should use the 40mg vial presentation of Humira.

Adults with hidradenitis suppurativa

The usual dose regimen for hidradenitis suppurativa is an initial dose of 160 mg (as 4 injections in one day or 2 injections per day for two consecutive days), followed by an 80 mg dose (as 2 injections on the same day) two weeks later. After two further weeks, continue with a dose of 40 mg every week. It is recommended that you use an antiseptic wash daily on the affected areas.

Adolescents with hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)

The recommended dose of Humira is an initial dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week starting one week later. If you have an inadequate response, your doctor may increase the dose frequency to 40 mg every week.

It is recommended that you use an antiseptic wash daily on the affected areas.

Adults with Crohn's disease

The usual dose regimen for Crohn's disease is 80 mg initially followed by 40 mg every other week two weeks later. If a faster response is required your doctor may prescribe an initial dose of 160 mg (as 4 injections in one day or 2 injections per day for two consecutive days), followed by 80 mg two weeks later, and thereafter as 40 mg every other week. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

Children or adolescents with Crohn's disease

Children or adolescents weighing less than 40 kg:

The usual dose regimen is 40 mg initially followed by 20 mg two weeks later. If a faster response is required, your doctor may prescribe an initial dose of 80 mg (as 2 injections in 1 day) followed by 40 mg two weeks later.

Thereafter, the usual dose is 20 mg every other week. Depending on your response, your doctor may increase the dose frequency to 20 mg every week.

Children or adolescents weighing 40 kg or more:

The usual dose regimen is 80 mg initially followed by 40 mg two weeks later. If a faster response is required, your doctor may prescribe an initial dose of 160 mg (as 4 injections in 1 day or as 2 injections per day for 2 consecutive days) followed by 80 mg two weeks later.

Thereafter, the usual dose is 40mg every other week. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

Patients requiring a dose less than 40 mg should use the 40mg vial presentation of Humira.

Adults with ulcerative colitis

The usual Humira dose for adults with ulcerative colitis is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days) and 80 mg at Week 2, and thereafter 40 mg every other week. Depending on your response, your doctor may increase the dose to 40 mg every week.

Adults with non-infectious uveitis

The usual dose for adults with non-infectious uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. You should continue to inject Humira for as long as your doctor has told you.

In non-infectious uveitis, corticosteroids or other medicines that influence the immune system may be continued while using Humira. Humira can also be given alone.

Children with chronic non-infectious uveitis from 2 years of age

Children weighing less than 30 kg:

The usual dose of Humira is 20 mg every other week with methotrexate.

Your doctor may also prescribe an initial dose of 40 mg which may be administered one week prior to the start of the usual dose.

Children weighing 30 kg or more:

The usual dose of Humira is 40 mg every other week with methotrexate.

Your doctor may also prescribe an initial dose of 80 mg which may be administered one week prior to the start of the usual dose.

Method and route of administration

Humira is administered by injection under the skin (by subcutaneous injection).

Instructions for preparing and giving an injection of Humira:

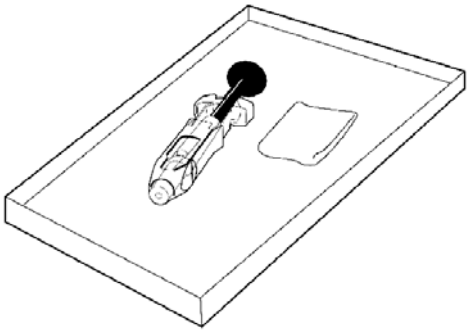
The following instructions explain how to inject Humira. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or his/her assistant on the technique of self-injection. Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection. After proper training, the injection can be self-administered or given by another person, for example a family member or friend.

This injection should not be mixed in the same syringe or vial with any other medicine.

1) Setting up

Wash your hands thoroughly
Set up the following items on a clean surface

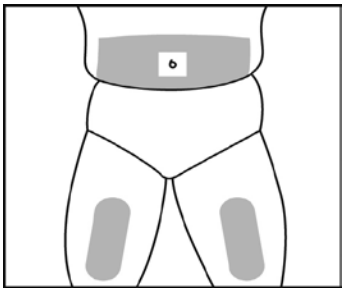
- One pre-filled syringe of Humira for injection
- One alcohol pad



Look at the expiry date on the syringe. Do not use the product after the month and year shown.

2) Choosing and preparing an injection site

Choose a site on your thigh or stomach



Each new injection should be given at least 3 cm from the last injection site.

- Do not inject in an area where the skin is reddened, bruised, or hard. This may mean there is an infection.
- Wipe the injection site with the enclosed alcohol pad, using a circular motion.
- Do not touch the area again before injecting.

3) Injecting Humira

- Do NOT shake the syringe.
- Remove cap from needle syringe, being careful not to touch the needle or let it touch any surface.
- With one hand, gently grasp the cleaned areas of skin and hold firmly

- With the other hand, hold syringe at 45-degree angle to skin, with the grooved side up.
- With one quick, short motion, push needle all the way into skin
- Release the skin with the first hand
- Push plunger to inject solution – it can take from 2 to 5 seconds to empty the syringe

- When the syringe is empty, remove the needle from skin, being careful to keep it at the same angle as when it was inserted
- Hold the syringe in one hand and with the other hand slide the outer protective shield over the exposed needle until it locks in place
- Using your thumb or a piece of gauze, apply pressure over the injection site for 10 seconds. A little bleeding may occur. Do not rub the injection site. Use a plaster if you want to.

4) Throwing away supplies

- The Humira syringe should NEVER be reused. NEVER recap a needle
- After injecting Humira, immediately throw away the used syringe in a special container as instructed by your doctor, nurse or pharmacist.
- Keep this container out of the sight and reach of children

If you use more Humira than you should:

If you accidentally inject Humira more frequently than told to by your doctor or pharmacist, you should call your doctor or pharmacist and tell him/her that you have taken more. Always take the outer carton of medicine with you, even if it is empty.

If you forget to use Humira:

If you forget to give yourself an injection, you should inject the next dose of Humira as soon as you remember. Then take your next dose as you would have on your originally scheduled day, had you not forgotten a dose.

If you stop using Humira:

The decision to stop using Humira should be discussed with your doctor. Your symptoms may return upon discontinuation.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 4 months after the last Humira injection.

Tell your doctor immediately if you notice any of the following:
- Severe rash, hives or other signs of allergic reaction;
- Swollen face, hands, feet;
- Trouble breathing, swallowing;
- Shortness of breath with exertion or upon lying down or swelling of the feet;

Tell your doctor as soon as possible if you notice any of the following:
- Signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination;
- Feeling weak or tired;
- Coughing;
- Tingling;
- Numbness;
- Double vision;
- Arm or leg weakness;
- A bump or open sore that doesn't heal;

- Signs and symptoms suggestive of blood disorders such as persistent fever, bruising, bleeding, paleness.

The symptoms described above can be signs of the below listed side effects, which have been observed with Humira:

Very common (may affect more than 1 in 10 people):

- injection site reactions (including pain, swelling, redness or itching);
- respiratory tract infections (including cold, runny nose, sinus infection, pneumonia);
- headache;
- abdominal pain;
- nausea and vomiting;
- rash;
- musculoskeletal pain.

Common (may affect up to 1 in 10 people):

- serious infections (including blood poisoning and influenza);
- skin infections (including cellulitis and shingles);
- ear infections;
- oral infections (including tooth infections and cold sores);
- reproductive tract infections;
- urinary tract infection;
- fungal infections;
- joint infections;
- benign tumours;
- skin cancer;
- allergic reactions (including seasonal allergy);
- dehydration;
- mood swings (including depression);
- anxiety;
- difficulty sleeping;
- sensation disorders such as tingling, prickling or numbness;
- migraine;
- nerve root compression (including low back pain and leg pain);
- vision disturbances;
- eye inflammation;
- inflammation of the eye lid and eye swelling;
- vertigo;
- cough;
- sensation of heart beating rapidly;
- high blood pressure;
- flushing;
- haematoma;
- asthma;
- shortness of breath;
- gastrointestinal bleeding;
- dyspepsia (indigestion, bloating, heart burn);
- acid reflux disease;
- sicca syndrome (including dry eyes and dry mouth);
- itching;
- itchy rash;

- bruising;
- inflammation of the skin (such as eczema);
- breaking of finger nails and toe nails;
- increased sweating;
- hair loss;
- new onset or worsening of psoriasis;
- muscle spasms;
- blood in urine;
- kidney problems;
- chest pain;
- oedema;
- fever;
- reduction in blood platelets which increases risk of bleeding or bruising;
- impaired healing.

Uncommon (may affect up to 1 in 100 people):

- opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered);
- neurological infections (including viral meningitis);
- eye infections;
- bacterial infections;
- diverticulitis (inflammation and infection of the large intestine);
- cancer;
- cancer that affects the lymph system;
- melanoma;
- immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis);
- vasculitis (inflammation of blood vessels);
- tremor;
- neuropathy;
- stroke;
- double vision;
- hearing loss, buzzing;
- sensation of heart beating irregularly such as skipped beats;
- heart problems that can cause shortness of breath or ankle swelling;
- heart attack;
- a sac in the wall of a major artery, inflammation and clot of a vein; blockage of a blood vessel;
- lung diseases causing shortness of breath (including inflammation);
- pulmonary embolism (blockage in an artery of the lung);
- pleural effusion (abnormal collection of fluid in the pleural space);
- inflammation of the pancreas which causes severe pain in the abdomen and back;
- difficulty in swallowing;
- facial oedema;
- gallbladder inflammation, gallbladder stones;
- fatty liver;
- night sweats;
- scar;
- abnormal muscle breakdown;
- systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems);
- sleep interruptions;
- impotence;

- inflammations.

Rare (may affect up to 1 in 1,000 people):

- leukemia (cancer affecting the blood and bone marrow);
- severe allergic reaction with shock;
- multiple sclerosis;
- nerve disorders (such as eye nerve inflammation and Guillain-Barré syndrome that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body);
- heart stops pumping;
- pulmonary fibrosis (scarring of the lung);
- intestinal perforation;
- hepatitis;
- reactivation of hepatitis B;
- autoimmune hepatitis (inflammation of the liver caused by the body's own immune system);
- cutaneous vasculitis (inflammation of blood vessels in the skin);
- Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash);
- facial oedema associated with allergic reactions;
- erythema multiforme (inflammatory skin rash);
- lupus-like syndrome.

Not known (frequency cannot be estimated from available data):

- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal);
- Merkel cell carcinoma (a type of skin cancer);
- liver failure;
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness).

Some side effects observed with Humira may not have symptoms and may only be discovered through blood tests. These include:

Very common (may affect more than 1 in 10people):

- low blood measurements for white blood cells;
- low blood measurements for red blood cells;
- increased lipids in the blood;
- elevated liver enzymes.

Common (may affect up to 1 in 10 people):

- high blood measurements for white blood cells;
- low blood measurements for platelets;
- increased uric acid in the blood;
- abnormal blood measurements for sodium;
- low blood measurements for calcium;
- low blood measurements for phosphate;
- high blood sugar;
- high blood measurements for lactate dehydrogenase;
- autoantibodies present in the blood.

Rare (may affect up to 1 in 1,000 people):

- low blood measurements for white blood cells, red blood cells and platelet count.

Not known (frequency cannot be estimated from the available data):

- liver failure.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Humira

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label/blister/carton after EXP.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

Alternative Storage:

When needed (for example when you are travelling), a single Humira pre-filled syringe may be stored at room temperature (up to 25°C) for a maximum period of 14 days – be sure to protect it from light. Once removed from the refrigerator for room temperature storage, the syringe **must be used within 14 days or discarded**, even if it is returned to the refrigerator.

You should record the date when the syringe is first removed from refrigerator, and the date after which it should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Humira contains

The active substance is adalimumab.
The other ingredients are mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections.

This medicinal product contains less than 1 mmol of sodium (23 mg) per 0.8 ml dose, i.e. essentially ‘sodium-free’ and does not contain preservatives.

What the Humira pre-filled syringe looks like and contents of the pack

The Humira pre-filled syringe is a glass syringe with needleguard containing a solution of adalimumab. Each pack contains 1 pre-filled syringe with needleguard for hospital administration or administration by a caregiver, with 1 alcohol pad.

Humira 40 mg solution for injection in pre-filled syringe is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.8 ml solution.

Not all pack sizes may be marketed. Humira is available as a vial, a pre-filled syringe, and a pre-filled pen.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

Package leaflet: Information for the patient

Humira 40 mg solution for injection in pre-filled pen
adalimumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Alert Card, which contains important safety information that you need to be aware of before you are given Humira and during treatment with Humira. Keep this Patient Alert Card with you.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet:

1. What Humira is and what it is used for

Humira contains the active substance adalimumab, a selective immunosuppressive agent. Humira is intended for treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and non-infectious uveitis. It is a medicine that decreases the inflammation process of these diseases. The active ingredient, adalimumab, is a human monoclonal antibody produced by cultured cells. Monoclonal antibodies are proteins that recognise and bind to other unique proteins. Adalimumab binds to a specific protein (tumour necrosis factor or TNFα), which is present at increased levels in inflammatory diseases such as rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and non-infectious uveitis.

<u>Rheumatoid arthritis</u>

Rheumatoid arthritis is an inflammatory disease of the joints.

Humira is used to treat rheumatoid arthritis in adults. If you have moderate to severe active rheumatoid arthritis, you may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira to treat your rheumatoid arthritis.

Humira can also be used to treat severe, active and progressive rheumatoid arthritis without previous methotrexate treatment.

Humira has been shown to slow down the damage to the cartilage and bone of the joints caused by the disease and to improve physical function.

Usually, Humira is used with methotrexate. If your doctor determines that methotrexate is inappropriate, Humira can be given alone.

Polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis

Polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis are inflammatory diseases.

Humira is used to treat polyarticular juvenile idiopathic arthritis in children and adolescents aged 2 to 17 years and enthesitis-related arthritis in children and adolescents aged 6 to 17 years. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira to treat your polyarticular juvenile idiopathic arthritis or enthesitis-related arthritis.

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, are inflammatory diseases of the spine.

Humira is used to treat ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis in adults. If you have ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your disease.

Psoriatic arthritis

Psoriatic arthritis is an inflammation of the joints associated with psoriasis.

Humira is used to treat psoriatic arthritis in adults. Humira has been shown to slow down the damage to the cartilage and bone of the joints caused by the disease and to improve physical function.

Plaque psoriasis in adults and children

Plaque psoriasis is a skin condition that causes red, flaky, crusty patches of skin covered with silvery scales. Plaque psoriasis can also affect the nails, causing them to crumble, become thickened and lift away from the nail bed which can be painful. Psoriasis is believed to be caused by a problem with the body’s immune system that leads to an increased production of skin cells.

Humira is used to treat moderate to severe plaque psoriasis in adults. Humira is also used to treat severe plaque psoriasis in children and adolescents aged 4 to 17 years for whom topical therapy and phototherapies have either not worked very well or are not suitable.

Hidradenitis suppurativa in adults and adolescents

Hidradenitis suppurativa (sometimes called acne inversa) is a chronic and often painful inflammatory skin disease. Symptoms may include tender nodules (lumps) and abscesses (boils) that may leak pus. It most commonly affects specific areas of the skin, such as under the breasts, the armpits, inner thighs, groin and buttocks. Scarring may also occur in affected areas.

Humira is used to treat hidradenitis suppurativa in adults and adolescents from 12 years of age. Humira can reduce the number of nodules and abscesses you have, and the pain that is often associated with the disease. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Crohn's disease in adults and children

Crohn's disease is an inflammatory disease of the digestive tract.

Humira is used to treat Crohn's disease in adults and children aged 6 to 17 years. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your Crohn's disease.

Ulcerative colitis

Ulcerative colitis is an inflammatory disease of the bowel.

Humira is used to treat ulcerative colitis in adults. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your disease.

Non-infectious uveitis in adults and children

Non-infectious uveitis is an inflammatory disease affecting certain parts of the eye.

Humira is used to treat
- Adults with non-infectious uveitis with inflammation affecting the back of the eye
- Children from 2 years of age with chronic non-infectious uveitis with inflammation affecting the front of the eye

This inflammation may lead to a decrease of vision and/or the presence of floaters in the eye (black dots or wispy lines that move across the field of vision). Humira works by reducing this inflammation.

2. What you need to know before you use Humira

Do not use Humira

- If you are allergic to adalimumab or any of the other ingredients of this medicine (listed in section 6).

- If you have a severe infection, including active tuberculosis (see "Warnings and precautions"). It is important that you tell your doctor if you have symptoms of infections, e.g. fever, wounds, feeling tired, dental problems.

- If you have moderate or severe heart failure. It is important to tell your doctor if you have had or have a serious heart condition (see "Warnings and precautions").

Warnings and precautions

Talk to your doctor or pharmacist before using Humira

- If you experience allergic reactions with symptoms such as chest tightness, wheezing, dizziness, swelling or rash do not inject more Humira and contact your doctor immediately.

- If you have an infection, including long-term or localized infection (for example, leg ulcer) consult your doctor before starting Humira. If you are unsure, please contact your doctor.

- You might get infections more easily while you are receiving Humira treatment. This risk may increase if your lung function is impaired. These infections may be serious and include

tuberculosis, infections caused by viruses, fungi, parasites or bacteria, or other opportunistic infections and sepsis that may, in rare cases, be life-threatening. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems. Your doctor may recommend temporary discontinuation of Humira.

- As cases of tuberculosis have been reported in patients treated with Humira, your doctor will check you for signs and symptoms of tuberculosis before starting Humira. This will include a thorough medical evaluation including your medical history and appropriate screening tests (for example chest X-ray and a tuberculin test). The conduct and results of these tests should be recorded on your Patient Alert Card. It is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. Tuberculosis can develop during therapy even if you have received preventative treatment for tuberculosis. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy tell your doctor immediately.

- Advise your doctor if you reside or travel in regions where fungal infections such as histoplasmosis, coccidioidomycosis or blastomycosis are endemic.

- Advise your doctor if you have a history of recurrent infections or other conditions that increase the risk of infections.

- Advise your doctor if you are a carrier of the hepatitis B virus (HBV), if you have active HBV or if you think you might be at risk of contracting HBV. Your doctor should test you for HBV. Humira can cause reactivation of HBV in people who carry this virus. In some rare cases, especially if you are taking other medicines that suppress the immune system, reactivation of HBV can be life-threatening.

