SCHEDULING STATUS S4

PROPRIETARY NAME (and dosage form)

HUMIRA 40 mg Solution for Injection

COMPOSITION

Each single use pre-filled syringe or vial of **HUMIRA** contains 40 mg adalimumab per 0.8 mℓ (50 mg/mℓ)

Inactive ingredients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injection.

PHARMACOLOGICAL CLASSIFICATION

A 30.2 – Antibodies

PHARMACOLOGICAL 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. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis (RA), including juvenile idiopathic arthritis (JIA), psoriatic arthiritis (PsA) and ankylosing spondylitis (AS) patients and play an important role in both pathologic inflammation and the joint destruction of these diseases. Increased levels of TNF are also found in psoriasis (Ps) plaques. In plaque psoriasis, treatment with adalimumab may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which adalimumab exerts its clinical effects is unknown.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration.

After treatment with adalimumab, 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 RA. A rapid decrease in CRP levels was also observed in patients with JIA or Crohn's disease. Serum levels of matrix metalloproteimases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after adalimumab administration. Patients with RA, PsA and AS often experience mild to moderate anaemia and decreased lymphocyte counts, as well as elevated neutrophil and platelet count. Patients treated with adalimumab usually experienced improvement in these haematological signs of chronic inflammation.

Increased levels of TNF are also found in psoriasis (Ps) plaques, which contribute to the inflammatory response, to the proliferation and decreased maturation of keratinocytes and to the associated vascular damages that are characteristic of the disease.

Pharmacokinetics

Absorption

Following a single 40 mg subcutaneous (SC) administration of adalimumab to 59 healthy adult subjects, absorption and distribution of adalimumab were slow, with mean peak serum concentration being reached about five days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64 %.

Distribution and Elimination

The single dose pharmacokinetics of adalimumab was determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (Vss) ranged from 4.7 to 6.0 ℓ, indicating that adalimumab distributes approximately equally between the vascular and extravascular fluids. Adalimumab is slowly eliminated, with clearances typically under 12 mℓ/h. The mean terminal phase half-life was approximately two weeks, ranging from 10 to 20 days across studies. The clearance and half-life were relatively unchanged over the studied dose range, and the terminal half-life was similar after IV and SC administration.

Adalimumab concentrations in the synovial fluid from several RA patients ranged from 31 % to 96 % of those in serum.

Steady-State Pharmacokinetics

Accumulation of adalimumab was predictable based on the half-life following SC administration of 40 mg of adalimumab every other week to patients with RA, with mean steady-state trough concentrations of 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 approximately proportionally with dose following 20, 40 and 80 mg every other week and every week SC dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

In patients with Crohn's disease, the loading dose of 160 mg adalimumab on week 0 followed by 80 mg adalimumab on week 2 achieves mean serum adalimumab trough concentrations of approximately 12 µg/mℓ at week 2 and week 4. Mean steady-state trough levels of approximately 7

µg/mℓ were observed at week 24 and week 56 in Crohn's disease patients who received a maintenance dose of 40 mg adalimumab 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 1200 patients revealed that co-administration of methotrexate had an intrinsic effect on adalimumab apparent clearance (CL/F). There was a trend towards higher apparent clearance of adalimumab with increasing bodyweight and in the presence of anti-adalimumab antibodies.

Other more minor factors identified were higher apparent clearance in patients receiving doses lower than the recommended dose, and in patients with high rheumatoid factor or CRP concentrations.

Special Populations

Pharmacokinetics in special populations were investigated using population pharmacokinetics analyses.

Paediatrics

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) adalimumab monotherapy and 10.9 ± 5.2 µg/mℓ (47.7% CV) with concomitant methotrexate. The mean steady-state trough serum adalimumab concentrations for subjects weighing <30 kg receiving 20 mg adalimumab subcutaneously every other week as monotherapy or with concomitant methotrexate were 6.8 µg/mℓ and 10.9 µg/mℓ, respectively. The mean steady-state

trough serum adalimumab concentrations for subjects weighing ≥30 kg receiving 40 mg adalimumab subcutaneously every other week as monotherapy or with concomitant methotrexate were 6.6 µg/mℓ and 8.1 µg/mℓ, respectively.

