HUMIRA 40 MG

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled syringe:
Each 0.8 ml single dose pre-filled syringe contains 40 mg of adalimumab.

Pre-filled pen:
Each 0.8 ml single dose pre-filled pen contains 40 mg of adalimumab.

Solution for injection for paediatric use:
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 a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.
Solution for injection in pre-filled pen.
Solution for injection in single dose vial

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.

Polyarticular juvenile idiopathic arthritis

Humira in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents aged 4 to 17 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 children aged less than 4 years.

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.

Ankylosing spondylitis

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

Crohn's disease

Humira is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Humira is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Psoriasis

Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

4.2 Posology and method of administration

Humira treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis , ankylosing spondylitis , Crohn's disease or psoriasis. 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.

Adults

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 decrease in their response may benefit from an increase in dose intensity to 40 mg adalimumab every week.

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.

Psoriatic arthritis and ankylosing spondylitis

The recommended dose of Humira for patients with psoriatic arthritis and ankylosing spondylitis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.

For all of the above indications, available data suggest that the 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.

Crohn's disease

The recommended Humira dose regimen for adult patients with Crohn's disease is 160 mg at Week 0 (dose can be administered as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), 80 mg at Week 2, followed by a maintenance dose of 40 mg every other week via subcutaneous injection beginning at Week 4.

Aminosalicylates, corticosteriods and/or immunomodulatory agents (e.g. 6-mercaptopurine and azathioprine) may be continued during treatment with Humira.

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

Some patients who have not responded by Week 4 may benefit from continued maintenance therapy through Week 12. Therapy continued beyond 12 weeks did not result in significantly more responses.

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.

Elderly patients

No dose adjustment is required.
Paediatric population:
Polyarticular Juvenile Idiopathic Arthritis

Humira has not been studied in children aged less than 4 years. Limited data are available for Humira treatment in paediatric patients with a weight below 15 kg.

Polyarticular Juvenile Idiopathic Arthritis Age 4 to 12 years

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 4 - 12 years, 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).

Table 1. Humira Dose in Milliliters (ml) by Height and Weight of Children for Polyarticular Juvenile Idiopathic 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 Age 13-17 years:

For adolescents aged 13-17 years, a dose of 40 mg administered every other week is administered as a single dose via subcutaneous injection (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.

Impaired renal and/or hepatic function

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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

Infections

Patients taking TNF-blockers 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 localized 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 as listeriosis, 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:

There have been reports of tuberculosis in patients receiving Humira. It should be noted that in the majority of those reports, tuberculosis was extra-pulmonary, ie disseminated.

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 history with a personal history of tuberculosis or possible previous exposure to patients 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). 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).

If latent tuberculosis is, suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below , the benefit/risk balance of therapy should be very carefully considered.

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

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, anti-tuberculosis therapy should also be considered before the initiation of Humira.

Use of anti-tuberculosis therapy should also be considered before the initiation of Humira in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Some patients who have previously received treatment for latent or active tuberculosis have developed active tuberculosis while being treated with Humira.

Patients should be instructed to seek medical advice if signs/symptoms (eg, persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection 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-blockers and this 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, dyspnea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock an invasivie fungal infection should be suspected and administration of Humira should be promptly discontinued and appropriate antifungal therapy should be initiated.

Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

Hepatitis B reactivation

Reactivation of hepatitis B has occurred in patients who are chronic carriers of this virus when receiving a TNF-antagonist including Humira,. Some cases have had fatal outcome. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating Humira therapy. 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 the treatment of 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 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.

Allergic reactions

Serious allergic adverse reactions have not been reported with subcutaneous administration of Humira during clinical trials. Non-serious allergic reactions associated with Humira were uncommon during clinical trials. In postmarketing, serious allergic reactions including anaphylaxis have been reported very rarely following Humira administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Humira should be discontinued immediately and appropriate therapy initiated.

The needle cover of the syringe contains natural rubber (latex). This may cause severe allergic reactions in patients sensitive to latex.

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. Furthermore, there is an increased background lymphoma risk 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 or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

Malignancies, some fatal, have been reported among children and adolescents who received treatment with TNF-blocking agents. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. The malignancies occurred after a median of 30 months of therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

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 Crohn's disease. A risk for the development of hepatosplenic T-cell lymphoma in patients treated with Humira cannot be excluded (see sections 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.