- If you are over 65 years you may be more susceptible to infections while taking Humira. You and your doctor should pay special attention to signs of infection while you are being treated with Humira. It is important to tell your doctor if you get symptoms of infections, such as fever, wounds, feeling tired or dental problems.

- If you are about to undergo surgery or dental procedures please inform your doctor that you are taking Humira. Your doctor may recommend temporary discontinuation of Humira.

- If you have or develop demyelinating disease such as multiple sclerosis, your doctor will decide if you should receive or continue to receive Humira. Tell your doctor immediately if you experience symptoms like changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body.

- Certain vaccines may cause infections and should not be given while receiving Humira. Please check with your doctor before you receive any vaccines. It is recommended that children, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy. If you received Humira while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately five months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy so they can decide when your baby should receive any vaccine.

- If you have mild heart failure and you are being treated with Humira, your heart failure status must be closely monitored by your doctor. It is important to tell your doctor if you have had or have a serious heart condition. If you develop new or worsening symptoms of heart failure (e.g. shortness of breath, or swelling of your feet), you must contact your doctor immediately. Your doctor will decide if you should receive Humira.

- In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that does not go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

- There have been very rare cases of certain kinds of cancer in children and adult patients taking Humira or other TNF blockers. People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting lymphoma (a kind of cancer that affects the lymph system), and leukemia (a kind of cancer that affects the blood and bone marrow). If you take Humira the risk of getting lymphoma, leukemia, or other cancers may increase. On rare occasions, a specific and severe type of lymphoma, has been observed in patients taking Humira. Some of those patients were also treated with azathioprine or 6- mercaptopurine. Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Humira. In addition cases of non-melanoma skin cancer have been observed in patients taking Humira. If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.

- There have been cases of cancers, other than lymphoma in patients with a specific type of lung disease called Chronic Obstructive Pulmonary Disease (COPD) treated with another TNF blocker. If you have COPD, or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.

Children and adolescents

- Vaccinations: if possible children should be up to date with all vaccinations before using Humira.
- Do not give Humira to children with polyarticular juvenile idiopathic arthritis below the age of 2 years.
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Other medicines and Humira

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Humira can be taken together with methotrexate or certain disease-modifying anti-rheumatic agents (sulfasalazine, hydroxychloroquine, leflunomide and injectable gold preparations), steroids or pain medications including non-steroidal anti-inflammatory drugs (NSAIDs).

You should not take Humira with medicines containing the active substance, anakinra or abatacept. If you have questions, please ask your doctor.

Humira with food and drink

Since Humira is injected under the skin (subcutaneously), food and drink should not affect Humira.

Pregnancy and breast-feeding

The effects of Humira in pregnant women are not known and so the use of Humira in pregnant women is not recommended. You are advised to avoid becoming pregnant and must use adequate contraception while using Humira and for at least 5 months after the last Humira treatment. If you become pregnant, you should consult your doctor.

It is not known whether adalimumab passes into breast milk.

If you are a breast-feeding mother, you should stop breast-feeding during Humira treatment and for at least 5 months after the last Humira treatment. If you received Humira during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy before the baby receives any vaccine (for more information see section on vaccination).

If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Humira may have a minor influence on your ability to drive, cycle or use machines. Room spinning sensation and vision disturbances may occur after taking Humira.

3. How to use Humira

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Humira is injected under the skin (subcutaneous use). The usual dose for adults with rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, and for patients with psoriatic arthritis is 40 mg adalimumab given every other week as a single dose.

In rheumatoid arthritis, methotrexate is continued while using Humira. If your doctor determines that methotrexate is inappropriate, Humira can be given alone.

If you have rheumatoid arthritis and you do not receive methotrexate with your Humira therapy, your doctor may decide to give 40 mg adalimumab every week.

Children with polyarticular juvenile idiopathic arthritis

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 2 to 12 years depends on the height and weight of the child. Your child's doctor will tell you the correct dose to use.

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 13 to 17 years, is 40mg every other week.

Children with enthesitis-related arthritis

The recommended dose of Humira for patients with enthesitis-related arthritis, aged 6 to 17 years depends on the height and weight of the child.

Adults with psoriasis

The usual dose for adults with psoriasis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. You should continue to inject Humira for as long as your doctor has told you. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

Children or adolescents with plaque psoriasis

The recommended dose of Humira for patients aged 4 to 17 years with plaque psoriasis depends on the weight of your child. Your child's doctor will tell you the correct dose to use.

Patients requiring a dose less than 40 mg should use the 40 mg vial presentation of Humira.

Adults with hidradenitis suppurativa

The usual dose regimen for hidradenitis suppurativa is an initial dose of 160 mg (as 4 injections in one day or 2 injections per day for two consecutive days), followed by an 80 mg dose (as 2 injections on the same day) two weeks later. After two further weeks, continue with a dose of 40 mg every week. It is recommended that you use an antiseptic wash daily on the affected areas.

Adolescents with hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)

The recommended dose of Humira is an initial dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week starting one week later. If you have an inadequate response, your doctor may increase the dose frequency to 40 mg every week.

It is recommended that you use an antiseptic wash daily on the affected areas.

Adults with Crohn's disease

The usual dose regimen for Crohn's disease is 80 mg initially followed by 40 mg every other week two weeks later. If a faster response is required your doctor may prescribe an initial dose of 160 mg (as 4 injections in one day or 2 injections per day for two consecutive days), followed by 80 mg two weeks later, and thereafter as 40 mg every other week. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

Children or adolescents with Crohn's disease

Children or adolescents weighing less than 40 kg:

The usual dose regimen is 40 mg initially followed by 20 mg two weeks later. If a faster response is required, your doctor may prescribe an initial dose of 80 mg (as 2 injections in 1 day) followed by 40 mg two weeks later.

Thereafter, the usual dose is 20 mg every other week. Depending on your response, your doctor may increase the dose frequency to 20 mg every week.

Children or adolescents weighing 40 kg or more:

The usual dose regimen is 80 mg initially followed by 40 mg two weeks later. If a faster response is required, your doctor may prescribe an initial dose of 160 mg (as 4 injections in 1 day or as 2 injections per day for 2 consecutive days) followed by 80 mg two weeks later.

Thereafter, the usual dose is 40mg every other week. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

Patients requiring a dose less than 40 mg should use the 40mg vial presentation of Humira.

Adults with ulcerative colitis

The usual Humira dose for adults with ulcerative colitis is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days) and

80 mg at Week 2, and thereafter 40 mg every other week. Depending on your response, your doctor may increase the dose to 40 mg every week.

Adults with non-infectious uveitis

The usual dose for adults with non-infectious uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. You should continue to inject Humira for as long as your doctor has told you.

In non-infectious uveitis, corticosteroids or other medicines that influence the immune system may be continued while using Humira. Humira can also be given alone.

Children with chronic non-infectious uveitis from 2 years of age

Children weighing less than 30 kg:

The usual dose of Humira is 20 mg every other week with methotrexate.

Your doctor may also prescribe an initial dose of 40 mg which may be administered one week prior to the start of the usual dose.

Children weighing 30 kg or more:

The usual dose of Humira is 40 mg every other week with methotrexate.

Your doctor may also prescribe an initial dose of 80 mg which may be administered one week prior to the start of the usual dose.

Method and route of administration

Humira is administered by injection under the skin (by subcutaneous injection).

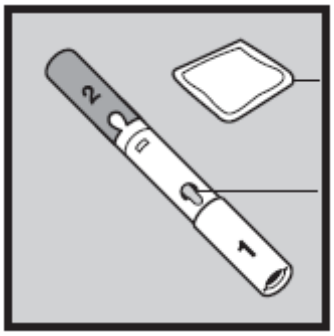
Injecting Humira yourself

The following instructions explain how to give yourself an injection of Humira using the pre-filled pen. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or his/her assistant on the technique of self-injection. Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection. After proper training, the injection can be self-administered or given by another person, for example a family member or friend.

What should I do before I give myself a subcutaneous injection of Humira?

1. Wash your hands thoroughly.
2. Take one dose tray containing a pre-filled pen of Humira from the refrigerator.
3. Do not shake or drop the pre-filled pen.
4. Set up the following items on a clean surface.

   One pre-filled pen of Humira
   One alcohol pad

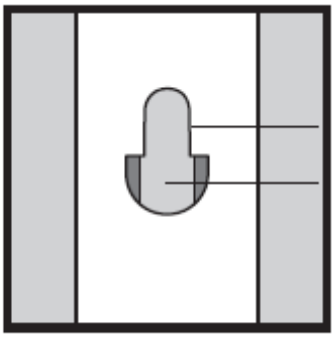


Pad

Window

5. Check the expiry date on the pre-filled pen label (EXP:) Do not use the product if the date has passed the month and year shown.

6. Hold the pre-filled pen with the grey cap (labelled ‘1’) pointing up. Check the appearance of the Humira solution through the window on the sides of the pre-filled pen. It must be clear and colourless. If it is cloudy or discoloured or has flakes or particles in it, you must not use it. Do not use a pre-filled pen that is frozen or if it has been left in direct sunlight. Only remove both the grey cap and the plum cap **immediately** before injection



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Clear Liquid in Syringe

Where should I give my injection?

1. Choose a site on the top of your thigh or stomach (except the area around the navel).

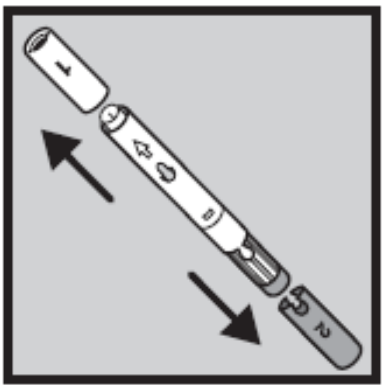
2. Change the place that you inject each time so that you do not become sore in one area. Each new injection should be given at least 3 cm from the last injection site.

3. Do not inject in an area where the skin is reddened, bruised, or hard. This may mean there is an infection.

How do I give my injection?

1. Wipe your skin by using the enclosed alcohol pad, using a circular motion. Do not touch the area again before injecting.

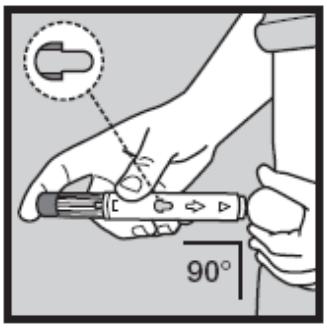
2. Only remove both the grey cap and the plum cap **immediately** before injection. Hold the grey body of the pre-filled pen with one hand. Place hand on the middle of the pen so that neither the grey cap (1) nor the plum cap (2) is covered. Hold the pre-filled pen with the grey cap (1) pointing up. With your other hand, pull the grey cap (1) straight off, check that the small black needle cover of the syringe has been removed with the cap, then discard cap. If a few small drops of liquid come out of the needle, that is okay. The white needle sleeve will now be exposed. Do not try to touch the needle housed in the barrel. **DO NOT RECAP** as you may damage the needle inside.

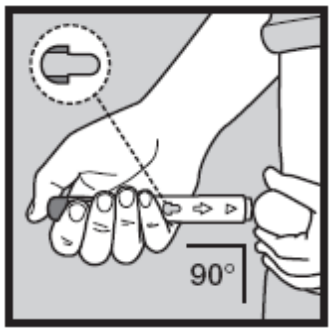


3. Pull the plum safety cap (labelled '2') straight off to expose the plum coloured activation button. The pre-filled pen is now ready to use. Do not press the plum activation button until properly positioned as this will result in discharge of medication. **DO NOT RECAP as this could cause the unit to discharge.**

Giving the injection

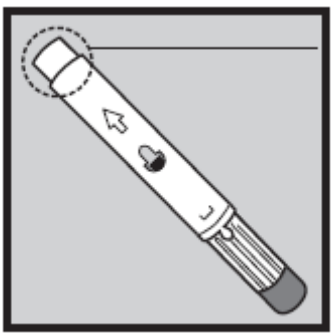
1. With your free hand, gently grasp a sizable area of the cleaned skin at the injection site and hold firmly (see below).
2. Place the white end of the pre-filled pen at a right angle (90 degrees) to the skin, so that you can see the window. The presence of one or more bubbles in the window is normal.
3. Holding the barrel of the pre-filled pen, press down slightly onto the injection site (holding in place without moving).
4. With your index finger or your thumb, press the plum coloured button on top once you are ready to begin the injection (see below). You will then hear a loud 'click' as the needle is released, and you will feel a small prick as the needle advances.
5. Keep pressing and continue to hold the pre-filled pen with steady pressure in place for about **10 seconds to ensure a complete injection.** Do not remove the pre-filled pen while the injection is being given.



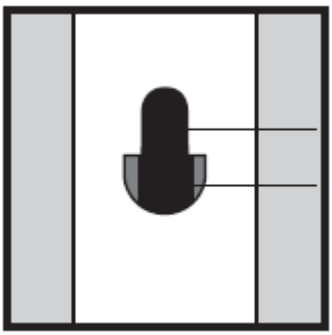


6. You will see a yellow indicator move into the window during the injection. The injection is complete when the yellow indicator stops moving. The yellow indicator is part of the plunger of the pre-filled pen. If the yellow indicator is not shown in the window, the plunger has not advanced adequately, and the injection is not complete.

7. Lift the pre-filled pen straight up from the injection site. The white needle sleeve will move down over the needle and lock into place over the needle tip. Do not try to touch the needle. The white needle sleeve is there to protect you from touching the needle.



White Needle Sleeve



Window

Yellow Indicator Visible

8. You may notice a spot of blood at the injection site. You can press a cotton ball or a piece of gauze over the injection site for 10 seconds. Do not rub the injection site. Use a plaster if you want to.

Throwing away supplies

Only use each pre-filled pen for one injection. Do not put either of the caps back on the pre-filled pen
After injecting Humira, immediately throw away the used pre-filled pen in a special container as instructed by your doctor, nurse or pharmacist
Keep this container out of the sight and reach of children

If you use more Humira than you should:

If you accidentally inject Humira more frequently than told to by your doctor or pharmacist, you should call your doctor or pharmacist and tell him/her that you have taken more. Always take the outer carton of the medicine with you, even if it is empty.

If you forget to use Humira:

If you forget to give yourself an injection, you should inject the next dose of Humira as soon as you remember. Then take your next dose as you would have on your originally scheduled day, had you not forgotten a dose.

If you stop using Humira:

The decision to stop using Humira should be discussed with your doctor. Your symptoms may return upon discontinuation.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 4 months after the last Humira injection.

Tell your doctor immediately if you notice any of the following:
- Severe rash, hives or other signs of allergic reaction;
- Swollen face, hands, feet;
- Trouble breathing, swallowing;
- Shortness of breath with exertion or upon lying down or swelling of the feet.

Tell your doctor as soon as possible if you notice any of the following:
- Signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination;
- Feeling weak or tired;
- Coughing;
- Tingling;
- Numbness;
- Double vision;
- Arm or leg weakness;
- A bump or open sore that doesn't heal;
- Signs and symptoms suggestive of blood disorders such as persistent fever, bruising, bleeding, paleness.

The symptoms described above can be signs of the below listed side effects, which have been observed with Humira:

Very common (may affect more than 1 in 10 people):

- injection site reactions (including pain, swelling, redness or itching);
- respiratory tract infections (including cold, runny nose, sinus infection, pneumonia);
- headache;
- abdominal pain;
- nausea and vomiting;
- rash;
- musculoskeletal pain.

Common (may affect up to 1 in 10 people):

- serious infections (including blood poisoning and influenza);
- skin infections (including cellulitis and shingles);
- ear infections;
- oral infections (including tooth infections and cold sores);
- reproductive tract infections;
- urinary tract infection;
- fungal infections;
- joint infections;
- benign tumours;
- skin cancer;

- allergic reactions (including seasonal allergy);
- dehydration;
- mood swings (including depression);
- anxiety;
- difficulty sleeping;
- sensation disorders such as tingling, prickling or numbness;
- migraine;
- nerve root compression (including low back pain and leg pain);
- vision disturbances;
- eye inflammation;
- inflammation of the eye lid and eye swelling;
- vertigo;
- sensation of heart beating rapidly;
- high blood pressure;
- flushing;
- haematoma;
- cough;
- asthma;
- shortness of breath;
- gastrointestinal bleeding;
- dyspepsia (indigestion, bloating, heart burn);
- acid reflux disease;
- sicca syndrome (including dry eyes and dry mouth);
- itching;
- itchy rash;
- bruising;
- inflammation of the skin (such as eczema);
- breaking of finger nails and toe nails;
- increased sweating;
- hair loss;
- new onset or worsening of psoriasis;
- muscle spasms;
- blood in urine;
- kidney problems;
- chest pain;
- oedema;
- fever;
- reduction in blood platelets which increases risk of bleeding or bruising;
- impaired healing.

Uncommon (may affect up to 1 in 100 people):

- opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered);
- neurological infections (including viral meningitis);
- eye infections;
- bacterial infections;
- diverticulitis (inflammation and infection of the large intestine);
- cancer;
- cancer that affects the lymph system;
- melanoma;
- immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis);
- vasculitis (inflammation of blood vessels);
- tremor;

- neuropathy;
- stroke;
- double vision;
- hearing loss, buzzing;
- sensation of heart beating irregularly such as skipped beats;
- heart problems that can cause shortness of breath or ankle swelling;
- heart attack;
- a sac in the wall of a major artery, inflammation and clot of a vein, blockage of a blood vessel;
- lung diseases causing shortness of breath (including inflammation);
- pulmonary embolism (blockage in an artery of the lung);
- pleural effusion (abnormal collection of fluid in the pleural space);
- inflammation of the pancreas which causes severe pain in the abdomen and back;
- difficulty in swallowing;
- facial oedema;
- gallbladder inflammation, gallbladder stones;
- fatty liver;
- night sweats;
- scar;
- abnormal muscle breakdown;
- systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems);
- sleep interruptions;
- impotence;
- inflammations.

Rare (may affect up to 1 in 1,000 people):

- leukemia (cancer affecting the blood and bone marrow);
- severe allergic reaction with shock;
- multiple sclerosis;
- nerve disorders (such as eye nerve inflammation and Guillain-Barré syndrome that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body);
- heart stops pumping;
- pulmonary fibrosis (scarring of the lung);
- intestinal perforation;
- hepatitis;
- reactivation of hepatitis B;
- autoimmune hepatitis (inflammation of the liver caused by the body's own immune system);
- cutaneous vasculitis (inflammation of blood vessels in the skin);
- Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash);
- facial oedema associated with allergic reactions;
- erythema multiforme (inflammatory skin rash);
- lupus-like syndrome.