Geriatrics

Age appeared to have a minimal effect on adalimumab apparent clearance. From the population analyses, the mean weight-adjusted clearances in patients 40 to 65 years (n=850) and ≥ 65 years (n=287) were 0.33 and 0.30 mℓ/h/kg, respectively.

Gender

No gender-related pharmacokinetic differences were observed after correction for the patient's body weight.

Race

From limited data in non-Caucasians, no important kinetic differences were observed for adalimumab.

Hepatic and Renal Insufficiency

No pharmacokinetic data is available in patients with hepatic or renal impairment.

Disease States

Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics.

Drug Interactions – Methotrexate

When adalimumab was administered to patients on stable methotrexate therapy, there were no statistically significant changes in the serum methotrexate concentration profiles. In contrast, after single and multiple dosing, methotrexate reduced adalimumab apparent clearances by 29 % and 44 % respectively (see **INTERACTIONS**).

INDICATIONS

Rheumatoid Arthritis

HUMIRA is indicated for the treatment of moderate to severe rheumatoid arthritis in adult patients, including recently diagnosed patients who have not been previously treated with methotrexate.

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

HUMIRA can be used in combination with methotrexate or given as monotherapy in the case of intolerance to methotrexate or when continued treatment with methotrexate is deemed inappropriate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms of psoriatic arthritis.

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 and to improve physical function.

HUMIRA can be used alone or in combination with disease modifying anti-rheumatic drugs.

Ankylosing Spondylitis

HUMIRA is indicated for the treatment of adults with 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 also indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have 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 are candidates for systemic therapy or phototherapy and when other systemic therapies are medically less appropriate.

Polyarticular Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients four years of age and older. **HUMIRA** can be used alone or in combination with methotrexate.

CONTRA-INDICATIONS

HUMIRA should not be administered to patients with known hypersensitivity to adalimumab or any of its excipients.

HUMIRA is contra-indicated in:

- Moderate to severe cardiac failure (NYHA class III/IV)
- Active tuberculosis or other severe infections

WARNINGS

Infections

Serious infections due to bacterial, mycobacterial, invasive fungal (disseminated or extrapulmonary histoplasmosis, aspergillosis, coccidioidomycosis) viral, parasitic, or other opportunistic infections have been reported in patients receiving TNF-blocking agents. Sepsis, rare cases of tuberculosis, candidiasis, listeriosis, and pneumocystis, have also been reported with the use of TNF-antagonists, including **HUMIRA**. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia. Hospitalization or fatal outcomes associated with infections have been reported. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease could predispose them to infections.

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.

Patients should be monitored closely for infections, including tuberculosis, before, during and after treatment with **HUMIRA**.

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 recurrent infection or with underlying conditions that may predispose patients to infections.

Other Opportunistic Infections

Opportunistic infections, including invasive fungal infections, have been observed in patients receiving Humira. These infections are not consistently recognized in patients taking TNF- blockers and this has resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes. Patients taking TNF-blockers are more susceptible to serious fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, aspergillosis, candidiasis, and other opportunistic infections.

Those who develop fever, malaise, weight loss, sweats, cough, dyspnea, and/or pulmonary infiltrates, or other serious systemic illness with or without concomitant shock should promptly seek medical attention for a diagnostic evaluation. For patients who reside or travel in regions where mycoses are endemic, invasive fungal infections should be suspected if they develop the signs and symptoms of possible systemic fungal infection. Patients are at risk of histoplasmosis and other invasive fungal infections and hence clinicians should consider empiric antifungal treatment until the pathogen(s) are identified. 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. Patients who develop a severe fungal infection are also advised to stop the TNF-blocker until infections are controlled.

Hepatitis B Reactivation

Use of TNF blockers has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation.

Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carries of HBV. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data are not available on the safety and efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, **HUMIRA** should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurologic Events

HUMIRA has been associated in rare cases with new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease, including multiple sclerosis. Prescribers should exercise caution in considering the use of **HUMIRA** in patients with pre-existing or recent-onset central nervous system demyelinating disorders.