Cases of acute and chronic leukemia have been reported in association with postmarketing TNF-blocker use in rheumatoid arthritis and other indications. Patients with rheumatoid arthritis may be at a higher risk (up to 2-fold) than the general population for the development of leukemia, even in the absence of TNF-blocking therapy.

In an exploratory clinical trial evaluating the use of another anti-TNF agent, 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.

Haematologic reactions

Rare reports of pancytopaenia including aplastic anaemia have been reported with TNF antagonists . Adverse events of the haematologic system, including medically significant cytopenia (eg 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 (eg 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 polyarticular juvenile idiopathic arthritis 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.

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 TNF-antagonists and anakinra

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).

Concurrent administration of TNF-antagonists and abatacept

Concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of Humira and abatacept is not recommended. (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 Population

The frequency of serious infections among HUMIRA treated subjects over 65 years of age (3.9%) was higher than for those under 65 years of age (1.4%). Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly.

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 TNF-antagonists and anakinra").

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

4.6 Pregnancy and lactation

For Humira, no 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 and fertility effects 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. 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.

Use during lactation

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.

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

Clinical Trials

Humira was studied in 6,728 patients in controlled and open label trials for up to 60 months. These trials included rheumatoid arthritis patients with short term and long standing disease, polyarticular juvenile idiopathic arthritis, as well as psoriatic arthritis, ankylosing spondylitis , Crohn's disease and psoriasis patients. The data in Table 2 is based on the pivotal controlled studies involving 4,419 patients receiving Humira and 2,552 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 4.5 % for patients taking Humira and 4.5 % for control treated patients.

Undesirable effects in paediatric patients with polyarticular juvenile idiopathic arthritis

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

Adverse events, for clinical studies in both clinical and laboratory parameters at least possibly causally-related to adalimumab are displayed by system organ class and frequency (very common ≥ 1/10; common > 1/100 to < 1/10; uncommon > 1/1000 to ≤ 1/100 rare ≥ 1/10,000 to < 1/1000) and very rare <1/10,000) in Table 2 below. 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.

Approximately 15% of patients can be expected to experience injection site reactions, based on one of the most common adverse events with adalimumab in controlled clinical studies.

Table 2
Undesirable Effects in Clinical Studies

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
	Uncommon	opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avum complex infection), neurological infections (including viral meningitis), eye infections, bacterial infections, joint infections
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Common	benign neoplasm, skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma)
	Uncommon	lymphoma**, solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma**
Blood and the lymphatic system disorders*	Very common	leucopaenia (including neutropaenia and agranulocytosis), anaemia
	Common	thrombocytopaenia, leucocytosis
	Uncommon	idiopathic thrombocytopaenic purpura
	Rare	pancytopaenia
Immune system disorders*	Common	hypersensitivity, allergies (including seasonal allergy)

System Organ Class	Frequency	Adverse Reaction
Metabolism and nutrition disorders	Very common	lipids increased
	Common	hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia hyperglycaemia, hypophosphataemia blood potassium increased
	Uncommon	dehydration
Psychiatric disorders	Common	mood alterations (including depression), anxiety, insomnia
Nervous system disorders*	Very common	headache
	Common	paraesthesias (including hypoasthesia), migraine, sciatica
	Uncommon	tremor
	Rare	multiple sclerosis
Eye disorders	Common	visual impairment, conjunctivitis
	Uncommon	blepharitis, eye swelling, diplopia
Ear and labyrinth disorders	Common	vertigo
	Uncommon	deafness, tinnitus
Cardiac disorders*	Common	tachycardia
	Uncommon	arrhythmia, congestive heart failure
	Rare	cardiac arrest
Vascular disorders	Common	hypertension, flushing, haematoma

System Organ Class	Frequency	Adverse Reaction
	Rare	vascular arterial occlusion, thrombophlebitis, aortic aneurysm
Respiratory, thoracic and mediastinal disorders*	Common	cough, asthma, dyspnoea
	Uncommon	chronic obstructive pulmonary disease, interstitial lung disease, pneumonitis
Gastrointestinal disorders	Very common	abdominal pain, nausea and vomiting
	Common	GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	pancreatitis, dysphagia, face oedema
Hepato-biliary disorders*	Very Common	liver enzymes elevated
	Uncommon	cholecystitis and cholelithiasis, bilirubin increased, hepatic steatosis
Skin and subcutaneous tissue disorders	Very Common	rash (including exfoliative rash),
	Common	pruritus, urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis, hyperhydrosis
	Uncommon	night sweats, scar
Musculoskeletal, connective tissue and bone disorders	Very common	musculoskeletal pain
	Common	muscle spasms (including blood creatine phosphokinase increased)
	Uncommon	rhabdomyolysis
	Rare	systemic lupus erythematosus