Not known (frequency cannot be estimated from available data):

- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal);
- Merkel cell carcinoma (a type of skin cancer);
- liver failure;
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness).

Some side effects observed with Humira may not have symptoms and may only be discovered through blood tests. These include:

Very common (may affect more than 1 in 10 people)

- low blood measurements for white blood cells;
- low blood measurements for red blood cells;
- increased lipids in the blood;
- elevated liver enzymes.

Common (may affect up to 1 in 10 people):

- high blood measurements for white blood cells;
- low blood measurements for platelets;
- increased uric acid in the blood;
- abnormal blood measurements for sodium;
- low blood measurements for calcium;
- low blood measurements for phosphate;
- high blood sugar;
- high blood measurements for lactate dehydrogenase;
- autoantibodies present in the blood.

Rare (may affect up to 1 in 1,000 people):

- low blood measurements for white blood cells, red blood cells and platelet count.

Not known (frequency cannot be estimated from the available data):

- liver failure.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Humira

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label/blister/carton after EXP.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

Alternative Storage:

When needed (for example when you are travelling), a single Humira pre-filled pen may be stored at room temperature (up to 25°C) for a maximum period of 14 days – be sure to protect it from light. Once removed from the refrigerator for room temperature storage, the pen **must be used within 14 days or discarded**, even if it is returned to the refrigerator.

You should record the date when the pen is first removed from refrigerator, and the date after which it should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Humira contains

The active substance is adalimumab.
The other ingredients are mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections.

This medicinal product contains less than 1 mmol of sodium (23 mg) per 0.8 ml dose, i.e. essentially 'sodium-free' and does not contain preservatives.

What the Humira pre-filled pen looks like and contents of the pack

Humira 40 mg solution for injection in pre-filled pen is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.8 ml solution.

The Humira pre-filled pen is a single-use grey- and plum-coloured pen which contains a glass syringe with Humira. There are two caps – one is grey and labelled '1' and the other is plum and labelled '2'. There is a window on each side of the pen through which you can see the Humira solution inside the syringe.

The Humira pre-filled pen is available in packs containing 1, 2, 4, and 6 pre-filled pens. The 1 pre-filled pen pack comes with 2 alcohol pads (1 spare). For the 2, 4, and 6 pre-filled pen packs, each pre-filled pen comes with 1 alcohol pad. Not all pack sizes may be marketed.

Humira is available as a vial, a pre-filled syringe and a pre-filled pen.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

Package leaflet: Information for the patient

Humira 40 mg solution for injection in pre-filled syringe
adalimumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Alert Card, which contains important safety information that you need to be aware of before you are given Humira and during treatment with Humira. Keep this Patient Alert Card with you.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet:

1. What Humira is and what it is used for

Humira contains the active substance adalimumab, a selective immuno suppressive agent.
Humira is intended for treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and non-infectious uveitis. It is a medicine that decreases the inflammation process of these diseases. The active ingredient, adalimumab, is a human monoclonal antibody produced by cultured cells. Monoclonal antibodies are proteins that recognise and bind to other unique proteins. Adalimumab binds to a specific protein (tumour necrosis factor or TNFα), which is present at increased levels in inflammatory diseases such as rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and non-infectious uveitis.

Rheumatoid arthritis

Rheumatoid arthritis is an inflammatory disease of the joints.

Humira is used to treat rheumatoid arthritis in adults. If you have moderate to severe active rheumatoid arthritis, you may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira to treat your rheumatoid arthritis.

Humira can also be used to treat severe, active and progressive rheumatoid arthritis without previous methotrexate treatment.

Humira has been shown to slow down the damage to the cartilage and bone of the joints caused by the disease and to improve physical function.

Usually, Humira is used with methotrexate. If your doctor determines that methotrexate is inappropriate, Humira can be given alone.

Polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis

Polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis are inflammatory diseases.

Humira is used to treat polyarticular juvenile idiopathic arthritis in children and adolescents aged 2 to 17 years and enthesitis-related arthritis in children and adolescents aged 6 to 17 years. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira to treat your polyarticular juvenile idiopathic arthritis or enthesitis-related arthritis.

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, are inflammatory diseases of the spine.

Humira is used to treat ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis in adults. If you have ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your disease.

Psoriatic arthritis

Psoriatic arthritis is an inflammation of the joints associated with psoriasis.

Humira is used to treat psoriatic arthritis in adults. Humira has been shown to slow down the damage to the cartilage and bone of the joints caused by the disease and to improve physical function.

Plaque psoriasis in adults and children

Plaque psoriasis is a skin condition that causes red, flaky, crusty patches of skin covered with silvery scales. Plaque psoriasis can also affect the nails, causing them to crumble, become thickened and lift away from the nail bed which can be painful. Psoriasis is believed to be caused by a problem with the body’s immune system that leads to an increased production of skin cells.

Humira is used to treat moderate to severe plaque psoriasis in adults. Humira is also used to treat severe plaque psoriasis in children and adolescents aged 4 to 17 years for whom topical therapy and phototherapies have either not worked very well or are not suitable.

Hidradenitis suppurativa in adults and adolescents

Hidradenitis suppurativa (sometimes called acne inversa) is a chronic and often painful inflammatory skin disease. Symptoms may include tender nodules (lumps) and abscesses (boils) that may leak pus. It most commonly affects specific areas of the skin, such as under the breasts, the armpits, inner thighs, groin and buttocks. Scarring may also occur in affected areas.

Humira is used to treat hidradenitis suppurativa in adults and adolescents from 12 years of age. Humira can reduce the number of nodules and abscesses you have, and the pain that is often

associated with the disease. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Crohn's disease in adults and children

Crohn's disease is an inflammatory disease of the digestive tract.

Humira is used to treat Crohn's disease in adults and children aged 6 to 17 years. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your Crohn's disease.

Ulcerative colitis

Ulcerative colitis is an inflammatory disease of the bowel.

Humira is used to treat ulcerative colitis in adults. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your disease.

Non-infectious uveitis in adults and children

Non-infectious uveitis is an inflammatory disease affecting certain parts of the eye.

Humira is used to treat
- Adults with non-infectious uveitis with inflammation affecting the back of the eye
- Children from 2 years of age with chronic non-infectious uveitis with inflammation affecting the front of the eye

This inflammation may lead to a decrease of vision and/or the presence of floaters in the eye (black dots or wispy lines that move across the field of vision). Humira works by reducing this inflammation.

2. What you need to know before you use Humira

Do not use Humira

- If you are allergic to adalimumab or any of the other ingredients of this medicine (listed in section 6).

- If you have a severe infection, including active tuberculosis (see "Warnings and precautions"). It is important that you tell your doctor if you have symptoms of infections, e.g. fever, wounds, feeling tired, dental problems.

- If you have moderate or severe heart failure. It is important to tell your doctor if you have had or have a serious heart condition (see "Warnings and precautions").

Warnings and precautions

Talk to your doctor or pharmacist before using Humira

- If you experience allergic reactions with symptoms such as chest tightness, wheezing, dizziness, swelling or rash do not inject more Humira and contact your doctor immediately.

- If you have an infection, including long-term or localized infection (for example, leg ulcer) consult your doctor before starting Humira. If you are unsure, please contact your doctor.

- You might get infections more easily while you are receiving Humira treatment. This risk may increase if your lung function is impaired. These infections may be serious and include tuberculosis, infections caused by viruses, fungi, parasites or bacteria, or other opportunistic infections and sepsis that may, in rare cases, be life-threatening. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems. Your doctor may recommend temporary discontinuation of Humira.

- As cases of tuberculosis have been reported in patients treated with Humira, your doctor will check you for signs and symptoms of tuberculosis before starting Humira. This will include a thorough medical evaluation including your medical history and appropriate screening tests (for example chest X-ray and a tuberculin test). The conduct and results of these tests should be recorded on your Patient Alert Card. It is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. Tuberculosis can develop during therapy even if you have received preventative treatment for tuberculosis. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy tell your doctor immediately.

- Advise your doctor if you reside or travel in regions where fungal infections such as histoplasmosis, coccidioidomycosis or blastomycosis are endemic.

- Advise your doctor if you have a history of recurrent infections or other conditions that increase the risk of infections.

- Advise your doctor if you are a carrier of the hepatitis B virus (HBV), if you have active HBV or if you think you might be at risk of contracting HBV. Your doctor should test you for HBV. Humira can cause reactivation of HBV in people who carry this virus. In some rare cases, especially if you are taking other medicines that suppress the immune system, reactivation of HBV can be life-threatening.

- If you are over 65 years you may be more susceptible to infections while taking Humira. You and your doctor should pay special attention to signs of infection while you are being treated with Humira. It is important to tell your doctor if you get symptoms of infections, such as fever, wounds, feeling tired or dental problems.

- If you are about to undergo surgery or dental procedures please inform your doctor that you are taking Humira. Your doctor may recommend temporary discontinuation of Humira.

- If you have or develop demyelinating disease such as multiple sclerosis, your doctor will decide if you should receive or continue to receive Humira. Tell your doctor immediately if you experience symptoms like changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body.

- Certain vaccines may cause infections and should not be given while receiving Humira. Please check with your doctor before you receive any vaccines. It is recommended that children, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy. If you received Humira while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately five months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy so they can decide when your baby should receive any vaccine.

- If you have mild heart failure and you are being treated with Humira, your heart failure status must be closely monitored by your doctor. It is important to tell your doctor if you have had

or have a serious heart condition. If you develop new or worsening symptoms of heart failure (e.g. shortness of breath, or swelling of your feet), you must contact your doctor immediately. Your doctor will decide if you should receive Humira.

- In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that does not go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

- There have been very rare cases of certain kinds of cancer in children and adult patients taking Humira or other TNF blockers. People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting lymphoma (a kind of cancer that affects the lymph system), and leukemia (a kind of cancer that affects the blood and bone marrow). If you take Humira the risk of getting lymphoma, leukemia, or other cancers may increase. On rare occasions, a specific and severe type of lymphoma has been observed in patients taking Humira. Some of those patients were also treated with azathioprine or 6- mercaptopurine. Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Humira. In addition cases of non-melanoma skin cancer have been observed in patients taking Humira. If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.

- There have been cases of cancers other than lymphoma in patients with a specific type of lung disease called Chronic Obstructive Pulmonary Disease (COPD) treated with another TNF blocker. If you have COPD, or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.

Children and adolescents

- Vaccinations: if possible children should be up to date with all vaccinations before using Humira.
- Do not give Humira to children with polyarticular juvenile idiopathic arthritis below the age of 2 years.

Other medicines and Humira

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Humira can be taken together with methotrexate or certain disease-modifying anti-rheumatic agents (sulfasalazine, hydroxychloroquine, leflunomide and injectable gold preparations), steroids or pain medications including non-steroidal anti-inflammatory drugs (NSAIDs).

You should not take Humira with medicines containing the active substance, anakinra or abatacept. If you have questions, please ask your doctor.

Humira with food and drink

Since Humira is injected under the skin (subcutaneously), food and drink should not affect Humira.

Pregnancy and breast-feeding

The effects of Humira in pregnant women are not known and so the use of Humira in pregnant women is not recommended. You are advised to avoid becoming pregnant and must use adequate contraception while using Humira and for at least 5 months after the last Humira treatment. If you become pregnant, you should consult your doctor.

It is not known whether adalimumab passes into breast milk.

If you are a breast-feeding mother, you should stop breast-feeding during Humira treatment and for at least 5 months after the last Humira treatment. If you received Humira during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy before the baby receives any vaccine (for more information see section on vaccination).

If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Humira may have a minor influence on your ability to drive, cycle or use machines. Room spinning sensation and vision disturbances may occur after taking Humira.

3. How to use Humira

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Humira is injected under the skin (subcutaneous use). The usual dose for adults with rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, and for patients with psoriatic arthritis is 40 mg adalimumab given every other week as a single dose.

In rheumatoid arthritis, methotrexate is continued while using Humira. If your doctor determines that methotrexate is inappropriate, Humira can be given alone.

If you have rheumatoid arthritis and you do not receive methotrexate with your Humira therapy, your doctor may decide to give 40 mg adalimumab every week.

Children with polyarticular juvenile idiopathic arthritis

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 2 to 12 years depends on the height and weight of the child. Your child's doctor will tell you the correct dose to use.
The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 13 to 17 years, is 40 mg every other week.

Children with enthesitis-related arthritis

The recommended dose of Humira for patients with enthesitis-related arthritis, aged 6 to 17 years depends on the height and weight of the child.

Adults with psoriasis

The usual dose for adults with psoriasis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. You should continue to inject Humira for as long as your doctor has told you. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

Children or adolescents with plaque psoriasis

The recommended dose of Humira for patients aged 4 to 17 years with plaque psoriasis depends on the weight of your child. Your child's doctor will tell you the correct dose to use.

Patients requiring a dose less than 40 mg should use the 40 mg vial presentation of Humira.

Adults with hidradenitis suppurativa

The usual dose regimen for hidradenitis suppurativa is an initial dose of 160 mg (as 4 injections in one day or 2 injections per day for two consecutive days), followed by an 80 mg dose (as 2 injections on the same day) two weeks later. After two further weeks, continue with a dose of 40 mg every week. It is recommended that you use an antiseptic wash daily on the affected areas.

Adolescents with hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)

The recommended dose of Humira is an initial dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week starting one week later. If you have an inadequate response, your doctor may increase the dose frequency to 40 mg every week.

It is recommended that you use an antiseptic wash daily on the affected areas.

Adults with Crohn's disease

The usual dose regimen for Crohn's disease is 80 mg initially followed by 40 mg every other week two weeks later. If a faster response is required your doctor may prescribe an initial dose of 160 mg (as 4 injections in one day or 2 injections per day for two consecutive days), followed by 80 mg two weeks later, and thereafter as 40 mg every other week. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

Children or adolescents with Crohn's disease

Children or adolescents weighing less than 40 kg:

The usual dose regimen is 40 mg initially followed by 20 mg two weeks later. If a faster response is required, your doctor may prescribe an initial dose of 80 mg (as 2 injections in 1 day) followed by 40 mg two weeks later.

Thereafter, the usual dose is 20 mg every other week. Depending on your response, your doctor may increase the dose frequency to 20 mg every week.

Children or adolescents weighing 40 kg or more:

The usual dose regimen is 80 mg initially followed by 40 mg two weeks later. If a faster response is required, your doctor may prescribe an initial dose of 160 mg (as 4 injections in 1 day or as 2 injections per day for 2 consecutive days) followed by 80 mg two weeks later.

Thereafter, the usual dose is 40 mg every other week. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

Patients requiring a dose less than 40 mg should use the 40 mg vial presentation of Humira.

Adults with ulcerative colitis

The usual Humira dose for adults with ulcerative colitis is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days) and 80 mg at Week 2, and thereafter 40 mg every other week. Depending on your response, your doctor may increase the dose to 40 mg every week.

Adults with non-infectious uveitis

The usual dose for adults with non-infectious uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. You should continue to inject Humira for as long as your doctor has told you.

In non-infectious uveitis, corticosteroids or other medicines that influence the immune system may be continued while using Humira. Humira can also be given alone.

Children with chronic non-infectious uveitis from 2 years of age

Children weighing less than 30 kg:

The usual dose of Humira is 20 mg every other week with methotrexate.

Your doctor may also prescribe an initial dose of 40 mg which may be administered one week prior to the start of the usual dose.

Children weighing 30 kg or more:

The usual dose of Humira is 40 mg every other week with methotrexate.

Your doctor may also prescribe an initial dose of 80 mg which may be administered one week prior to the start of the usual dose.

Method and route of administration

Humira is administered by injection under the skin (by subcutaneous injection).

Instructions for preparing and giving an injection of Humira:

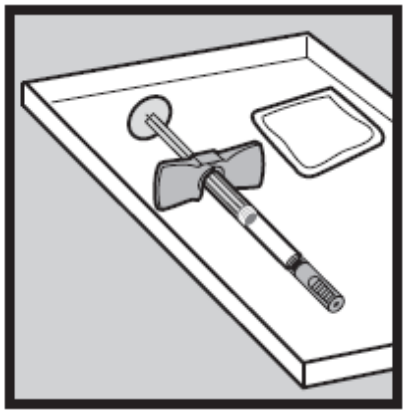
The following instructions explain how to inject Humira. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or his/her assistant on the technique of self-injection. Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection. After proper training, the injection can be self-administered or given by another person, for example a family member or friend.

This injection should not be mixed in the same syringe or vial with any other medicine.

1) Setting up

Wash your hands thoroughly
Set up the following items on a clean surface

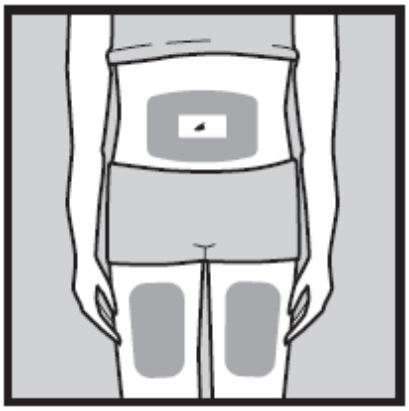
- One pre-filled syringe of Humira for injection
- One alcohol pad



Look at the expiry date on the syringe. Do not use the product after the month and year shown.

2) Choosing and preparing an injection site

Choose a site on your thigh or stomach

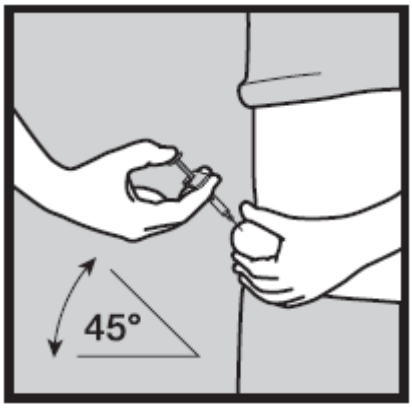


Each new injection should be given at least 3 cm from the last injection site.

- Do not inject in an area where the skin is reddened, bruised, or hard. This may mean there is an infection.
- Wipe the injection site with the enclosed alcohol pad, using a circular motion.
- Do not touch the area again before injecting.

3) Injecting Humira

- Do NOT shake the syringe.
- Remove cap from needle syringe, being careful not to touch the needle or let it touch any surface.
- With one hand, gently grasp the cleaned areas of skin and hold firmly



- With the other hand, hold syringe at 45-degree angle to skin, with the grooved side up.
- With one quick, short motion, push needle all the way into skin
- Release the skin with the first hand
- Push plunger to inject solution – it can take from 2 to 5 seconds to empty the syringe
- When the syringe is empty, remove the needle from skin, being careful to keep it at the same angle as when it was inserted
- Using your thumb or a piece of gauze, apply pressure over the injection site for 10 seconds. A little bleeding may occur. Do not rub the injection site. Use a plaster if you want to.