Malignancies

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. The size of the control group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusion.

Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. During the long-term open label trials with **HUMIRA**, the overall rate of malignancies was similar to what would be expected for an age, gender and race matched general population. 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.
No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving **HUMIRA**. Thus additional caution should be exercised in considering **HUMIRA** treatment of these patients.

Very rare postmarketing reports of hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with **HUMIRA**. Most of the patients had prior infliximab therapy as well as concomitant azathioprine or 6-mercaptopurine use for Crohn's disease. The causal association of HSTCL with **HUMIRA** is not clear.
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.

Paediatrics

HUMIRA has not been studied in children less than 4 years of age and there are limited data on **HUMIRA** treatment in children with weight <15 kg (see **SPECIAL PRECAUTIONS**).

Geriatric

The frequency of serious infection among HUMIRA treated subjects over 65 years of age was higher than for those under 65 years of age. Of the total number of subjects in clinical studies of Humira, 12% were 65 years and over, while approximately 2.5% were 75 and over. Because there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

INTERACTIONS

HUMIRA has been studied in rheumatoid arthritis patients taking concomitant methotrexate. The data does not suggest the need for dose adjustment of either **HUMIRA** or methotrexate.

Interactions between **HUMIRA** and drugs other than methotrexate have not been evaluated in formal pharmacokinetic studies. In clinical trials, no interactions have been observed when **HUMIRA** was administered with commonly used DMARD's (sulfasalazine, hydroxychloroquine, leflunomide and parenteral gold), glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs or analgesics.

There is no experience with the efficacy and safety in patients previously treated with other TNF antagonists.

PREGNANCY AND LACTATION

Pregnancy

No clinical data on pregnant women for **HUMIRA** is available. Therefore, **HUMIRA** should not be used during pregnancy.

Women of childbearing potential should be advised not to become pregnant during **HUMIRA** therapy.

Labour and Delivery

There is no known effect of **HUMIRA** on labour or delivery.

Nursing Mothers

It is not known whether **HUMIRA** is excreted in human milk or absorbed systemically after ingestion. **HUMIRA** should not be used in mothers breastfeeding their infants.

DOSAGE AND DIRECTIONS FOR USE

Rheumatoid Arthritis

The recommended dose of **HUMIRA** for adult patients with rheumatoid arthritis is 40 mg administered every other week as a single dose via subcutaneous injection. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, analgesics or other DMARD's may be continued during treatment with **HUMIRA**.

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

Psoriatic Arthritis

The recommended dose of **HUMIRA** for adult patients with psoriatic arthritis is 40 mg administered every other week as a single dose via subcutaneous injection. Glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, analgesics or disease modifying anti-rheumatic drugs can be continued during treatment with **HUMIRA**.

Ankylosing Spondylitis

The recommended dose of **HUMIRA** for adult patients with ankylosing spondylitis is 40 mg administered every other week as a single dose via subcutaneous injection. Glucocorticoids,

salicylates, nonsteroidal anti-inflammatory drugs, analgesics or disease modifying anti-rheumatic drugs can be continued during treatment with **HUMIRA**.

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 injections in one day or as two injection per day for two consecutive days), 80 mg at week 2, followed 2 weeks later by a maintenance dose of 40 mg every other week via subcutaneous injection.

Aminosalicylates, corticosteroids, and/or immunomodulatory agents (e.g. 6-mercaptopurine and azathioprine) may be continued during treatment with **HUMIRA**. Some patients may derive additional benefit from increasing the dosing frequency of **HUMIRA** to 40 mg 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. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

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.

Polyarticular Juvenile Idiopathic Arthritis

The clinical study to support the indication was done using a dose by body surface area throughout the controlled phase. In the open label part of the study, the dosing was changed to a fixed dose according to a body weight cut-off.

The FDA recommended dose of **HUMIRA** for patients 4 to 17 years of age with polyarticular juvenile idiopathic arthritis is based on weight as shown below. Methotrexate, glucocorticoids, salicylates, NSAIDs or analgesics may be continued during treatment with **HUMIRA**.