System Organ Class	Frequency	Adverse Reaction
Renal and urinary disorders	Common Uncommon	haematuria, renal impairment nocturia
Reproductive system and breast disorders	Uncommon	erectile dysfunction
General disorders and administration site conditions*	Very Common Common Uncommon	injection site reaction (including injection site erythema) chest pain, oedema 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 and poisoning*	Common	impaired healing

* further information is found elsewhere in sections 4.3, 4.4 and 4.8
** including open label extension studies

Injection site reactions

In the pivotal controlled trials, 15 % of patients treated with Humira developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 9% 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, the rate of infection was 1.50per patient year in the Humira treated patients and 1.42 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 0.043 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 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 171 patients with an exposure of 192.5 patient years during a Humira trial in juvenile idiopathic arthritis patients

During the controlled portions of pivotal Humira trials of at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis Crohn's disease and psoriasis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.6 (4.0, 10.8)per 1000 patient-years among 3,917 Humira treated patients versus a rate of 4.2 (1.8, 10.41) per 1000 patient-years among 2,247 control patients (median duration of treatment was 5.6 months for Humira and 4.0 months for control-treated patients). The rate (95% confidence interval) of non-melanoma skin cancers was 9.9 (6.6, 14.8) per 1000 patient-years among Humira-treated patients and 2.5 (0.8, 7.9) per 1000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) 2.5 (1.1, 5.5) per 1000 patient-years among Humira-treated patients and 0.8 (0.1, 6.0) per 1000 patient-years among control patients. The rate (95% confidence interval) of lymphomas was 0.8 (0.2, 3.3) per 1000 patient-years among Humira-treated patients and 0.8 (0.1, 6.0) per 1000 patient-years among control patients.

When combining the controlled portion of these trials and ongoing open label extension studies with a median duration of approximately 3.4 years including 4,954 patients and over 21,021 patient-years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 9.1 per 1000 patient years. The observed rate of non-melanoma skin cancers is approximately 10.1 per 1000 patient years, and the observed rate of lymphomas is approximately 1.1 per 1000 patient years.

In post-marketing experience from January 2003, predominately in patients with rheumatoid arthritis, the reported rate of malignancies other than lymphomas and non-melanoma skin cancers is approximately 1.7 per 1000 patient years. The reported rates for non-melanoma skin cancers and lymphomas are approximately 0.2 and 0.4 per 1000 patient 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 3441 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.

Psoriasis: New-onset and Worsening

Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, and cases of worsening of pre-existing psoriasis have been reported with the use of TNF-blockers, including Humira. Many of these patients were taking concomitant immunosuppressants (e.g., MTX, corticosteroids). Some of these patients required hospitalization. Most patients had improvement of their psoriasis following discontinuation of their TNF-blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF-blocker. Discontinuation of Humira should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Liver Enzyme Elevations

Rheumatoid arthritis clinical trials: in controlled rheumatoid arthritis clinical trials (RA studies I − IV), elevations of ALT were similar in patients receiving adalimumab or placebo. In patients with early rheumatoid arthritis (disease duration of less than 3 years) (RA study V), elevations of ALT were more common in the combination arm (Humira /methotrexate) compared to the methotrexate monotherapy arm or the Humira monotherapy arm. . In the JIA trial the few transaminase elevations were small and

similar in the placebo and adalimumab exposed patients, and mostly occurred in combination with methotrexate.

Psoriatic arthritis clinical trials: elevations in ALT were more common in psoriatic arthritis patients ((PsA studies I - II) compared with patients in rheumatoid arthritis clinical studies.

In all rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis studies, patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment.

Crohn's disease clinical trials: in controlled clinical trials, elevations of ALT were similar in patients receiving adalimumab or placebo.
Psoriasis clinical trials: in controlled psoriasis clinical trials, elevations of ALT were similar in patients receiving adalimumab or placebo.