4) Throwing away supplies

- The Humira syringe should NEVER be reused. NEVER recap a needle.
- After injecting Humira, immediately throw away the used syringe in a special container as instructed by your doctor, nurse or pharmacist.
- Keep this container out of the sight and reach of children.

If you use more Humira than you should:

If you accidentally inject Humira more frequently than told to by your doctor or pharmacist, you should call your doctor or pharmacist and tell him/her that you have taken more. Always take the outer carton of the medicine with you, even if it is empty.

If you forget to use Humira:

If you forget to give yourself an injection, you should inject the next dose of Humira as soon as you remember. Then take your next dose as you would have on your originally scheduled day, had you not forgotten a dose.

If you stop using Humira:

The decision to stop using Humira should be discussed with your doctor. Your symptoms may return upon discontinuation.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 4 months after the last Humira injection.

Tell your doctor immediately if you notice any of the following:
- Severe rash, hives or other signs of allergic reaction;
- Swollen face, hands, feet;
- Trouble breathing, swallowing;
- Shortness of breath with exertion or upon lying down or swelling of the feet.

Tell your doctor as soon as possible if you notice any of the following:
- Signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination;
- Feeling weak or tired;
- Coughing;
- Tingling;
- Numbness;

- Double vision;
- Arm or leg weakness;
- A bump or open sore that doesn't heal;
- Signs and symptoms suggestive of blood disorders such as persistent fever, bruising, bleeding, paleness.

The symptoms described above can be signs of the below listed side effects, which have been observed with Humira:

Very common (may affect more than 1 in 10 people):

- injection site reactions (including pain, swelling, redness or itching);
- respiratory tract infections (including cold, runny nose, sinus infection, pneumonia);
- headache;
- abdominal pain;
- nausea and vomiting;
- rash;
- musculoskeletal pain.

Common (may affect up to 1 in 10people):

- serious infections (including blood poisoning and influenza);
- skin infections (including cellulitis and shingles);
- ear infections;
- oral infections (including tooth infections and cold sores);
- reproductive tract infections;
- urinary tract infection;
- fungal infections;
- joint infections;
- benign tumours;
- skin cancer;
- allergic reactions (including seasonal allergy);
- dehydration;
- mood swings (including depression);
- anxiety;
- difficulty sleeping;
- sensation disorders such as tingling, prickling or numbness;
- migraine;
- nerve root compression (including low back pain and leg pain);
- vision disturbances;
- eye inflammation;
- inflammation of the eye lid and eye swelling;
- vertigo;
- sensation of heart beating rapidly;
- high blood pressure;
- flushing;
- haematoma;
- cough;
- asthma;
- shortness of breath;
- gastrointestinal bleeding;
- dyspepsia (indigestion, bloating, heart burn);
- acid reflux disease;

- sicca syndrome (including dry eyes and dry mouth);
- itching;
- itchy rash;
- bruising;
- inflammation of the skin (such as eczema);
- breaking of finger nails and toe nails;
- increased sweating;
- hair loss;
- new onset or worsening of psoriasis;
- muscle spasms;
- blood in urine;
- kidney problems;
- chest pain;
- oedema;
- fever;
- reduction in blood platelets which increases risk of bleeding or bruising;
- impaired healing.

Uncommon (may affect up to 1 in 100 people):

- opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered);
- neurological infections (including viral meningitis);
- eye infections;
- bacterial infections;
- diverticulitis (inflammation and infection of the large intestine);
- cancer;
- cancer that affects the lymph system;
- melanoma;
- immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis);
- vasculitis (inflammation of blood vessels);
- tremor;
- neuropathy;
- stroke;
- double vision;
- hearing loss, buzzing;
- sensation of heart beating irregularly such as skipped beats;
- heart problems that can cause shortness of breath or ankle swelling;
- heart attack;
- a sac in the wall of a major artery, inflammation and clot of a vein; blockage of a blood vessel;
- lung diseases causing shortness of breath (including inflammation);
- pulmonary embolism (blockage in an artery of the lung);
- pleural effusion (abnormal collection of fluid in the pleural space);
- inflammation of the pancreas which causes severe pain in the abdomen and back;
- difficulty in swallowing;
- facial oedema;
- gallbladder inflammation, gallbladder stones;
- fatty liver;
- night sweats;
- scar;
- abnormal muscle breakdown;

- systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems);
- sleep interruptions;
- impotence;
- inflammations.

Rare (may affect up to 1 in 1,000 people):

- leukaemia (cancer affecting the blood and bone marrow);
- severe allergic reaction with shock;
- multiple sclerosis;
- nerve disorders (such as eye nerve inflammation and Guillain-Barré syndrome that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body);
- heart stops pumping;
- pulmonary fibrosis (scarring of the lung);
- intestinal perforation;
- hepatitis;
- reactivation of hepatitis B;
- autoimmune hepatitis (inflammation of the liver caused by the body's own immune system)
- cutaneous vasculitis (inflammation of blood vessels in the skin);
- Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash);
- facial oedema associated with allergic reactions;
- erythema multiforme (inflammatory skin rash);
- lupus-like syndrome.

Not known (frequency cannot be estimated from available data):

- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal);
- Merkel cell carcinoma (a type of skin cancer);
- liver failure;
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness).

Some side effects observed with Humira may not have symptoms and may only be discovered through blood tests. These include:

Very common (may affect more than 1 in 10 people):

- low blood measurements for white blood cells;
- low blood measurements for red blood cells;
- increased lipids in the blood;
- elevated liver enzymes.

Common (may affect up to 1 in 10 people):

- high blood measurements for white blood cells;
- low blood measurements for platelets;
- increased uric acid in the blood;
- abnormal blood measurements for sodium;
- low blood measurements for calcium;
- low blood measurements for phosphate;
- high blood sugar;
- high blood measurements for lactate dehydrogenase;
- autoantibodies present in the blood.

Rare (may affect up to 1 in 1,000 people):

- low blood measurements for white blood cells, red blood cells and platelet count.

Not known (frequency cannot be estimated from available data):

- liver failure.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Humira

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label/blister/carton after EXP.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

Alternative Storage:

When needed (for example when you are travelling), a single Humira pre-filled syringe may be stored at room temperature (up to 25°C) for a maximum period of 14 days – be sure to protect it from light. Once removed from the refrigerator for room temperature storage, the syringe **must be used within 14 days or discarded**, even if it is returned to the refrigerator.

You should record the date when the syringe is first removed from refrigerator, and the date after which it should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Humira contains

The active substance is adalimumab.
The other ingredients are mannitol, polysorbate 80 and water for injections.

This medicinal product contains less than 1 mmol of sodium (23 mg) per 0.4 ml dose, i.e. essentially ‘sodium-free’ and does not contain preservatives.

What the Humira pre-filled syringe looks like and contents of the pack

Humira 40 mg solution for injection in pre-filled syringe is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.4 ml solution.

The Humira pre-filled syringe is a glass syringe containing a solution of adalimumab. Each pack contains 1, 2, 4 or 6 pre-filled syringes for patient use with 1, 2, 4 or 6 alcohol pads, respectively.

Not all pack sizes may be marketed.

Humira is available as a vial, a pre-filled syringe and a pre-filled pen.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

Package leaflet: Information for the patient

Humira 40 mg solution for injection in pre-filled pen
Active substance: adalimumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a **Patient Alert Card**, which contains important safety information that you need to be aware of before you begin using Humira and during treatment with Humira. Keep this **Patient Alert Card** with you.
- If you have any questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Humira is and what it is used for

Humira contains the active substance adalimumab, which is a human monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind to other unique proteins. Humira belongs to a group of medicines that block the activity of tumour necrosis factor (TNF) in the body (TNF blockers). TNF is a specific protein involved in inflammatory processes of the body.

Humira is used to treat
- Rheumatoid arthritis
- Polyarticular juvenile idiopathic arthritis
- Enthesitis-related arthritis
- Ankylosing spondylitis
- Axial spondyloarthritis without radiographic evidence of ankylosing spondylitis
- Psoriatic arthritis
- Plaque psoriasis
- Hidradenitis suppurativa
- Crohn’s disease
- Ulcerative colitis
- Non-infectious uveitis

For more information, please see below.

Rheumatoid arthritis

Rheumatoid arthritis is an inflammatory disease of the joints.

Humira is used to treat moderate to severe rheumatoid arthritis in adults. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira.

Humira can also be used to treat severe, active and progressive rheumatoid arthritis without previous methotrexate treatment.

Humira can slow down the damage to the joints caused by the inflammatory disease and can help them move more freely.

Your doctor will decide if Humira should be used with methotrexate or alone.

Polyarticular juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis is an inflammatory disease of the joints.

Humira is used to treat polyarticular juvenile idiopathic arthritis in patients from 2 years of age. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira.

Your doctor will decide if Humira should be used with methotrexate or alone.

Enthesitis-related arthritis

Enthesitis-related arthritis is an inflammatory disease of the joints and the places where tendons join the bone.

Humira is used to treat enthesitis-related arthritis in patients from 6 years of age. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira.

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis are inflammatory diseases of the spine.

Humira is used to treat severe ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis in adults. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Psoriatic arthritis

Psoriatic arthritis is an inflammatory disease of the joints that is usually associated with psoriasis.

Humira is used to treat psoriatic arthritis in adults. Humira can slow down the damage to the joints caused by the disease and can help them move more freely. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Plaque psoriasis

Plaque psoriasis is a skin condition that causes red, flaky, crusty patches of skin covered with silvery scales. Plaque psoriasis can also affect the nails, causing them to crumble, become thickened and lift away from the nail bed which can be painful.

Humira is used to treat

- moderate to severe chronic plaque psoriasis in adults and
- severe chronic plaque psoriasis in children and adolescents aged 4 to 17 years for whom topical therapy and phototherapies have either not worked very well or are not suitable.

Hidradenitis suppurativa

Hidradenitis suppurativa (sometimes called acne inversa) is a chronic and often painful inflammatory skin disease. Symptoms may include tender nodules (lumps) and abscesses (boils) that may leak pus. It most commonly affects specific areas of the skin, such as under the breasts, the armpits, inner thighs, groin and buttocks. Scarring may also occur in affected areas.

Humira is used to treat
- moderate to severe hidradenitis suppurativa in adults and
- moderate to severe hidradenitis suppurativa in adolescents from 12 years of age.

Humira can reduce the number of nodules and abscesses caused by the disease, and the pain that is often associated with the disease. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Crohn's disease

Crohn's disease is an inflammatory disease of the digestive tract.

Humira is used to treat
- moderate to severe Crohn's disease in adults and
- moderate to severe Crohn's disease in children and adolescents aged 6 to 17 years

You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Ulcerative colitis

Ulcerative colitis is an inflammatory disease of the large intestine.

Humira is used to treat moderate to severe ulcerative colitis in adults. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Non-infectious uveitis

Non-infectious uveitis is an inflammatory disease affecting certain parts of the eye.

Humira is used to treat
- adults with non-infectious uveitis with inflammation affecting the back of the eye
- children with chronic non-infectious uveitis from 2 years of age with inflammation affecting the front of the eye

This inflammation may lead to a decrease of vision and/or the presence of floaters in the eye (black dots or wispy lines that move across the field of vision). Humira works by reducing this inflammation. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

2. What you need to know before you use Humira

Do not use Humira:

- If you are allergic to adalimumab or any of the other ingredients of this medicine (listed in section 6).

- If you have active tuberculosis or other severe infections (see "Warnings and precautions"). It is important that you tell your doctor if you have symptoms of infections, for example, fever, wounds, feeling tired, dental problems.

- If you have moderate or severe heart failure. It is important to tell your doctor if you have had or have a serious heart condition (see "Warnings and precautions").

Warnings and precautions

Talk to your doctor or pharmacist before using Humira.

Allergic reactions

- If you get allergic reactions with symptoms such as chest tightness, wheezing, dizziness, swelling or rash do not inject more Humira and contact your doctor immediately.

Infections

- If you have an infection, including long-term infection or an infection in one part of the body (for example, leg ulcer) consult your doctor before starting Humira. If you are unsure, please contact your doctor.

- You might get infections more easily while you are receiving Humira treatment. This risk may increase if you have problems with your lungs. These infections may be serious and include:
    - tuberculosis
    - infections caused by viruses, fungi, parasites or bacteria
    - other infections (for example, fungal infections)
    - severe infection in the blood (sepsis)

  In rare cases, these infections can be life-threatening. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems. Your doctor may tell you to stop using Humira for some time.

- Tell your doctor if you live or travel in regions where fungal infections (for example, histoplasmosis, coccidioidomycosis or blastomycosis) are very common.

- Tell your doctor if you have had infections which keep coming back or other conditions that increase the risk of infections.

- If you are over 65 years you may be more likely to get infections while taking Humira. You and your doctor should pay special attention to signs of infection while you are being treated with Humira. It is important to tell your doctor if you get symptoms of infections, such as fever, wounds, feeling tired or dental problems.

Tuberculosis

- It is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. If you have active tuberculosis, do not use Humira.

- As cases of tuberculosis have been reported in patients treated with Humira, your doctor will check you for signs and symptoms of tuberculosis before starting Humira. This will include a thorough medical evaluation including your medical history and appropriate screening tests (for example, chest X-ray and a tuberculin test). The conduct and results of these tests should be recorded on your **Patient Alert Card**.
- Tuberculosis can develop during therapy even if you have received treatment for the prevention of tuberculosis.
- If symptoms of tuberculosis (for example, cough that does not go away, weight loss, lack of energy, mild fever), or any other infection appear during or after therapy tell your doctor immediately.

Hepatitis B

- Tell your doctor if you are a carrier of the hepatitis B virus (HBV), if you have active HBV or if you think you might be at risk of getting HBV.
    - Your doctor should test you for HBV. In people who carry HBV, Humira can cause the virus to become active again.
    - In some rare cases, especially if you are taking other medicines that suppress the immune system, reactivation of HBV can be life-threatening.

Surgery

- If you are about to have surgery or dental procedures please inform your doctor that you are taking Humira. Your doctor may recommend temporary discontinuation of Humira.

Demyelinating disease

- If you have or develop multiple sclerosis or another demyelinating disease, your doctor will decide if you should receive or continue to receive Humira. Tell your doctor immediately if you experience symptoms like changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body.

Vaccinations

- Certain vaccines may cause infections and should not be given while receiving Humira.

    - Please check with your doctor before you receive any vaccines.
    - It is recommended that, if possible, children should be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy.
    - If you received Humira while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately five months after the last Humira dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy so they can decide when your baby should receive any vaccine.

Heart problems

- It is important that you tell your doctor if you have or have had serious heart problems.

    - If you have mild heart failure, your doctor will monitor your condition.
    - If you develop new or worsening symptoms of heart failure (for example, shortness of breath, or swelling of your feet), you must contact your doctor immediately. Your doctor will decide if you should receive Humira.

- If you develop a fever that does not go away, develop light bruises or bleed very easily or look very pale, call your doctor right away. In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. Your doctor may decide to stop treatment.

Cancer

- There have been very rare cases of certain kinds of cancer in children and adult patients taking Humira or other TNF blockers.

    - People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting lymphoma (a kind of cancer that affects the lymph system), and leukaemia (a kind of cancer that affects the blood and bone marrow).
    - If you take Humira the risk of getting lymphoma, leukaemia, or other cancers may increase. On rare occasions, an uncommon and severe type of lymphoma, has been seen in patients taking Humira. Some of those patients were also treated with azathioprine or 6-mercaptopurine.
    - Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Humira.
    - Cases of non-melanoma skin cancer have been observed in patients taking Humira.
    - If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.

- There have been cases of cancers, other than lymphoma in patients with a specific type of lung disease called Chronic Obstructive Pulmonary Disease (COPD) treated with another TNF blocker. If you have COPD, or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.

Children and adolescents

- Vaccinations: if possible children should be up to date with all vaccinations before using Humira.

Other medicines and Humira

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You should not take Humira with medicines containing the active substances:
- anakinra
- abatacept.

Humira can be taken together with:
- methotrexate
- certain disease-modifying anti-rheumatic agents (for example, sulfasalazine, hydroxychloroquine, leflunomide and injectable gold preparations)
- steroids or pain medications including non-steroidal anti-inflammatory drugs (NSAIDs).

If you have questions, please ask your doctor.

Pregnancy and breast-feeding

The use of Humira in pregnant women is not recommended. You are advised to avoid becoming pregnant and must use adequate contraception while using Humira and for at least 5 months after the last Humira treatment. If you become pregnant, you should consult your doctor.

If you receive Humira during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy before the baby receives any vaccine. For more information see section on vaccination.

It is not known whether adalimumab passes into breast milk.

You should stop breast-feeding during Humira treatment and for at least 5 months after the last Humira treatment.

If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Humira may have a small effect on your ability to drive, cycle or use machines. Room spinning sensation and vision disturbances may occur after taking Humira.

3. How to use Humira

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended doses for Humira in each of the approved uses are shown in the following table.

Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	40 mg every other week	In rheumatoid arthritis, methotrexate is continued while using Humira. If your doctor decides that methotrexate is inappropriate, Humira can be given alone. If you have rheumatoid arthritis and you do not receive methotrexate with your Humira therapy, your doctor may decide to give Humira 40 mg every week.

Polyarticular juvenile idiopathic arthritis		
Age or body weight	**How much and how often to take?**	**Notes**
Adolescents and adults from 13 years of age	40 mg every other week.	
Children from 2 to 12 years of age	Dose depends on the height and weight of the patient. The doctor will tell you the correct dose to use.	

Enthesitis-related arthritis

Age or body weight	How much and how often to take?	Notes
Children, adolescents and adults from 6 years of age	Dose depends on the height and weight of the patient. The doctor will tell you the correct dose to use.	

Plaque psoriasis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week starting one week after the first dose.	If you have an inadequate response, your doctor may increase the dose frequency to 40 mg every week.
Children and adolescents from 4 years of age	Dose depends on the weight of the child. The doctor will tell you the correct dose to use.	