Paediatric Patients (4 – 17 years)	**DOSE**
15 kg (33 lbs) to <30 kg (66 lbs)	20 mg every other week
≥30 kg (66 lbs)	40 mg every other week

Limited data are available for **HUMIRA** treatment in paediatric patients with a weight below 15 kg.

The EU recommended dose of **HUMIRA** for patients with polyarticular juvenile idiopathic arthritis aged 13 years and above is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.

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 with this time period.

Preparation of HUMIRA

HUMIRA is intended for use under the guidance and supervision of a physician. Patients may self-inject **HUMIRA** if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in injection technique.

Sites for self-injection include the thigh or abdomen. Injection sites should be rotated. New injections should never be given into areas where the skin is tender, bruised, red or hard.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

HUMIRA should not be mixed in the same syringe or vial with any other medicine.

Any unused product or waste material should be disposed of in accordance with local requirements.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side Effects

Adverse reactions from clinical trials

HUMIRA was studied in 6593 patients in controlled and open label trials for up to 60 months. These trials included rheumatoid arthritis patients with short term and long term standing disease, polyarticular juvenile idiopathic arthritis as well as psoriatic arthritis, ankylosing spondylitis, Crohn's disease and psoriasis patients. The data in the Table 1 below is based on the controlled pivotal studies involving 4355 patients receiving **HUMIRA** and 2487 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.

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

Adverse events at least possibly causally-related to **HUMIRA**, for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and psoriasis studies, both clinical and laboratory,

are displayed by system organ class and frequency (very common ≥1/10; common ≥1/100 ≤ 1/10; uncommon ≥1/1000 ≤ 1/100; rare ≥ 1/10 000 ≤ 1/1000) in Table 1 below.

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 Contraindications, Warnings and Precautions and Adverse Reactions.

TABLE 1 : ADVERSE REACTIONS IN CLINICAL STUDIES

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE EVENTS
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 and malignant (including cysts and polyps) *	Common Uncommon	benign neoplasm, skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma) lymphoma**, solid organ neoplasms (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma **
Blood and the lymphatic system disorders *	Very common Common Uncommon Rare	leucopenia (including neutropenia and agranulocytosis), anemia thrombocytopenia idiopathic thrombocytopenic purpura pancytopenia
Immune system disorders *	Common	hypersensitivity (including seasonal allergy)
Metabolism and nutrition disorders	Very common Common Uncommon	lipids increased hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia, hyperglycemia, hypophosphotemia, blood potassium increased dehydration
Psychiatric disorders	Common	mood alterations (including depression) anxiety, insomnia

Nervous system disorders	Very Common Common Uncommon Rare	headache paraesthesias (including hypoasthesia), migraine, sciatica tremor multiple sclerosis
Eye disorders	Common Uncommon	visual impairment, conjunctivitis blepharitis, eye swelling, diplopia
Ear and labyrinth disorders	Common Uncommon	vertigo deafness, tinnitus
Cardiac disorders *	Common Uncommon Rare	tachycardia, arrhythmia, congestive heart failure cardiac arrest
Vascular disorders	Common Rare	hypertension, flushing, haematoma vascular arterial occlusion, thrombophlebitis, aortic aneurysm
Respiratory, thoracic and mediastinal disorders	Common Uncommon	cough, asthma, dyspnoea chronic obstructive pulmonary disease, interstitial lung disease, pneumonitis
Gastrointestinal disorders	Very Common Common Uncommon	abdominal pain, nausea and vomiting GI haemorrhage, dyspepsia, gastro-oesophageal reflux disease, sicca syndrome pancreatitis, dysphagia, face oedema

Hepato-biliary disorders *	Very Common Uncommon	liver enzymes elevated cholecystitis and cholelithiasis, bilirubin increased, hepatic steatosis
Skin and subcutaneous tissue disorders	Very Common Common Uncommon	rash (including exfoliative rash), pruritus, urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis, hyperhydrosis night sweats, scar
Musculoskeletal, connective tissue and bone disorders	Very Common Common Uncommon Rare	musculoskeletal pain muscle spasms (including blood creatine phosphokinase increased) rhabdomyolysis systemic lupus erythematosus
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 tests positive (including double stranded DNA antibody), blood lactate dehydrogenase increased
Injury and poisoning	Common	impaired healing