Additional Adverse Reactions from Postmarketing Surveillance or Phase IV Clinical Trials

The additional adverse reactions in Table 3 have been reported from postmarketing surveillance or Phase IV clinical trials:

Table 3
Undesirable Effects in Postmarketing Surveillance and Phase IV Clinical Studies

System Organ Class	Adverse Reaction
Infections and Infestations	diverticulitis
Neoplasm benign, malignant and unspecified (including cysts and polyps)*	hepatosplenic T-cell lymphoma, leukemia
Immune system disorders*	Anaphylaxis, sarcoidosis
Nervous system disorders*	demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome, cerebrovascular accident)
Respiratory, thoracic and mediastinal disorders	pulmonary embolism pleural effusion, pulmonary fibrosis
Gastrointestinal disorders*	intestinal perforation
Hepatobiliary disorders*	reactivation of hepatitis B
Skin and subcutaneous tissue disorders	cutaneous vasculitis, Stevens-Johnson syndrome, angioedema, new onset or worsening of psoriasis (including palmoplantar pustular psoriasis, erythema multiforme, alopecia
Musculoskeletal and connective tissue disorders	lupus-like syndrome
Cardiac disorders	myocardial infarction

* further information is found elsewhere in sections 4.3, 4.4 and 4.8

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: Selective immunosuppressive agents. ATC code: L04AB04

Mechanism of action

Adalimumab binds specifically to TNF and neutralizes 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} of 0.1-0.2 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.

In patients with Crohn's disease, a rapid decrease in CRP levels was also observed as well as a reduction of the number of cells expressing inflammatory markers in the colon including a significant reduction of expression of TNFα. Endoscopic studies in intestinal mucosa have shown evidence of mucosal healing in adalimumab treated patient.

A rapid decrease in CRP levels was also observed in patients with polyarticular juvenile idiopathic arthritis.

Clinical trials

Rheumatoid arthritis

Humira was evaluated in over 3000 patients in all rheumatoid arthritis clinical trials. Some patients were treated for up to 60 months duration. The efficacy and safety of Humira for the treatment of rheumatoid arthritis were assessed in five randomised, double-blind and well-controlled 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 doses of 12.5 to 25 mg or have been intolerant to 10 mg of methotrexate. 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. Thereafter, patients enrolled in an open-label extension phase in which 40 mg of Humira was administered every other week up to 60 months.

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.

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. RAStudies 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 s-tudy 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 addition, ACR response rates were maintained in the majority of patients followed in the open-label extension phase to Week 104. There were 114 out of 207 patients who continued on Humira 40 mg every other week for 60 months. Among those, 86, 72, and 41 patients had ACR 20/50/70 response, respectively at Month 60.

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 Table5).

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

At Week 52, 42.9% of patients who received Humira/methotrexate combination therapy achieved clinical remission (DAS28 < 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).

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).Data from the open-label extension phase indicate that the reduction in rate of progression of structural damage is maintained For 60 months in a subset of patients. 113/ of 207 of patients originally treated with 40 mg Humira every other week were evaluated radiographically at 5 years. Among those, 66 patients showed no progression of structural damage defined by a change in the TSS of zero 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).

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, improvement in physical function was maintained through Week 260 (60 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 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.

Polyarticular juvenile idiopathic arthritis (JIA)

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 (%)	Minumum, 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 enroll into the open label extension phase

Table 9
Ped ACR 30 Responses in the JIA study

Stratum	MTX		Without MTX	
Phase				
OL-LI 16 week				
Ped ACR 30 response (n/N)	94.1% (80/85)		74.4% (64/86)	
Efficacy Outcomes				
Double Blind 32 week	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).

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 eow.

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)

	Study VI		Study VII	
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.

Ankylosing spondylitis

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 11).

Table 11 - 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.

Crohn's disease

The safety and efficacy of multiple doses 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; the placebo group received placebo at Weeks 0 and 2, the 160/80 group received 160 mg Humira at Week 0 and 80 mg at Week 2, the 80/40 group received 80 mg at Week 0 and 40 mg at Week 2, and the 40/20 group received 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 . In CD Study III, 854 patients received open-label 80 mg Humira at Week 0 and 40 mg Humira at Week 2. Patients were then randomised at Week 4 to 40 mg every other Week Humira, 40 mg Humira 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 12.

Table 12: 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 160/80 mg N=76**	**Placebo N=166**	**Humira 160/80 mg N=159**
Week 4				
Clinical remission	12%	36%*	7%	21%*

Clinical response (CR-100)	24%	50%**	25%	38%**
Clinical response (CR-70)	34%	58%**	34%	52%**

All p-values are pairwise comparisons of proportions for Humira *vs*. 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) 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 anti-TNF therapy. Maintenance of remission and response rates are presented in Table 12. Clinical remission results remained relatively constant irrespective of previous TNF antagonist exposure.