Hidradenitis suppurativa		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by an 80 mg dose (two 40 mg injections in one day) two weeks later. After two further weeks, continue with a dose of 40 mg every week.	It is recommended that you use an antiseptic wash daily on the affected areas.
Adolescents from 12 years of age, weighing at least 30 kg	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week starting one week later.	If you have an inadequate response, your doctor may increase the dose frequency to 40 mg every week It is recommended that you use an antiseptic wash daily on the affected areas.

Crohn's disease		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week two weeks later. If a faster response is required your doctor may prescribe a first dose of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg (two 40 mg injections in one day) two weeks later.	Your doctor may increase the dose frequency to 40 mg every week.

	Thereafter, the usual dose is 40 mg every other week.	
Children and adolescents from 6 years of age weighing 40 kg or more	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg two weeks later. If a faster response is required, the doctor may prescribe a first dose of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg (two 40 mg injections in one day) two weeks later. Thereafter, the usual dose is 40 mg every other week.	Your doctor may increase the dose frequency to 40 mg every week.
Children and adolescents from 6 years of age weighing less than 40 kg	First dose of 40 mg, followed by 20 mg two weeks later. If a faster response is required, the doctor may prescribe a first dose of 80 mg (two 40 mg injections in one day), followed by 40 mg two weeks later. Thereafter, the usual dose is 20 mg every other week.	Your doctor may increase the dose frequency to 20 mg every week.

Ulcerative colitis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg (two 40 mg injections in one day) two weeks later. Thereafter, the usual dose is 40 mg every other week.	Your doctor may increase the dose frequency to 40 mg every week.

Non-infectious uveitis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week starting one week after the first dose.	Corticosteroids or other medicines that influence the immune system may be continued while using Humira. Humira can also be given alone.
Children from 2 years of age weighing less than 30 kg	20 mg every other week	Your doctor may prescribe an initial dose of 40 mg to be administered one week prior to the start of the usual dose of 20 mg every other week. Humira is recommended for use in combination with methotrexate.
Children from 2 years of age weighing at least 30 kg	40 mg every other week	Your doctor may prescribe an initial dose of 80 mg to be

		administered one week prior to the start of the usual dose of 40 mg every other week. Humira is recommended for use in combination with methotrexate.

Method and route of administration

Humira is administered by injection under the skin (by subcutaneous injection).

Detailed instructions on how to inject Humira are provided in section 7 'Injecting Humira'.

If you use more Humira than you should

If you accidentally inject Humira more frequently than told to by your doctor or pharmacist, you should call your doctor or pharmacist and tell them that you have taken more. Always take the outer carton of the medicine with you, even if it is empty.

If you forget to use Humira

If you forget to give yourself an injection, you should inject the next dose of Humira as soon as you remember. Then take your next dose as you would have on your originally scheduled day, had you not forgotten a dose.

If you stop using Humira

The decision to stop using Humira should be discussed with your doctor. Your symptoms may return if you stop using Humira.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 4 months after the last Humira injection.

Tell your doctor immediately if you notice any of the following

- severe rash, hives or other signs of allergic reaction
- swollen face, hands, feet
- trouble breathing, swallowing
- shortness of breath with physical activity or upon lying down or swelling of the feet

Tell your doctor as soon as possible if you notice any of the following

- signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination
- feeling weak or tired
- coughing
- tingling
- numbness
- double vision
- arm or leg weakness

- a bump or open sore that doesn't heal
- signs and symptoms suggestive of blood disorders such as persistent fever, bruising, bleeding, paleness

The symptoms described above can be signs of the below listed side effects, which have been observed with Humira.

Very common (may affect more than 1 in 10 people)

- injection site reactions (including pain, swelling, redness or itching)
- respiratory tract infections (including cold, runny nose, sinus infection, pneumonia)
- headache
- abdominal pain
- nausea and vomiting
- rash
- musculoskeletal pain

Common (may affect up to 1 in 10 people)

- serious infections (including blood poisoning and influenza)
- skin infections (including cellulitis and shingles)
- ear infections
- oral infections (including tooth infections and cold sores)
- reproductive tract infections
- urinary tract infection
- fungal infections
- joint infections
- benign tumours
- skin cancer
- allergic reactions (including seasonal allergy)
- dehydration
- mood swings (including depression)
- anxiety
- difficulty sleeping
- sensation disorders such as tingling, prickling or numbness
- migraine
- nerve root compression (including low back pain and leg pain)
- vision disturbances
- eye inflammation
- inflammation of the eye lid and eye swelling
- vertigo (feeling of dizziness or spinning)
- sensation of heart beating rapidly
- high blood pressure
- flushing
- haematoma (collection of blood outside of blood vessels)
- cough
- asthma
- shortness of breath
- gastrointestinal bleeding
- dyspepsia (indigestion, bloating, heart burn)
- acid reflux disease
- sicca syndrome (including dry eyes and dry mouth)
- itching

- itchy rash
- bruising
- inflammation of the skin (such as eczema)
- breaking of finger nails and toe nails
- increased sweating
- hair loss
- new onset or worsening of psoriasis
- muscle spasms
- blood in urine
- kidney problems
- chest pain
- oedema (swelling)
- fever
- reduction in blood platelets which increases risk of bleeding or bruising
- impaired healing

Uncommon (may affect up to 1 in 100 people)

- opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered)
- neurological infections (including viral meningitis)
- eye infections
- bacterial infections
- diverticulitis (inflammation and infection of the large intestine)
- cancer
- cancer that affects the lymph system
- melanoma
- immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis)
- vasculitis (inflammation of blood vessels)
- tremor (shaking)
- neuropathy (disorder of the nerves)
- stroke
- double vision
- hearing loss, buzzing
- sensation of heart beating irregularly such as skipped beats
- heart problems that can cause shortness of breath or ankle swelling
- heart attack
- a sac in the wall of a major artery, inflammation and clot of a vein, blockage of a blood vessel
- lung diseases causing shortness of breath (including inflammation)
- pulmonary embolism (blockage in an artery of the lung)
- pleural effusion (abnormal collection of fluid in the pleural space)
- inflammation of the pancreas which causes severe pain in the abdomen and back
- difficulty in swallowing
- facial oedema (swelling of the face)
- gallbladder inflammation, gallbladder stones
- fatty liver
- night sweats
- scar
- abnormal muscle breakdown
- systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems)
- sleep interruptions

- impotence
- inflammations

Rare (may affect up to 1 in 1,000 people)

- leukaemia (cancer affecting the blood and bone marrow)
- severe allergic reaction with shock
- multiple sclerosis
- nerve disorders (such as eye nerve inflammation and Guillain-Barré syndrome that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body)
- heart stops pumping
- pulmonary fibrosis (scarring of the lung)
- intestinal perforation (hole in the intestine)
- hepatitis
- reactivation of hepatitis B
- autoimmune hepatitis (inflammation of the liver caused by the body's own immune system)
- cutaneous vasculitis (inflammation of blood vessels in the skin)
- Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash)
- facial oedema (swelling of the face) associated with allergic reactions
- erythema multiforme (inflammatory skin rash)
- lupus-like syndrome

Not known (frequency cannot be estimated from the available data)

- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal)
- Merkel cell carcinoma (a type of skin cancer)
- liver failure
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)

Some side effects observed with Humira may not have symptoms and may only be discovered through blood tests. These include:

Very common (may affect more than 1 in 10 people)

- low blood measurements for white blood cells
- low blood measurements for red blood cells
- increased lipids in the blood
- elevated liver enzymes

Common (may affect up to 1 in 10 people)

- high blood measurements for white blood cells
- low blood measurements for platelets
- increased uric acid in the blood
- abnormal blood measurements for sodium
- low blood measurements for calcium
- low blood measurements for phosphate
- high blood sugar
- high blood measurements for lactate dehydrogenase
- autoantibodies present in the blood

Rare (may affect up to 1 in 1,000 people)

- low blood measurements for white blood cells, red blood cells and platelet count

Not known (frequency cannot be estimated from the available data)

- liver failure

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Humira

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label/blister/carton after EXP.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

Alternative Storage:

When needed (for example, when you are travelling), a single Humira pre-filled pen may be stored at room temperature (up to 25°C) for a maximum period of 14 days – be sure to protect it from light. Once removed from the refrigerator for room temperature storage, the pen **must be used within 14 days or discarded**, even if it is returned to the refrigerator.

You should record the date when the pen is first removed from refrigerator, and the date after which it should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Humira contains

The active substance is adalimumab.
The other ingredients are mannitol, polysorbate 80 and water for injections.

What the Humira pre-filled pen looks like and contents of the pack

Humira 40 mg solution for injection in pre-filled pen is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.4 ml solution.

The Humira pre-filled pen is a single-use grey- and plum-coloured pen which contains a glass syringe with Humira. There are two caps – one is grey and labelled ‘1’ and the other is plum and labelled ‘2’. There is a window on each side of the pen through which you can see the Humira solution inside the syringe.

The Humira pre-filled pen is available in packs containing 1, 2, 4, and 6 pre-filled pens. The 1 pre-filled pen pack comes with 2 alcohol pads (1 spare). For the 2, 4, and 6 pre-filled pen packs, each pre-filled pen comes with 1 alcohol pad. Not all pack sizes may be marketed.

Humira is available as a vial, a pre-filled syringe and a pre-filled pen.

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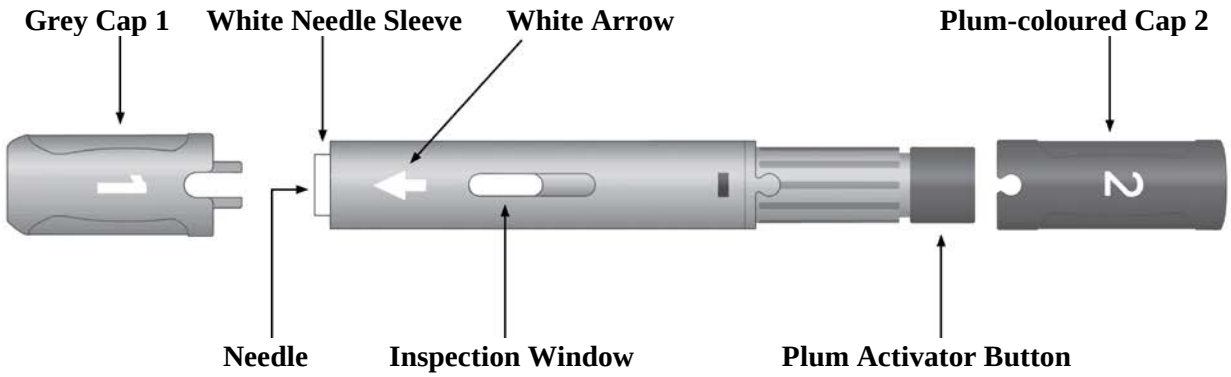
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

7. Injecting Humira

- The following instructions explain how to give yourself an injection of Humira using the pre-filled pen. First read all the instructions carefully and then follow them step by step.
- You will be instructed by your doctor, nurse or pharmacist on the technique of self-injection.
- Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection.
- After proper training, the injection can be given by yourself or given by another person, for example, a family member or friend.
- Only use each pre-filled pen for one injection.

Humira Pre-filled Pen



Do not use the pre-filled pen and call your doctor or pharmacist if the

- liquid is cloudy, discoloured, or has flakes or particles in it
- expiry (EXP) date has passed
- liquid has been frozen or left in direct sunlight
- pre-filled pen has been dropped or crushed

Do not remove the caps until just before injection. Keep Humira out of the sight and reach of children.

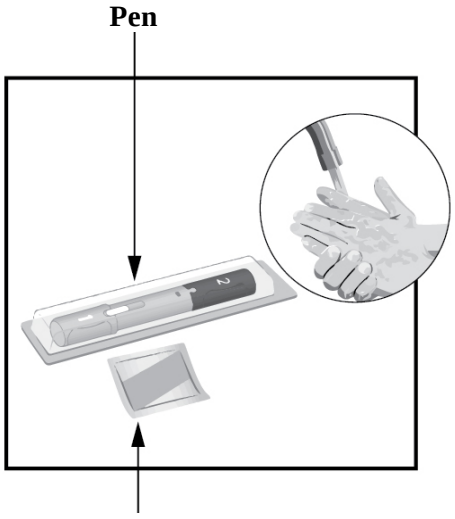
STEP 1

Take Humira out of the refrigerator.

Leave Humira at room temperature for **15 to 30 minutes** before injecting.

- **Do not** remove the Grey or Plum-coloured Caps while allowing Humira to reach room temperature
- **Do not** warm Humira in any other way. For example, **do not** warm it in a microwave or in hot water

STEP 2



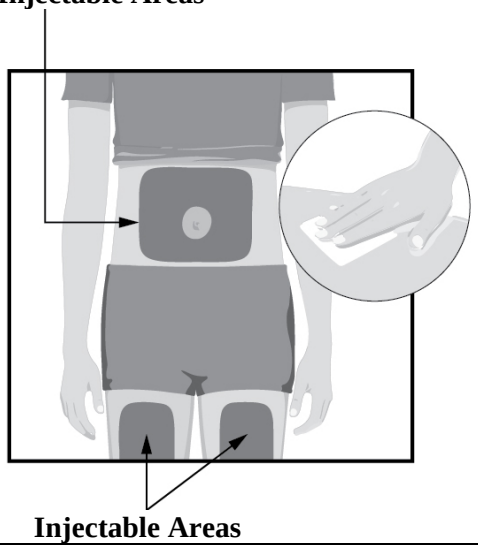
Check expiry (EXP) date. **Do not** use the pre-filled pen if expiry (EXP) date has passed.

Place the following on a clean, flat surface

- 1 single-use pre-filled pen and
- 1 alcohol pad

Wash and dry your hands.

STEP 3



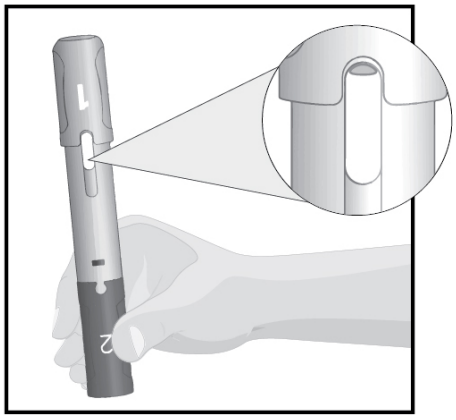
Choose an injection site:

- On the front of your thighs or
- Your belly (abdomen) at least 5 cm from your belly button (naval)
- At least 3 cm from your last injection site

Wipe the injection site in a circular motion with the alcohol pad.

- **Do not** inject through clothes
- **Do not** inject into skin that is sore, bruised, red, hard, scarred, has stretch marks, or areas with psoriasis plaques

STEP 4



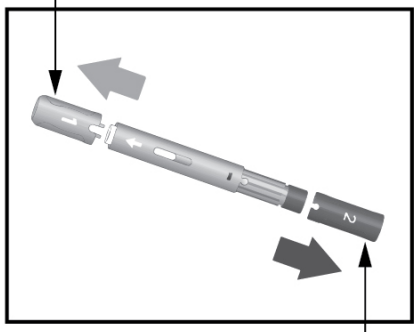
Hold the pre-filled pen with the Grey Cap 1 pointing up.

Check the inspection window.

- It is normal to see 1 or more bubbles in the window
- Make sure the liquid is clear and colourless
- **Do not** use the pre-filled pen if the liquid is cloudy or has particles
- **Do not** use the pre-filled pen if it has been dropped or crushed

STEP 5

Cap 1



Cap 2

Pull the Grey Cap 1 straight off. Throw the cap away. Do not recap.

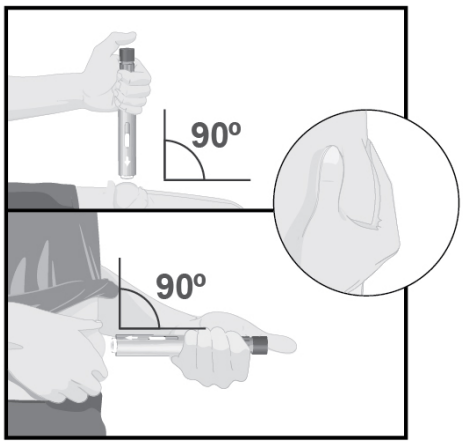
- Check that the small black needle cover of the syringe has been removed with the cap
- It is normal to see a few drops of liquid come out of the needle

Pull the Plum-coloured Cap 2 straight off. Throw the cap away. Do not recap.

The pre-filled pen is now ready to use.

Turn the pre-filled pen so that the white arrow points toward the injection site.

STEP 6



Squeeze the skin at your injection site with your other hand to make a raised area and hold it firmly.

Point the white arrow toward the injection site (thigh or abdomen).

Place the white needle sleeve straight **(90˚ angle)** against the injection site.

Hold the pre-filled pen so that you can see the inspection window.

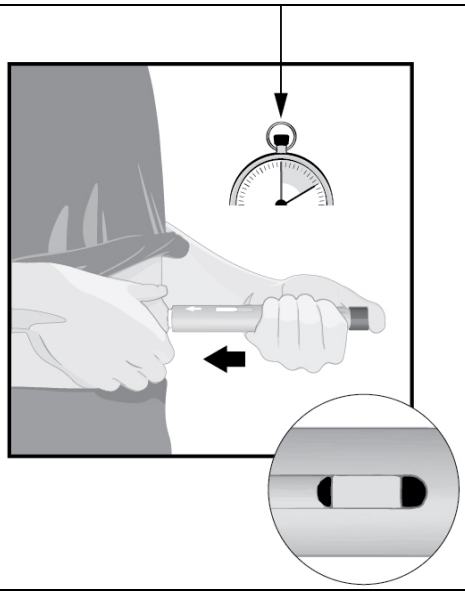
STEP 7

10 Seconds

Push and keep pushing the pre-filled pen down against the injection site.

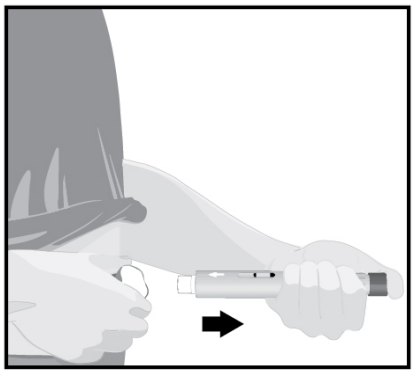
Press the plum activator button and count slowly for **10** seconds.

- A loud **"click"** will signal the start of the injection
- **Keep pushing** the pre-filled pen down against the injection site.



The injection is complete when the yellow indicator has stopped moving.

STEP 8



When the injection is completed, slowly pull the pre-filled pen from the skin. The white needle sleeve will cover the needle tip.