Further information found elsewhere in Contraindications, Warnings & Precautions and Adverse Reactions
****Includes open label extension studies***

Juvenile Idiopathic Arthritis

HUMIRA has been studied in 171 paediatric patients 4-17 years of age with polyarticular juvenile idiopathic arthritis. In general, the adverse reactions in paediatric patients were similar in frequency and type to those seen in adult patients.

Injection Site Reaction

In the pivotal controlled trials, 15% of patients treated with **HUMIRA** developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared with 9% of patients receiving control treatment. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

Infections

In the pivotal controlled trials, the rate of infection was 1.58 per patient year in the **HUMIRA** treated patients and 1.42 per patient year in the control-treated patients. The incidence of serious infections was 0.04 per patient year in **HUMIRA**-treated patients and 0.03 per patient year in control-treated patients. The infections consisted primarily of upper respiratory tract infections,

bronchitis and urinary tract infections. Most patients continued on **HUMIRA** after the infection resolved.

In the 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 extrapulmonary locations) at an overall rate of approximately 0.026/1000 patient years and invasive opportunistic infections (e.g. disseminated histoplasmosis, Pneumocystis carinii pneumonia, aspergillosis and listeriosis) at an overall rate of approximately 0.0075/1000 patient years.

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 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 5.9 (3.5, 9.9) per 1000 patient-years among 3853 **HUMIRA** treated patients versus a rate of 4.3 (1.8, 10.4) per 1000 patient-years among 2183 control patients (median duration of treatment was 5.5 months for **HUMIRA** and 4.0 months for control-treated patients).

The rate (95 % confidence interval) of non-melanoma skin cancers was 8.8 (5.7, 13.5) per 1000 patient-years among **HUMIRA** treated patients and 2.6 (0.8, 8.0) per 1000 patient-years among control patients.

Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) of 2.5(1.1, 5.6) per 1000 patient years among **HUMIRA** treated patients and 0.9(0.1, 6.1) 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 0.9 (0.1, 6.1) per 1000 patient-years among control patients.

The observed rate of malignancies, other than lymphoma and non-melanoma skin cancers, is approximately 8.3 per 1000 patient years in the controlled portion of clinical trials and ongoing open label extension studies. The observed rate of non-melanoma skin cancers is approximately 9.3 per 1000 patient years, and the observed rate of lymphomas is approximately 1.2 per 1000 patient years. The median duration of these studies is approximately 2.7 years and included 4,767 patients who were on Humira for at least 1 year or who developed a malignancy within a year of starting therapy, representing over 15,332 patient years of therapy.

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis Studies I - V. In these adequate and well-controlled 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 titers reported positive titers at week 24. Two patients out of 3989 treated with **HUMIRA** in all RA, PsA and AS studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patient improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with **HUMIRA** on the development of autoimmune disease is unknown.

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

In patients with early rheumatoid arthritis (disease duration of less than 3 years), elevations of ALT are more common in the combination arm (Humira/methotrexate) compared to the methotrexate monotherapy arm or the **HUMIRA** monotherapy arm.

Elevations in ALT are more common in psoriatic arthritis patients compared with patients with rheumatoid arthritis.

In the juvenile idiopathic arthritis trial, the few transaminase elevations were small and similar in the placebo and adalimumab exposed patients and mostly occurred in combination with methotrexate.

In all indications patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment.

Additional adverse reactions from Postmarketing Surveillance or Phase IV Clinical Trials

Adverse events have been reported during post-approval use of **HUMIRA**. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to **HUMIRA** exposure.