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

Table 13: 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%*
Clinical response (CR-70)	28%	54%*	56%*
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%*
Clinical response (CR-70)	18%	43%*	49%*
Patients in steroid-free remission for >=90 days[a]	5% (3/66)	29% (17/58)*	20% (15/74)**

* p<0.001 for Humira *vs*. placebo pairwise comparisons of proportions

** p<0.02 for Humira *vs*. placebo pairwise comparisons of proportions

[a] Of those receiving corticosteroids at baseline

Among patients who were not in response at Week 4, 43% 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.

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.

Psoriasis Study I (REVEAL) evaluated 1212 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 enroll 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 14 and 15).

Table 14: 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 center-adjusted rate [b] p<0.001, Humira vs. placebo		

Table 15: 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-randomization 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).

A total of 94 patients were randomized to Humira therapy in Psoriasis Study II, and continued Humira in the open label extension trial. PASI 75 and PGA clear or minimal response rates in these patients were 58.1% and 46.2%, respectively, after an additional 108 weeks of open-label therapy (total of 124 weeks).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. Median time to relapse (decline to PGA "moderate" or worse) was approximately 5 months. No 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).

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% and were evaluated at 12 weeks after dose escalation, 93/349 (26.6%) of patients achieved PASI 75 response.

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 RA Studies I, II and III were tested at multiple timepoints for anti-adalimumab antibodies during the 6 to 12 month period. In the pivotal trials, anti-adalimumab antibodies were identified in 58/1053 (5.5%) patients treated with adalimumab, compared to 2/370 (0.5%) 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, adalimumab antibodies were identified in 27/171 subjects (15.8%) treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 22/86 (25.6%), compared to 5/85 (5.9%) 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 %) treated with adalimumab.

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

In plaque psoriasis patients on long term adalimumab monotherapy who participated in a withdrawal and retreatment study, the rate of antibodies to adalimumab after retreatment (2.3%) was similar to the rate observed prior to withdrawal (1.8%).

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

Patient Reported Outcomes

In CLASSIC I and GAIN, statistically significant improvement in the disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at week 4 in patients randomized to HUMIRA 160/80 mg compared to placebo. Statistically significant improvement from baseline in IBDQ total scores was seen at weeks 26 and 56 in CHARM among the adalimumab treatment groups compared to the placebo group.

5.2 Pharmacokinetic properties

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 Humira 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) the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5.6 ± 5.6 μg/mL (102 %CV) Humira monotherapy and 10.9 ± 5.2 μg/mL (47.7% CV) with concomitant methotrexate.

In patients with Crohn's disease, the 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 mcg/ml during the induction period. Mean steady-state trough levels of approximately 7 mcg/ml were observed in Crohn's disease patients who received a maintenance dose of 40 mg Humira every other week.

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

Population pharmacokinetic analyses with data from over 1300 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. 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 neutralizing 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

24 months

6.4 Special precautions for storage

Pre-filled syringe:
Store in a refrigerator (2°C – 8°C). Keep the syringe in the outer carton. Do not freeze.
Pre-filled pen:
Store in a refrigerator (2°C – 8°C). Keep the pre-filled pen in the outer carton. Do not freeze.
Humira 40 mg solution for injection for paediatric use:
Store in a refrigerator (2°C – 8°C). Keep the vial in the outer carton. Do not freeze.

6.5 Nature and contents of container

Pre-filled syringe:
Humira 40 mg solution for injection in single-use pre-filled syringe (type I glass) for patient use:

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.

Not all pack sizes may be marketed.

Pre-filled pen:
Humira 40 mg solution for injection in single-use pre-filled pen for patient use:

Packs of:
- 1 pre-filled pen with 1 alcohol pad in a blister.
- 2 pre-filled pen, each with 1 alcohol pad, in a blister.
- 4 pre-filled pen, each with 1 alcohol pad, in a blister.

- 6 pre-filled pen, each with 1 alcohol pad, in a blister.

Not all pack sizes may be marketed.

Humira 40 mg solution for injection for paediatric use:

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 Instructions for use and handling and disposal

Humira 40mg solution for injection does not contain preservatives; therefore Any unused product or waste material should be disposed of in accordance with local requirements.

Manufacturer:
Abbott Laboratories LTD., UK (for pre-filled pen & vial)
Abbott GmbH & CO .KG, Germany (for pre-filled syringe)

7. MARKETING AUTHORISATION HOLDER

Abbott Laboratories S.A., P.O Box 58099, Tel Aviv 61580

8. MARKETING AUTHORISATION NUMBER

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