If there are more than a few drops of liquid on the injection site, contact your doctor, nurse or pharmacist.

After completing the injection, place a cotton ball or gauze pad on the skin over the injection site.

- **Do not** rub
- Slight bleeding at the injection site is normal

STEP 9

Throw away the used pre-filled pen in a special disposal container as instructed by your doctor, nurse or pharmacist.

- **Do not** recycle or throw the pre-filled pen in the household waste
- **Always** keep the pre-filled pen and the special disposal container out of the sight and reach of children

The caps, alcohol pad, cotton ball or gauze pad, blister, and packaging may be put in your household waste.

Package leaflet: Information for the patient

Humira 80 mg solution for injection in pre-filled syringe
Active substance: adalimumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a **Patient Alert Card**, which contains important safety information that you need to be aware of before you begin using Humira and during treatment with Humira. Keep this **Patient Alert Card** with you.
- If you have any questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Humira is and what it is used for

Humira contains the active substance adalimumab, which is a human monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind to other unique proteins. Humira belongs to a group of medicines that block the activity of tumour necrosis factor (TNF) in the body (TNF blockers). TNF is a specific protein involved in inflammatory processes of the body.

Humira is used to treat
- Plaque psoriasis
- Hidradenitis suppurativa
- Crohn’s disease
- Ulcerative colitis
- Non-infectious uveitis

For more information, please see below.

Plaque psoriasis

Plaque psoriasis is a skin condition that causes red, flaky, crusty patches of skin covered with silvery scales. Plaque psoriasis can also affect the nails, causing them to crumble, become thickened and lift away from the nail bed which can be painful.

Humira is used to treat moderate to severe chronic plaque psoriasis in adults.

Hidradenitis suppurativa

Hidradenitis suppurativa (sometimes called acne inversa) is a chronic and often painful inflammatory skin disease. Symptoms may include tender nodules (lumps) and abscesses (boils) that may leak pus.

It most commonly affects specific areas of the skin, such as under the breasts, the armpits, inner thighs, groin and buttocks. Scarring may also occur in affected areas.

Humira is used to treat
- moderate to severe hidradenitis suppurativa in adults and
- moderate to severe hidradenitis suppurativa in adolescents from 12 years of age.

Humira can reduce the number of nodules and abscesses caused by the disease, and the pain that is often associated with the disease. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Crohn's disease

Crohn's disease is an inflammatory disease of the digestive tract.

Humira is used to treat
- Crohn's disease in adults and
- Crohn's disease in children and adolescents aged 6 to 17 years

You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Ulcerative colitis

Ulcerative colitis is an inflammatory disease of the large intestine.

Humira is used to treat ulcerative colitis in adults. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Non-infectious uveitis

Non-infectious uveitis is an inflammatory disease affecting certain parts of the eye.

Humira is used to treat
- adults with non-infectious uveitis with inflammation affecting the back of the eye
- children with chronic non-infectious uveitis from 2 years of age with inflammation affecting the front of the eye

This inflammation may lead to a decrease of vision and/or the presence of floaters in the eye (black dots or wispy lines that move across the field of vision). Humira works by reducing this inflammation. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

2. What you need to know before you use Humira

Do not use Humira:

- If you are allergic to adalimumab or any of the other ingredients of this medicine (listed in section 6).

- If you have active tuberculosis or other severe infections (see "Warnings and precautions"). It is important that you tell your doctor if you have symptoms of infections, for example, fever, wounds, feeling tired, dental problems.

- If you have moderate or severe heart failure. It is important to tell your doctor if you have had or have a serious heart condition (see “Warnings and precautions”).

Warnings and precautions

Talk to your doctor or pharmacist before using Humira.

Allergic reactions

- If you get allergic reactions with symptoms such as chest tightness, wheezing, dizziness, swelling or rash do not inject more Humira and contact your doctor immediately.

Infections

- If you have an infection, including long-term infection or an infection in one part of the body (for example, leg ulcer) consult your doctor before starting Humira. If you are unsure, please contact your doctor.

- You might get infections more easily while you are receiving Humira treatment. This risk may increase if you have problems with your lungs. These infections may be serious and include:

    - tuberculosis

    - infections caused by viruses, fungi, parasites or bacteria

    - severe infection in the blood (sepsis)

  In rare cases, these infections can be life-threatening. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems. Your doctor may tell you to stop using Humira for some time.

- Tell your doctor if you live or travel in regions where fungal infections (for example, histoplasmosis, coccidioidomycosis or blastomycosis) are very common.

- Tell your doctor if you have had infections which keep coming back or other conditions that increase the risk of infections.

- If you are over 65 years you may be more likely to get infections while taking Humira. You and your doctor should pay special attention to signs of infection while you are being treated with Humira. It is important to tell your doctor if you get symptoms of infections, such as fever, wounds, feeling tired or dental problems.

Tuberculosis

- It is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. If you have active tuberculosis, do not use Humira.

    - As cases of tuberculosis have been reported in patients treated with Humira, your doctor will check you for signs and symptoms of tuberculosis before starting Humira. This will include a thorough medical evaluation including your medical history and appropriate screening tests (for example, chest X-ray and a tuberculin test). The conduct and results of these tests should be recorded on your **Patient Alert Card**.

- Tuberculosis can develop during therapy even if you have received treatment for the prevention of tuberculosis.

- If symptoms of tuberculosis (for example, cough that does not go away, weight loss, lack of energy, mild fever), or any other infection appear during or after therapy tell your doctor immediately.

Hepatitis B

- Tell your doctor if you are a carrier of the hepatitis B virus (HBV), if you have active HBV or if you think you might be at risk of getting HBV.

    - Your doctor should test you for HBV. In people who carry HBV, Humira can cause the virus to become active again.

    - In some rare cases, especially if you are taking other medicines that suppress the immune system, reactivation of HBV can be life-threatening.

Surgery

- If you are about to have surgery or dental procedures please inform your doctor that you are taking Humira. Your doctor may recommend temporary discontinuation of Humira.

Demyelinating disease

- If you have or develop multiple sclerosis or another demyelinating disease, your doctor will decide if you should receive or continue to receive Humira. Tell your doctor immediately if you experience symptoms like changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body.

Vaccinations

- Certain vaccines may cause infections and should not be given while receiving Humira.
    - Please check with your doctor before you receive any vaccines.

    - It is recommended that, if possible, children should be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy.

    - If you received Humira while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately five months after the last Humira dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy so they can decide when your baby should receive any vaccine.

Heart problems

- It is important that you tell your doctor if you have or have had serious heart problems.

    - If you have mild heart failure, your doctor will monitor your condition.

    - If you develop new or worsening symptoms of heart failure (for example, shortness of breath, or swelling of your feet), you must contact your doctor immediately. Your doctor will decide if you should receive Humira.

- If you develop a fever that does not go away, develop light bruises or bleed very easily or look very pale, call your doctor right away. In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. Your doctor may decide to stop treatment.

Cancer

- There have been very rare cases of certain kinds of cancer in children and adult patients taking Humira or other TNF blockers.
    - People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting lymphoma (a kind of cancer that affects the lymph system), and leukaemia (a kind of cancer that affects the blood and bone marrow).
    - If you take Humira the risk of getting lymphoma, leukaemia, or other cancers may increase. On rare occasions, an uncommon and severe type of lymphoma has been seen in patients taking Humira. Some of those patients were also treated with azathioprine or 6- mercaptopurine.
    - Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Humira.
    - Cases of non-melanoma skin cancer have been observed in patients taking Humira.
    - If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.
- There have been cases of cancers, other than lymphoma, in patients with a specific type of lung disease called Chronic Obstructive Pulmonary Disease (COPD) treated with another TNF blocker. If you have COPD, or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.

Children and adolescents

- Vaccinations: if possible children should be up to date with all vaccinations before using Humira.

Other medicines and Humira

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You should not take Humira with medicines containing the active substances:
- anakinra
- abatacept.

Humira can be taken together with:
- methotrexate
- certain disease-modifying anti-rheumatic agents (for example, sulfasalazine, hydroxychloroquine, leflunomide and injectable gold preparations)
- steroids or pain medications including non-steroidal anti-inflammatory drugs (NSAIDs).

If you have questions, please ask your doctor.

Pregnancy and breast-feeding

The use of Humira in pregnant women is not recommended. You are advised to avoid becoming pregnant and must use adequate contraception while using Humira and for at least 5 months after the last Humira treatment. If you become pregnant, you should consult your doctor.

If you receive Humira during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy before the baby receives any vaccine. For more information see section on vaccination.

It is not known whether adalimumab passes into breast milk.

You should stop breast-feeding during Humira treatment and for at least 5 months after the last Humira treatment.

If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Humira may have a small effect on your ability to drive, cycle or use machines. Room spinning sensation and vision disturbances may occur after taking Humira.

3. How to use Humira

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended doses for Humira in each of the approved uses are shown in the following table. Your doctor may prescribe another strength of Humira if you need a different dose.

Plaque psoriasis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 80 mg (one 80 mg injection), followed by 40 mg every other week starting one week after the first dose.	If you have an inadequate response, your doctor may increase the dose frequency to 40 mg every week.

Hidradenitis suppurativa		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 160 mg (two 80 mg injections in one day or one 80 mg injection per day for two consecutive days), followed by an 80 mg dose (one 80 mg injection) two weeks later. After two further weeks, continue with a dose of 40 mg every week.	It is recommended that you use an antiseptic wash daily on the affected areas.

Adolescents from 12 years of age, weighing at least 30 kg	First dose of 80 mg (one 80 mg injection), followed by 40 mg every other week starting one week later.	If you have an inadequate response, your doctor may increase the dose frequency to 40 mg every week It is recommended that you use an antiseptic wash daily on the affected areas.

Crohn's disease		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 80 mg (one 80 mg injection), followed by 40 mg every other week two weeks later. If a faster response is required your doctor may prescribe a first dose of 160 mg (two 80 mg injections in one day or one 80 mg injection per day for two consecutive days), followed by 80 mg (one 80 mg injection) two weeks later. Thereafter, the usual dose is 40 mg every other week.	Your doctor may increase the dose frequency to 40 mg every week.
Children and adolescents from 6 years of age weighing 40 kg or more	First dose of 80 mg (one 80 mg injection), followed by 40 mg two weeks later. If a faster response is required, the doctor may prescribe a first dose of 160 mg (two 80 mg injections in one day or one 80 mg injection per day for two consecutive days), followed by 80 mg (one 80 mg injection) two weeks later. Thereafter, the usual dose is 40 mg every other week.	Your doctor may increase the dose frequency to 40 mg every week.
Children and adolescents from 6 years of age weighing less than 40 kg	First dose of 40 mg, followed by 20 mg two weeks later. If a faster response is required, the doctor may prescribe a first dose of 80 mg (one 80 mg injection), followed by 40 mg two weeks later. Thereafter, the usual dose is 20 mg every other week.	Your doctor may increase the dose frequency to 20 mg every week.

Ulcerative colitis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 160 mg (two 80 mg injections in one day or one 80 mg injection per day for two consecutive days), followed by 80 mg (one 80 mg injection) two weeks later. Thereafter, the usual dose is 40 mg every other week.	Your doctor may increase the dose frequency to 40 mg every week.

Non-infectious uveitis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 80 mg (one 80 mg injection), followed by 40 mg every other week starting one week after the first dose.	Corticosteroids or other medicines that influence the immune system may be continued while using Humira. Humira can also be given alone.
Children from 2 years of age weighing less than 30 kg	20 mg every other week	Your doctor may prescribe an initial dose of 40 mg to be administered one week prior to the start of the usual dose of 20 mg every other week. Humira is recommended for use in combination with methotrexate.
Children from 2 years of age weighing at least 30 kg	40 mg every other week	Your doctor may prescribe an initial dose of 80 mg to be administered one week prior to the start of the usual dose of 40 mg every other week. Humira is recommended for use in combination with methotrexate.

Method and route of administration

Humira is administered by injection under the skin (by subcutaneous injection).

Detailed instructions on how to inject Humira are provided in section 7 'Injecting Humira'.

If you use more Humira than you should

If you accidentally inject Humira more frequently than told to by your doctor or pharmacist, you should call your doctor or pharmacist and tell them that you have taken more. Always take the outer carton of the medicine with you, even if it is empty.

If you forget to use Humira

If you forget to give yourself an injection, you should inject the next dose of Humira as soon as you remember. Then take your next dose as you would have on your originally scheduled day, had you not forgotten a dose.

If you stop using Humira

The decision to stop using Humira should be discussed with your doctor. Your symptoms may return if you stop using Humira.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 4 months after the last Humira injection.

Tell your doctor immediately if you notice any of the following

- severe rash, hives or other signs of allergic reaction
- swollen face, hands, feet
- trouble breathing, swallowing
- shortness of breath with physical activity or upon lying down or swelling of the feet

Tell your doctor as soon as possible if you notice any of the following

- signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination
- feeling weak or tired
- coughing
- tingling
- numbness
- double vision
- arm or leg weakness
- a bump or open sore that doesn't heal
- signs and symptoms suggestive of blood disorders such as persistent fever, bruising, bleeding, paleness

The symptoms described above can be signs of the below listed side effects, which have been observed with Humira.

Very common (may affect more than 1 in 10 people)

- injection site reactions (including pain, swelling, redness or itching)
- respiratory tract infections (including cold, runny nose, sinus infection, pneumonia)
- headache
- abdominal pain
- nausea and vomiting
- rash
- musculoskeletal pain

Common (may affect up to 1 in 10 people)

- serious infections (including blood poisoning and influenza)
- skin infections (including cellulitis and shingles)
- ear infections
- oral infections (including tooth infections and cold sores)

- reproductive tract infections
- urinary tract infection
- fungal infections
- joint infections
- benign tumours
- skin cancer
- allergic reactions (including seasonal allergy)
- dehydration
- mood swings (including depression)
- anxiety
- difficulty sleeping
- sensation disorders such as tingling, prickling or numbness
- migraine
- nerve root compression (including low back pain and leg pain)
- vision disturbances
- eye inflammation
- inflammation of the eye lid and eye swelling
- vertigo (feeling of dizziness or spinning)
- sensation of heart beating rapidly
- high blood pressure
- flushing
- haematoma (collection of blood outside of blood vessels)
- cough
- asthma
- shortness of breath
- gastrointestinal bleeding
- dyspepsia (indigestion, bloating, heart burn)
- acid reflux disease
- sicca syndrome (including dry eyes and dry mouth)
- itching
- itchy rash
- bruising
- inflammation of the skin (such as eczema)
- breaking of finger nails and toe nails
- increased sweating
- hair loss
- new onset or worsening of psoriasis
- muscle spasms
- blood in urine
- kidney problems
- chest pain
- oedema (swelling)
- fever
- reduction in blood platelets which increases risk of bleeding or bruising
- impaired healing

Uncommon (may affect up to 1 in 100 people)

- opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered)
- neurological infections (including viral meningitis)
- eye infections
- bacterial infections

- diverticulitis (inflammation and infection of the large intestine)
- cancer
- cancer that affects the lymph system
- melanoma
- immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis)
- vasculitis (inflammation of blood vessels)
- tremor (shaking)
- neuropathy (disorder of the nerves)
- stroke
- double vision
- hearing loss, buzzing
- sensation of heart beating irregularly such as skipped beats
- heart problems that can cause shortness of breath or ankle swelling
- heart attack
- a sac in the wall of a major artery, inflammation and clot of a vein; blockage of a blood vessel
- lung diseases causing shortness of breath (including inflammation)
- pulmonary embolism (blockage in an artery of the lung)
- pleural effusion (abnormal collection of fluid in the pleural space)
- inflammation of the pancreas which causes severe pain in the abdomen and back
- difficulty in swallowing
- facial oedema (swelling of the face)
- gallbladder inflammation, gallbladder stones
- fatty liver
- night sweats
- scar
- abnormal muscle breakdown
- systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems)
- sleep interruptions
- impotence
- inflammations

Rare (may affect up to 1 in 1,000 people)

- leukaemia (cancer affecting the blood and bone marrow)
- severe allergic reaction with shock
- multiple sclerosis
- nerve disorders (such as eye nerve inflammation and Guillain-Barré syndrome that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body)
- heart stops pumping
- pulmonary fibrosis (scarring of the lung)
- intestinal perforation (hole in the intestine)
- hepatitis
- reactivation of hepatitis B
- autoimmune hepatitis (inflammation of the liver caused by the body's own immune system)
- cutaneous vasculitis (inflammation of blood vessels in the skin)
- Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash)
- facial oedema (swelling of the face) associated with allergic reactions
- erythema multiforme (inflammatory skin rash)
- lupus-like syndrome

Not known (frequency cannot be estimated from the available data)

- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal)
- Merkel cell carcinoma (a type of skin cancer)
- liver failure
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)

Some side effects observed with Humira may not have symptoms and may only be discovered through blood tests. These include:

Very common (may affect more than 1 in 10 people)

- low blood measurements for white blood cells
- low blood measurements for red blood cells
- increased lipids in the blood
- elevated liver enzymes

Common (may affect up to 1 in 10 people)

- high blood measurements for white blood cells
- low blood measurements for platelets
- increased uric acid in the blood
- abnormal blood measurements for sodium
- low blood measurements for calcium
- low blood measurements for phosphate
- high blood sugar
- high blood measurements for lactate dehydrogenase
- autoantibodies present in the blood

Rare (may affect up to 1 in 1,000 people)

- low blood measurements for white blood cells, red blood cells and platelet count

Not known (frequency cannot be estimated from the available data)

- liver failure

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Humira

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label/blister/carton after EXP.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

Alternative Storage:

When needed (for example when you are travelling), a single Humira pre-filled syringe may be stored at room temperature (up to 25°C) for a maximum period of 14 days – be sure to protect it from light. Once removed from the refrigerator for room temperature storage, the syringe **must be used within 14 days or discarded**, even if it is returned to the refrigerator.

You should record the date when the syringe is first removed from refrigerator, and the date after which it should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Humira contains

The active substance is adalimumab.
The other ingredients are mannitol, polysorbate 80 and water for injections.

What the Humira pre-filled syringe looks like and contents of the pack

Humira 80 mg solution for injection in pre-filled syringe is supplied as a sterile solution of 80 mg adalimumab dissolved in 0.8 ml solution.

The Humira pre-filled syringe is a glass syringe containing a solution of adalimumab.

The Humira pre-filled syringe is available in a pack containing 1 pre-filled syringe for patient use with 1 alcohol pad.