TABLE 2: ADDITIONAL ADVERSE REACTIONS FROM POSTMARKETING SURVEILLANCE OR PHASE IV CLINICAL TRIALS

BODY SYSTEM	ADVERSE REACTION
Immune system disorders	anaphylaxis
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
Gastrointestinal disorders	intestinal perforation
Nervous system disorders	demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome), cerebrovascular accident
Musculoskeletal and connective tissue disorders	lupus-like syndrome
Cardiac disorders	myocardial infarction
Neoplasms benign, malignant and unspecified (including cysts and polyps)	hepatosplenic T-cell lymphoma, leukemia
Infections and Infestations	diverticulitis
Vascular disorders	pulmonary embolism

Special Precautions

Allergy

Serious allergic reactions associated with **HUMIRA** were rare during clinical trials. In post-marketing, 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.

Tuberculosis

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) associated with administration of **HUMIRA** in clinical trials has been reported. While cases were observed at all doses, the incidence of tuberculosis reactivations was particularly increased at doses of **HUMIRA** that were higher than the recommended dose. Invasive fungal infections, and other opportunistic infections have been observed in patients receiving **HUMIRA**. Some of these infections, including tuberculosis, have been fatal (see **WARNINGS**).

Before initiation of therapy with **HUMIRA**, all patients should 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 (e.g., chest X-ray and tuberculin skin test) should be performed in accordance with local recommendations.

Treatment of latent tuberculosis infection should be initiated prior to therapy with **HUMIRA**. When tuberculin skin testing is performed for latent tuberculosis infection, an induration size of 5 mm or greater should be considered positive, even if vaccinated previously with Bacille Calmette-Guerin (BCG).

The possibility of undetected latent tuberculosis should be considered especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or who had close contact with a person with active tuberculosis.

If active tuberculosis is diagnosed, **HUMIRA** therapy must not be initiated.

If latent tuberculosis is diagnosed, appropriate anti-tuberculosis prophylaxis in accordance with local recommendations should be intiated before starting treatment with **HUMIRA**. Anti-tuberculosis therapy prior to initiating **HUMIRA** should also be considered in patients who have a negative test for latent tuberculosis but have risk factors for TB infection. The decision to initiate anti-tuberculosis therapy in these patients should only be made after taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy. If necessary, consultation should occur with a physician with expertise in the treatment of tuberculosis.

Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with **HUMIRA**. However, active tuberculosis has developed in patients receiving **HUMIRA** whose screening for latent tuberculosis infection was negative, and some patients who have previously received treatment for latent or active tuberculosis have developed active tuberculosis while being treated with TNF blocking agents.

Patients receiving **HUMIRA** should be monitored for signs and symptoms of active tuberculosis, particularly because tests for latent tuberculosis infection may be falsely negative. The risk of false negative tuberculin skin test results should be considered especially in patients who are severely ill or immunocompromised.

Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

As HIV positive patients have a high incidence of cutaneous anergy, which may result in false negative tuberculin tests, particular attention should be given to the diagnosis of latent tuberculosis infection in these patients.

No data exists on the use of HUMIRA in HIV positive patients. Therefore, the risks of serious infections must be carefully balanced with the benefits of HUMIRA treatment prior to the initiation of therapy in HIV positive patients.

Patients should be instructed to seek medical advice if signs/symptoms (e.g. persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur. Extra care should be taken with HIV positive patients where the clinical course of tuberculosis may be particularly aggressive.

Haematologic Events

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse events of the haematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been reported with **HUMIRA**. The causal relationship of these reports to **HUMIRA** remains unclear. 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.

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 contra-indicated in moderate or severe heart failure. Treatment with **HUMIRA** must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

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- and B-cells and NK-cells, monocyte/macrophages, and neutrophils.

Vaccinations

In a randomised, double-blind, placebo-controlled study in 226 adult rheumatoid arthritis patients treated with **HUMIRA**, antibody responses to concomitant pneumococcal and influenza vaccines were assessed. Protective antibody levels to the pneumococcal antigens were achieved by 86 % of patients in the **HUMIRA** group compared to 82 % in the placebo group. A total of 37 % of **HUMIRA**-treated subjects and 40 % of placebo-treated subjects achieved at least a 2-fold increase in at least 3 out of 5 pneumococcal antigens. In the same study 98 % of patients in the **HUMIRA** group and 95 % in the placebo group achieved protective antibody levels to the influenza antigens. A total of 52 % of **HUMIRA**-treated subjects and 63 % of placebo-treated subjects achieved at least a 4-fold increase in at least 2 out of 3 influenza antigens.