Humira is available as a vial, a pre-filled syringe and a pre-filled pen.

Marketing Authorisation Holder

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Manufacturer

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

7. Injecting Humira

- The following instructions explain how to give yourself a subcutaneous injection of Humira using the pre-filled syringe. First read all the instructions carefully and then follow them step by step.

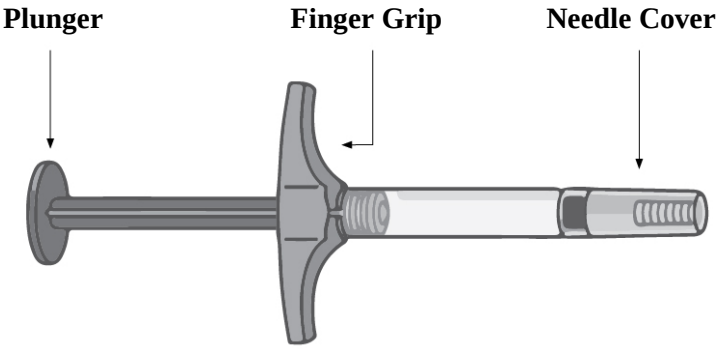
- You will be instructed by your doctor, nurse or pharmacist on the technique of self-injection.

- Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection.

- After proper training, the injection can be given by yourself or given by another person, for example, a family member or friend.

- Only use each pre-filled syringe for one injection.

Humira Pre-filled Syringe

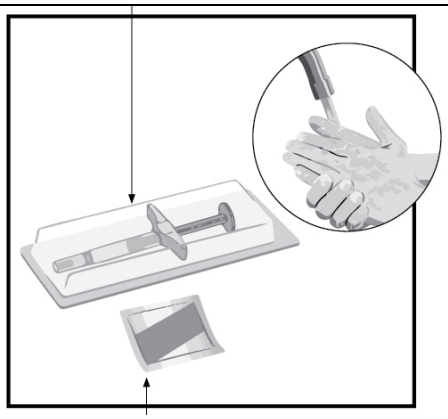


Do not use the pre-filled syringe and call your doctor or pharmacist if the

- liquid is cloudy, discoloured, or has flakes or particles in it
- expiry (EXP) date has passed
- liquid has been frozen or left in direct sunlight
- pre-filled syringe has been dropped or crushed

Do not remove the needle cover until just before injection. Keep Humira out of the sight and reach of children.

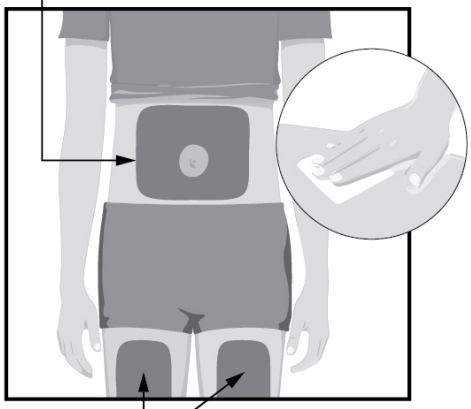
STEP 1 Take Humira out of the refrigerator. Leave Humira at room temperature for **15 to 30 minutes** before injecting. • **Do not** remove the needle cover while allowing Humira to reach room temperature • **Do not** warm Humira in any other way. For example, **do not** warm it in a microwave or in hot water	
STEP 2 **Syringe**	Check the expiry (EXP) date. **Do not** use the pre-filled syringe if expiry (EXP) date has passed. Place the following on a clean, flat surface • 1 single-use pre-filled syringe and • 1 alcohol pad Wash and dry your hands.



Pad

STEP 3

Injectable Areas



Injectable Areas

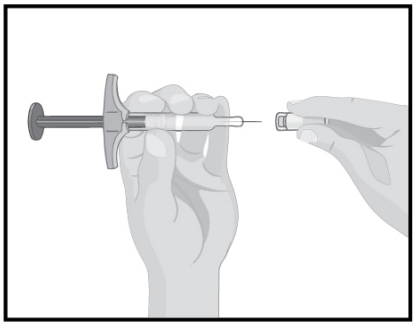
Choose an injection site:

- On the front of your thighs or
- Your belly (abdomen) at least 5 cm from your belly button (navel)
- At least 3 cm from your last injection site

Wipe the injection site in a circular motion with the alcohol pad.

- **Do not** inject through clothes
- **Do not** inject into skin that is sore, bruised, red, hard, scarred, has stretch marks, or areas with psoriasis plaques

STEP 4



Hold the pre-filled syringe in one hand.

Check the liquid in the pre-filled syringe.

- Make sure the liquid is clear and colourless
- **Do not** use the pre-filled syringe if the liquid is cloudy or has particles
- **Do not** use the pre-filled syringe if it has been dropped or crushed

Gently pull the needle cover straight off with the other hand. Throw the needle cover away. Do not recap.

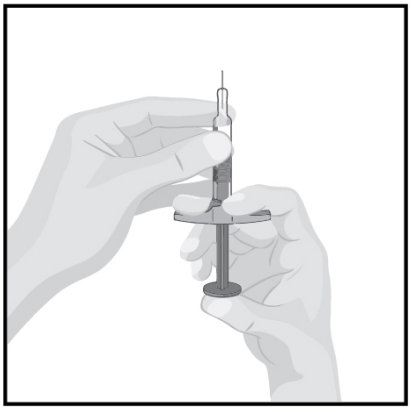
- **Do not** touch the needle with your fingers or let the needle touch anything

STEP 5

Hold the pre-filled syringe with the needle facing up.

- Hold the pre-filled syringe at eye level with one hand so you can see the air in the pre-filled syringe

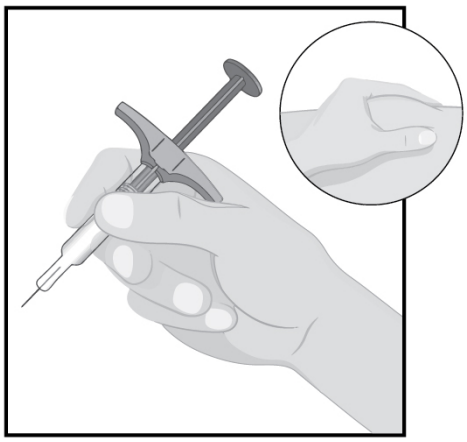
Slowly push the plunger in to push the air out through the



needle.

- It is normal to see a drop of liquid at the end of the needle

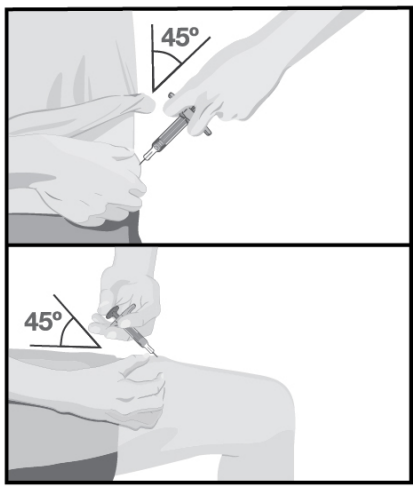
STEP 6



Hold the body of the pre-filled syringe in one hand between the thumb and index fingers, like you would a pencil.

Squeeze the skin at your injection site with your other hand to make a raised area and hold it firmly.

STEP 7



Insert the needle all the way into the skin at about a 45-degree angle with one quick, short motion.

- After the needle is in, let go of the skin you are holding

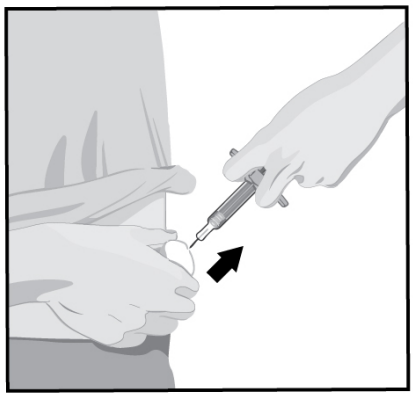
Slowly push the plunger all the way in until all of the liquid is injected and the pre-filled syringe is empty.

STEP 8

When the injection is completed, slowly pull the needle out of the skin while keeping the pre-filled syringe at the same angle.

After completing the injection, place a cotton ball or gauze pad on the skin over the injection site.

- **Do not** rub
- Slight bleeding at the injection site is normal



STEP 9

Throw away the used pre-filled syringe in a special disposal container as instructed by your doctor, nurse or pharmacist. **Never** recap a needle.

- **Do not** recycle or throw the pre-filled syringe in the household waste
- **Always** keep the pre-filled syringe and the special disposal container out of the sight and reach of children

The needle cover, alcohol pad, cotton ball or gauze pad, blister and packaging may be put in your household waste.

Package leaflet: Information for the patient

Humira 80 mg solution for injection in pre-filled pen
Active substance: adalimumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a **Patient Alert Card**, which contains important safety information that you need to be aware of before you begin using Humira and during treatment with Humira. Keep this **Patient Alert Card** with you.
- If you have any questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Humira is and what it is used for

Humira contains the active substance adalimumab, which is a human monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind to other unique proteins. Humira belongs to a group of medicines that block the activity of tumour necrosis factor (TNF) in the body (TNF blockers). TNF is a specific protein involved in inflammatory processes of the body.

Humira is used to treat
- Plaque psoriasis
- Hidradenitis suppurativa
- Crohn’s disease
- Ulcerative colitis
- Non-infectious uveitis

For more information, please see below.

Plaque psoriasis

Plaque psoriasis is a skin condition that causes red, flaky, crusty patches of skin covered with silvery scales. Plaque psoriasis can also affect the nails, causing them to crumble, become thickened and lift away from the nail bed which can be painful.

Humira is used to treat
- moderate to severe chronic plaque psoriasis in adults

Hidradenitis suppurativa

Hidradenitis suppurativa (sometimes called acne inversa) is a chronic and often painful inflammatory skin disease. Symptoms may include tender nodules (lumps) and abscesses (boils) that may leak pus. It most commonly affects specific areas of the skin, such as under the breasts, the armpits, inner thighs, groin and buttocks. Scarring may also occur in affected areas.

Humira is used to treat
- moderate to severe hidradenitis suppurativa in adults and
- moderate to severe hidradenitis suppurativa in adolescents aged 12 to 17 years

Humira can reduce the number of nodules and abscesses caused by the disease, and the pain that is often associated with the disease. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Crohn's disease

Crohn's disease is an inflammatory disease of the digestive tract.

Humira is used to treat
- moderate to severe Crohn's disease in adults and
- moderate to severe Crohn's disease in children and adolescents aged 6 to 17 years

You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Ulcerative colitis

Ulcerative colitis is an inflammatory disease of the large intestine.

Humira is used to treat moderate to severe ulcerative colitis in adults. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Non-infectious uveitis

Non-infectious uveitis is an inflammatory disease affecting certain parts of the eye.

Humira is used to treat
- adults with non-infectious uveitis with inflammation affecting the back of the eye
- children with chronic non-infectious uveitis from 2 years of age with inflammation affecting the front of the eye

This inflammation may lead to a decrease of vision and/or the presence of floaters in the eye (black dots or wispy lines that move across the field of vision). Humira works by reducing this inflammation. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

2. What you need to know before you use Humira

Do not use Humira:

- If you are allergic to adalimumab or any of the other ingredients of this medicine (listed in section 6).

- If you have active tuberculosis or other severe infections (see “Warnings and precautions”). It is important that you tell your doctor if you have symptoms of infections, for example, fever, wounds, feeling tired, dental problems.

- If you have moderate or severe heart failure. It is important to tell your doctor if you have had or have a serious heart condition (see “Warnings and precautions”).

Warnings and precautions

Talk to your doctor or pharmacist before using Humira.

Allergic reactions

- If you get allergic reactions with symptoms such as chest tightness, wheezing, dizziness, swelling or rash do not inject more Humira and contact your doctor immediately.

Infections

- If you have an infection, including long-term infection or an infection in one part of the body (for example, leg ulcer) consult your doctor before starting Humira. If you are unsure, please contact your doctor.

- You might get infections more easily while you are receiving Humira treatment. This risk may increase if you have problems with your lungs. These infections may be serious and include:
    - tuberculosis
    - infections caused by viruses, fungi, parasites or bacteria
    - severe infection in the blood (sepsis)

  In rare cases, these infections can be life-threatening. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems. Your doctor may tell you to stop using Humira for some time.

- Tell your doctor if you live or travel in regions where fungal infections (for example, histoplasmosis, coccidioidomycosis or blastomycosis) are very common.

- Tell your doctor if you have had infections which keep coming back or other conditions that increase the risk of infections.

- If you are over 65 years you may be more likely to get infections while taking Humira. You and your doctor should pay special attention to signs of infection while you are being treated with Humira. It is important to tell your doctor if you get symptoms of infections, such as fever, wounds, feeling tired or dental problems.

Tuberculosis

- It is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. If you have active tuberculosis, do not use Humira.

    - As cases of tuberculosis have been reported in patients treated with Humira, your doctor will check you for signs and symptoms of tuberculosis before starting Humira. This will include a thorough medical evaluation including your medical history and appropriate screening tests (for example, chest X-ray and a tuberculin test). The conduct and results of these tests should be recorded on your **Patient Alert Card**.

- Tuberculosis can develop during therapy even if you have received treatment for the prevention of tuberculosis.
- If symptoms of tuberculosis (for example, cough that does not go away, weight loss, lack of energy, mild fever), or any other infection appear during or after therapy tell your doctor immediately.

Hepatitis B

- Tell your doctor if you are a carrier of the hepatitis B virus (HBV), if you have active HBV or if you think you might be at risk of getting HBV.
    - Your doctor should test you for HBV. In people who carry HBV, Humira can cause the virus to become active again.
    - In some rare cases, especially if you are taking other medicines that suppress the immune system, reactivation of HBV can be life-threatening.

Surgery

- If you are about to have surgery or dental procedures please inform your doctor that you are taking Humira. Your doctor may recommend temporary discontinuation of Humira.

Demyelinating disease

- If you have or develop multiple sclerosis or another demyelinating disease, your doctor will decide if you should receive or continue to receive Humira. Tell your doctor immediately if you experience symptoms like changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body.

Vaccinations

- Certain vaccines may cause infections and should not be given while receiving Humira.

    - Please check with your doctor before you receive any vaccines.
    - It is recommended that, if possible, children should be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy.
    - If you received Humira while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately five months after the last Humira dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy so they can decide when your baby should receive any vaccine.

Heart problems

- It is important that you tell your doctor if you have or have had serious heart problems.

    - If you have mild heart failure, your doctor will monitor your condition.
    - If you develop new or worsening symptoms of heart failure (for example, shortness of breath, or swelling of your feet), you must contact your doctor immediately. Your doctor will decide if you should receive Humira.

- If you develop a fever that does not go away, develop light bruises or bleed very easily or look very pale, call your doctor right away. In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. Your doctor may decide to stop treatment.

Cancer

- There have been very rare cases of certain kinds of cancer in children and adult patients taking Humira or other TNF blockers.

    - People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting lymphoma (a kind of cancer that affects the lymph system), and leukaemia (a kind of cancer that affects the blood and bone marrow).
    - If you take Humira the risk of getting lymphoma, leukaemia, or other cancers may increase. On rare occasions, an uncommon and severe type of lymphoma, has been seen in patients taking Humira. Some of those patients were also treated with azathioprine or 6-mercaptopurine.
    - Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Humira.
    - Cases of non-melanoma skin cancer have been observed in patients taking Humira.
    - If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.

- There have been cases of cancers, other than lymphoma in patients with a specific type of lung disease called Chronic Obstructive Pulmonary Disease (COPD) treated with another TNF blocker. If you have COPD, or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.

Children and adolescents

- Vaccinations: if possible children should be up to date with all vaccinations before using Humira.

Other medicines and Humira

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You should not take Humira with medicines containing the active substances:
- anakinra
- abatacept.

Humira can be taken together with:
- methotrexate
- certain disease-modifying anti-rheumatic agents (for example, sulfasalazine, hydroxychloroquine, leflunomide and injectable gold preparations)
- steroids or pain medications including non-steroidal anti-inflammatory drugs (NSAIDs).

If you have questions, please ask your doctor.

Pregnancy and breast-feeding

The use of Humira in pregnant women is not recommended. You are advised to avoid becoming pregnant and must use adequate contraception while using Humira and for at least 5 months after the last Humira treatment. If you become pregnant, you should consult your doctor.

If you receive Humira during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy before the baby receives any vaccine. For more information see section on vaccination.

It is not known whether adalimumab passes into breast milk.

You should stop breast-feeding during Humira treatment and for at least 5 months after the last Humira treatment.

If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Humira may have a small effect on your ability to drive, cycle or use machines. Room spinning sensation and vision disturbances may occur after taking Humira.

3. How to use Humira

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended doses for Humira in each of the approved uses are shown in the following table. Your doctor may prescribe another strength of Humira if you need a different dose.

Plaque psoriasis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 80 mg (one 80 mg injection), followed by 40 mg every other week starting one week after the first dose.	If you have an inadequate response, your doctor may increase the dose frequency to 40 mg every week.

Hidradenitis suppurativa		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 160 mg (two 80 mg injections in one day or one 80 mg injection per day for two consecutive days), followed by an 80 mg dose (one 80 mg injection) two weeks later. After two further weeks, continue with a dose of 40 mg every week.	It is recommended that you use an antiseptic wash daily on the affected areas.
Adolescents from 12 to 17 years of age weighing 30 kg or more	First dose of 80 mg (one 80 mg injection), followed by 40 mg every other week starting one week later.	If you have an inadequate response, your doctor may increase the dose frequency to 40 mg every week It is recommended that you use an antiseptic wash daily on the affected areas.

Crohn's disease		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 80 mg (one 80 mg injection), followed by 40 mg every other week two weeks later. If a faster response is required your doctor may prescribe a first dose of 160 mg (two 80 mg injections in one day or one 80 mg injection per day for two consecutive days), followed by 80 mg (one 80 mg injection) two weeks later. Thereafter, the usual dose is 40 mg every other week.	Your doctor may increase the dose frequency to 40 mg every week.
Children and adolescents from 6 to 17 years of age weighing 40 kg or more	First dose of 80 mg (one 80 mg injection), followed by 40 mg two weeks later. If a faster response is required, the doctor may prescribe a first dose of 160 mg (two 80 mg injections in one day or one 80 mg injection per day for two consecutive days), followed by 80 mg (one 80 mg injection) two weeks later. Thereafter, the usual dose is 40 mg every other week.	Your doctor may increase the dose frequency to 40 mg every week.
Children and adolescents from 6 to 17 years of age weighing less than 40 kg	First dose of 40 mg, followed by 20 mg two weeks later. If a faster response is required, the doctor may prescribe a first dose of 80 mg (one 80 mg injection), followed by 40 mg two weeks later. Thereafter, the usual dose is 20 mg every other week.	Your doctor may increase the dose frequency to 20 mg every week.

Ulcerative colitis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 160 mg (two 80 mg injections in one day or one 80 mg injection per day for two consecutive days), followed by 80 mg (one 80 mg injection) two weeks later. Thereafter, the usual dose is 40 mg every other week.	Your doctor may increase the dose frequency to 40 mg every week.

Non-infectious uveitis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 80 mg (one 80 mg injection), followed by 40 mg every other week starting one week after the first dose.	Corticosteroids or other medicines that influence the immune system may be continued while using Humira. Humira can also be given alone.
Children from 2 years of age weighing less than 30 kg	20 mg every other week	Your doctor may prescribe an initial dose of 40 mg to be administered one week prior to the start of the usual dose of 20 mg every other week. Humira is recommended for use in combination with methotrexate.
Children from 2 years of age weighing at least 30 kg	40 mg every other week	Your doctor may prescribe an initial dose of 80 mg to be administered one week prior to the start of the usual dose of 40 mg every other week. Humira is recommended for use in combination with methotrexate.

Method and route of administration

Humira is administered by injection under the skin (by subcutaneous injection).

Detailed instructions on how to inject Humira are provided in section 7 'Injecting Humira'.

If you use more Humira than you should

If you accidentally inject Humira more frequently than told to by your doctor or pharmacist, you should call your doctor or pharmacist and tell them that you have taken more. Always take the outer carton of the medicine with you, even if it is empty.

If you forget to use Humira

If you forget to give yourself an injection, you should inject the next dose of Humira as soon as you remember. Then take your next dose as you would have on your originally scheduled day, had you not forgotten a dose.

If you stop using Humira

The decision to stop using Humira should be discussed with your doctor. Your symptoms may return if you stop using Humira.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 4 months after the last Humira injection.

Tell your doctor immediately if you notice any of the following

- severe rash, hives or other signs of allergic reaction
- swollen face, hands, feet
- trouble breathing, swallowing
- shortness of breath with physical activity or upon lying down or swelling of the feet

Tell your doctor as soon as possible if you notice any of the following

- signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination
- feeling weak or tired
- coughing
- tingling
- numbness
- double vision
- arm or leg weakness
- a bump or open sore that doesn't heal
- signs and symptoms suggestive of blood disorders such as persistent fever, bruising, bleeding, paleness

The symptoms described above can be signs of the below listed side effects, which have been observed with Humira.

Very common (may affect more than 1 in 10 people)

- injection site reactions (including pain, swelling, redness or itching)
- respiratory tract infections (including cold, runny nose, sinus infection, pneumonia)
- headache
- abdominal pain
- nausea and vomiting
- rash
- musculoskeletal pain

Common (may affect up to 1 in 10 people)

- serious infections (including blood poisoning and influenza)

- skin infections (including cellulitis and shingles)
- ear infections
- oral infections (including tooth infections and cold sores)
- reproductive tract infections
- urinary tract infection
- fungal infections
- joint infections
- benign tumours
- skin cancer
- allergic reactions (including seasonal allergy)
- dehydration
- mood swings (including depression)
- anxiety
- difficulty sleeping
- sensation disorders such as tingling, prickling or numbness
- migraine
- nerve root compression (including low back pain and leg pain)
- vision disturbances
- eye inflammation
- inflammation of the eye lid and eye swelling
- vertigo (feeling of dizziness or spinning)
- sensation of heart beating rapidly
- high blood pressure
- flushing
- haematoma (collection of blood outside of blood vessels)
- cough
- asthma
- shortness of breath
- gastrointestinal bleeding
- dyspepsia (indigestion, bloating, heart burn)
- acid reflux disease
- sicca syndrome (including dry eyes and dry mouth)
- itching
- itchy rash
- bruising
- inflammation of the skin (such as eczema)
- breaking of finger nails and toe nails
- increased sweating
- hair loss
- new onset or worsening of psoriasis
- muscle spasms
- blood in urine
- kidney problems
- chest pain
- oedema (swelling)
- fever
- reduction in blood platelets which increases risk of bleeding or bruising
- impaired healing

Uncommon (may affect up to 1 in 100 people)

- opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered)

- neurological infections (including viral meningitis)
- eye infections
- bacterial infections
- diverticulitis (inflammation and infection of the large intestine)
- cancer
- cancer that affects the lymph system
- melanoma
- immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis)
- vasculitis (inflammation of blood vessels)
- tremor (shaking)
- neuropathy (disorder of the nerves)
- stroke
- double vision
- hearing loss, buzzing
- sensation of heart beating irregularly such as skipped beats
- heart problems that can cause shortness of breath or ankle swelling
- heart attack
- a sac in the wall of a major artery, inflammation and clot of a vein, blockage of a blood vessel
- lung diseases causing shortness of breath (including inflammation)
- pulmonary embolism (blockage in an artery of the lung)
- pleural effusion (abnormal collection of fluid in the pleural space)
- inflammation of the pancreas which causes severe pain in the abdomen and back
- difficulty in swallowing
- facial oedema (swelling of the face)
- gallbladder inflammation, gallbladder stones
- fatty liver
- night sweats
- scar
- abnormal muscle breakdown
- systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems)
- sleep interruptions
- impotence
- inflammations

Rare (may affect up to 1 in 1,000 people)

- leukaemia (cancer affecting the blood and bone marrow)
- severe allergic reaction with shock
- multiple sclerosis
- nerve disorders (such as eye nerve inflammation and Guillain-Barré syndrome that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body)
- heart stops pumping
- pulmonary fibrosis (scarring of the lung)
- intestinal perforation (hole in the intestine)
- hepatitis
- reactivation of hepatitis B
- autoimmune hepatitis (inflammation of the liver caused by the body's own immune system)
- cutaneous vasculitis (inflammation of blood vessels in the skin)
- Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash)
- facial oedema (swelling of the face) associated with allergic reactions
- erythema multiforme (inflammatory skin rash)

- lupus-like syndrome

Not known (frequency cannot be estimated from the available data)

- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal)
- Merkel cell carcinoma (a type of skin cancer)
- liver failure
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)

Some side effects observed with Humira may not have symptoms and may only be discovered through blood tests. These include:

Very common (may affect more than 1 in 10 people)

- low blood measurements for white blood cells
- low blood measurements for red blood cells
- increased lipids in the blood
- elevated liver enzymes

Common (may affect up to 1 in 10 people)

- high blood measurements for white blood cells
- low blood measurements for platelets
- increased uric acid in the blood
- abnormal blood measurements for sodium
- low blood measurements for calcium
- low blood measurements for phosphate
- high blood sugar
- high blood measurements for lactate dehydrogenase
- autoantibodies present in the blood

Rare (may affect up to 1 in 1,000 people)

- low blood measurements for white blood cells, red blood cells and platelet count

Not known (frequency cannot be estimated from the available data)

- liver failure

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Humira

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label/blister/carton after EXP.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

Alternative Storage:

When needed (for example, when you are travelling), a single Humira pre-filled pen may be stored at room temperature (up to 25°C) for a maximum period of 14 days – be sure to protect it from light. Once removed from the refrigerator for room temperature storage, the pen **must be used within 14 days or discarded**, even if it is returned to the refrigerator.

You should record the date when the pen is first removed from refrigerator, and the date after which it should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Humira contains

The active substance is adalimumab.
The other ingredients are mannitol, polysorbate 80 and water for injections.

What the Humira pre-filled pen looks like and contents of the pack

Humira 80 mg solution for injection in pre-filled pen is supplied as a sterile solution of 80 mg adalimumab dissolved in 0.8 ml solution.

The Humira pre-filled pen is a single-use grey- and plum-coloured pen which contains a glass syringe with Humira. There are two caps – one is grey and labelled ‘1’ and the other is plum and labelled ‘2’. There is a window on each side of the pen through which you can see the Humira solution inside the syringe.

The Humira pre-filled pen is available in a pack containing 1pre-filled pen with 2 alcohol pads (1 spare).

Humira may be available as a vial, a pre-filled syringe and/or a pre-filled pen.

Marketing Authorisation Holder

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

7. Injecting Humira

- The following instructions explain how to give yourself a subcutaneous injection of Humira using the pre-filled pen. First read all the instructions carefully and then follow them step by step.

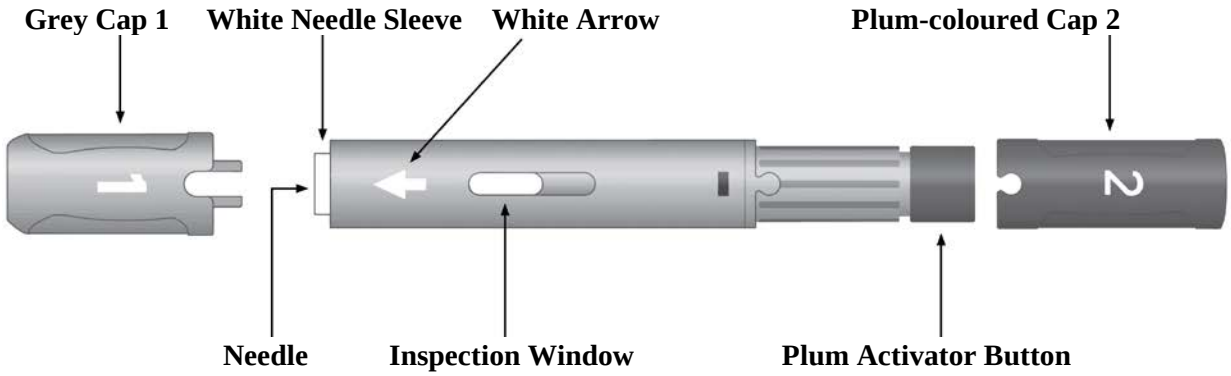
- You will be instructed by your doctor, nurse or pharmacist on the technique of self-injection.

- Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection.

- After proper training, the injection can be given by yourself or given by another person, for example, a family member or friend.

- Only use each pre-filled pen for one injection.

Humira Pre-filled Pen

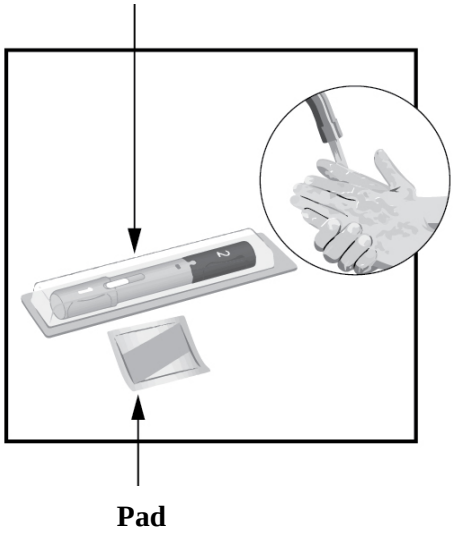


Do not use the pre-filled pen and call your doctor or pharmacist if the

- liquid is cloudy, discoloured, or has flakes or particles in it
- expiry (EXP) date has passed
- liquid has been frozen or left in direct sunlight
- pre-filled pen has been dropped or crushed

Do not remove the caps until just before injection. Keep Humira out of the sight and reach of children.

STEP 1 Take Humira out of the refrigerator. Leave Humira at room temperature for **15 to 30 minutes** before injecting. • **Do not** remove the Grey or Plum-coloured Caps while allowing Humira to reach room temperature • **Do not** warm Humira in any other way. For example, **do not** warm it in a microwave or in hot water
STEP 2 Check expiry (EXP) date. **Do not** use the pre-filled pen if



expiry (EXP) date has passed.

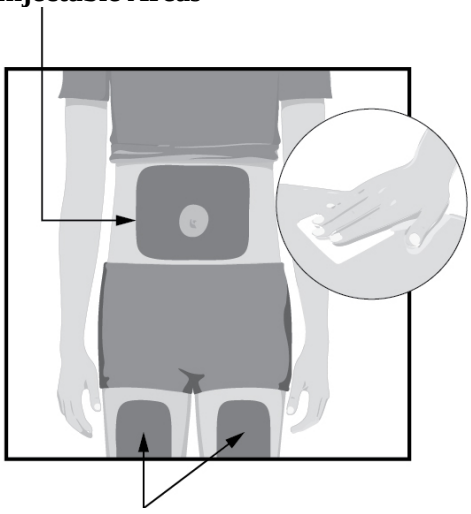
Place the following on a clean, flat surface

- 1 single-use pre-filled pen and
- 1 alcohol pad

Wash and dry your hands.

STEP 3

Injectable Areas



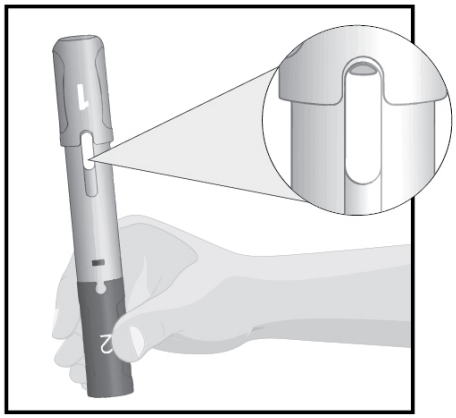
Choose an injection site:

- On the front of your thighs or
- Your belly (abdomen) at least 5 cm from your belly button (naval)
- At least 3 cm from your last injection site

Wipe the injection site in a circular motion with the alcohol pad.

- **Do not** inject through clothes
- **Do not** inject into skin that is sore, bruised, red, hard, scarred, has stretch marks, or areas with psoriasis plaques

STEP 4



Hold the pre-filled pen with the Grey Cap 1 pointing up.

Check the inspection window.

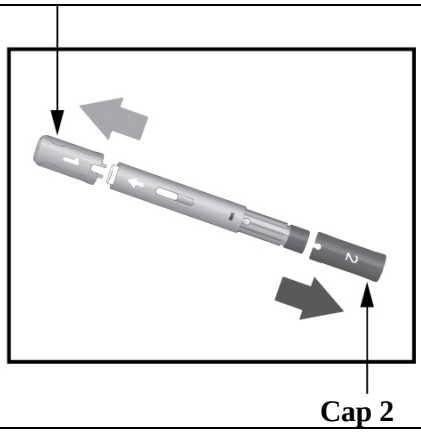
- It is normal to see 1 or more bubbles in the window
- Make sure the liquid is clear and colourless
- **Do not** use the pre-filled pen if the liquid is cloudy or has particles
- **Do not** use the pre-filled pen if it has been dropped or crushed

STEP 5

Cap 1

Pull the Grey Cap 1 straight off. Throw the cap away. Do not recap.

- Check that the small black needle cover of the syringe has been removed with the cap



Cap 2

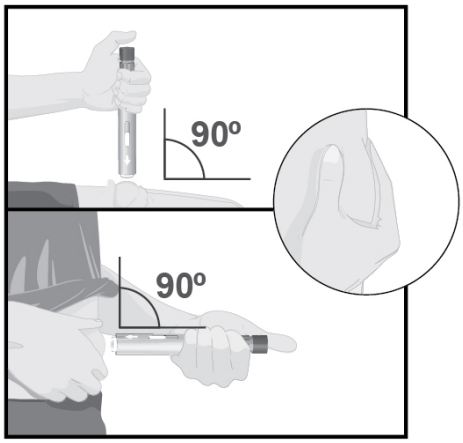
- It is normal to see a few drops of liquid come out of the needle

Pull the Plum-coloured Cap 2 straight off. Throw the cap away. Do not recap.

The pre-filled pen is now ready to use.

Turn the pre-filled pen so that the white arrow points toward the injection site.

STEP 6



Squeeze the skin at your injection site with your other hand to make a raised area and hold it firmly.

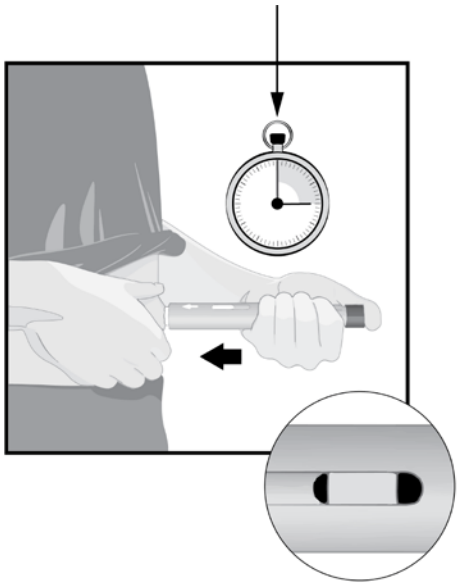
Point the white arrow toward the injection site (thigh or abdomen).

Place the white needle sleeve straight **(90˚ angle)** against the injection site.

Hold the pre-filled pen so that you can see the inspection window.

STEP 7

15 Seconds



Push and keep pushing the pre-filled pen down against the injection site.

Press the plum activator button and count slowly for **15** seconds.

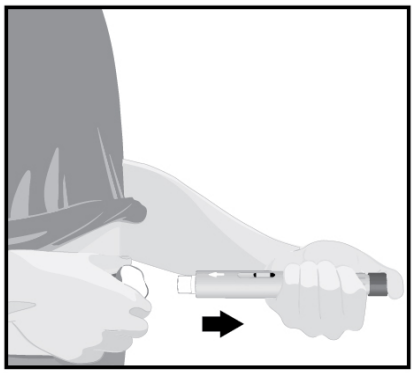
- A loud **"click"** will signal the start of the injection
- **Keep pushing** the pre-filled pen down against the injection site.

The injection is complete when the yellow indicator has stopped moving.

STEP 8

When the injection is completed, slowly pull the pre-filled pen from the skin. The white needle sleeve will cover the needle tip.

If there are more than a few drops of liquid on the injection site, contact your doctor, nurse or pharmacist.



After completing the injection, place a cotton ball or gauze pad on the skin over the injection site.

- **Do not** rub
- Slight bleeding at the injection site is normal

STEP 9

Throw away the used pre-filled pen in a special disposal container as instructed by your doctor, nurse or pharmacist.

- **Do not** recycle or throw the pre-filled pen in the household waste
- **Always** keep the pre-filled pen and the special disposal container out of the sight and reach of children

The caps, alcohol pad, cotton ball or gauze pad, blister, and packaging may be put in your household waste.