It is recommended that polyarticular juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating **HUMIRA** therapy.

Patients on **HUMIRA** may receive concurrent vaccinations, except for live vaccines. No data is available on the secondary transmission of infection by live vaccines in patients receiving **HUMIRA**.

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**, treatment should be discontinued.

Drug/Laboratory Test Interaction

There is no known interference between **HUMIRA** and laboratory tests.

Paediatric Use

HUMIRA has not been studied in children less than 4 years of age and there are limited data on **HUMIRA** treatment in children with weight <15 kg. The safety and efficacy of **HUMIRA** in paediatric patients for indications other than juvenile idiopathic arthritis have not been established.

Geriatric Use

Of the total number of subjects in clinical studies with **HUMIRA**, 12% were 65 and over, while approximately 2.5% were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects. No dose adjustment is needed for this population.

Use with Anakinra

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent, with no added benefit. Because of the nature of the adverse events seen with combination therapy, similar toxicities may also result from combination with anakinra and other TNF blocking agents. Therefore, the combination of **HUMIRA** and anakinra is not recommended (see **INTERACTIONS**).

Use with 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. This combination has not demonstrated increased clinical benefit. Thus the combined use of TNF antagonists and abatacept is not recommended.

Immunogenicity

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

Patients in RA Studies I, II and III were tested at multiple timepoints for antibodies to **HUMIRA** during the 6 to 12 month period. In the pivotal trials, anti-adalimumab antibodies were identified in 58/1053 (5.5%) patients treated with **HUMIRA**, compared to 2/370 (0.5%) on placebo. In patients

not given concomitant methotrexate, the incidence was 12.4%, compared to 0.6% when **HUMIRA** was used as add-on to methotrexate.

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

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

In patients with Crohn's disease, **HUMIRA** antibodies were identified in 7/269 subjects (2.6%) treated with **HUMIRA**.

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

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

The maximum tolerated dose of **HUMIRA** has not been established in humans. No dose-limiting toxicities have been observed during clinical trials with **HUMIRA**. Multiple doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

IDENTIFICATION

Aqueous solution practically free from visible particles.

PRESENTATION

HUMIRA 40 mg is supplied as a sterile solution of 40 mg adalimumab per 0.8 mℓ for parenteral administration in the following packaging configurations:

- **HUMIRA 40 mg** solution for injection in a single-use, pre-filled, colourless glass syringe (*for patient use*):
  - ⇨ Carton containing 1 blister with 1 single-dose, pre-filled syringe and 1 alcohol pad.
  - ⇨ Carton containing 2 blisters, each containing 1 single-dose, pre-filled syringe and 1 alcohol pad.

- **HUMIRA 40 mg** solution for injection in a single-use, pre-filled, colourless glass syringe with needle guard (*hospital and caregiver use*):
  - ⇨ Carton containing 1 blister with 1 single-dose, pre-filled syringe with needleguard, and 1 alcohol pad.

- **HUMIRA 40 mg** solution for injection in a single-use, colourless glass vial.
  - ⇨ Carton containing 1 blister with 1 single-dose vial, 1 empty sterile injection syringe in a pouch and 2 alcohol pads. The vial is fitted with a rubber stopper, aluminium crimp and flip-off seal.

- **HUMIRA 40 mg** solution for injection in a pre-filled Pen
  - ⇨ Humira is dispensed in a carton containing an alcohol prep and dose tray. Each tray consists of a single-use Pen, containing a 1 ml prefilled glass syringe with a fixed needle, providing 40 mg (0.8 ml) of Humira.

STORAGE INSTRUCTIONS

Store at 2 – 8 ºC (in a refrigerator) and store the syringe or vial in the outer carton.

DO NOT FREEZE. Discard any unused portions.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

37/30.2/0252

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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