APPROVED PROFESSIONAL INFORMATION:

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death [see Section 4.4].

HUMIRA should be discontinued if a patient develops a serious infection or sepsis.

SCHEDULING STATUS

Schedule 4

1 NAME OF THE MEDICINE

HUMIRA 20 mg / 0,2 mL Solution for Injection

HUMIRA 40 mg / 0,4 mL Solution for Injection

HUMIRA 80 mg / 0,8 mL Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

HUMIRA 20 mg / 0,2 mL Solution for Injection:

Each single use pre-filled syringe of HUMIRA contains 20 mg adalimumab per 0,2 mL (100 mg/mL)

HUMIRA 40 mg / 0,4 mL Solution for Injection:

Each single use pre-filled syringe of HUMIRA contains 40 mg adalimumab per 0,4 mL (100 mg/mL)

HUMIRA 80 mg / 0,8 mL Solution for Injection

Each single use pre-filled syringe of HUMIRA contains 80 mg adalimumab per 0,8 mL (100 mg / mL)

“Sugar Free”

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection. (injection)

HUMIRA is a clear, colourless aqueous solution which is practically free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults

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 (DMARD's).

Plaque 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.

HUMIRA is indicated for moderate to severe **nail psoriasis** in adult patients who are candidates for systemic therapy.

Axial Spondyloarthritis including ankylosing spondylitis

HUMIRA is indicated for the treatment of adults with severe axial spondyloarthritis, including ankylosing spondylitis, who have had an inadequate response to conventional therapy or are intolerant to NSAIDs.

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.

Ulcerative colitis

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

Hidradenitis Suppurativa

HUMIRA is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.

Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

Paediatrics

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 two years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Paediatric Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in paediatric patients, 6 years of age and older, with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy.

Paediatric Plaque Psoriasis

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

Paediatric Uveitis

HUMIRA is indicated for the treatment of chronic non-infectious uveitis in paediatric patients 2 years of age and older.

Paediatric Ulcerative Colitis

HUMIRA is indicated for inducing and maintaining clinical remission in paediatric patients 5 years of age or older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

4.2. Posology and method of administration

Posology

<u>Adults</u>

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 medicines, analgesics or other DMARD's may be continued during treatment with HUMIRA.

In rheumatoid arthritis, some patients not taking concomitant MTX may derive additional benefit from increasing the dosage of HUMIRA to 40 mg every week or 80 mg every other week.

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. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory medicines, analgesics or disease modifying anti-rheumatic drugs (DMARD's) can be continued during treatment with HUMIRA.

Axial spondyloarthritis including Ankylosing spondylitis

The recommended dose of HUMIRA for patients with Axial spondyloarthritis including ankylosing spondylitis is 40 mg administered every other week as a single dose via subcutaneous injection. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory medicines, analgesics or disease modifying anti-rheumatic medicines 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 initially at Day 1 (given as 160 mg in one day or as 80 mg per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Another two weeks later (Day 29) begin a maintenance dose of 40 mg every other week.
Aminosalicylates, corticosteroids, and/or immunomodulatory medicines (e.g. 6-mercaptopurine and azathioprine) may be continued during treatment with HUMIRA.

Some patients who experience decrease in their response may derive additional benefit from an increase in dosage to 40 mg HUMIRA every week or 80 mg every other 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.

Ulcerative colitis

The recommended HUMIRA induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at Week 0 (given as 160 mg in one day or as 80 mg per day for two consecutive days) and 80 mg at Week 2. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Aminosalicylates, corticosteroids, and/or immunomodulatory medicines (e.g., 6-mercaptopurine and azathioprine) may be continued during treatment with HUMIRA.

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

Some patients who experience decrease in their response may benefit from an increase in dosage to 40 mg HUMIRA every week or 80 mg every other week.

Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment. HUMIRA should only be continued in patients who have responded during the first 8 weeks of therapy.

Plaque Psoriasis

The recommended dose of HUMIRA for adult patients with plaque psoriasis 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.

Patients with inadequate response after 16 weeks may benefit from an increase in dosage to 40 mg every week or 80 mg every other week. The benefits and risks of continued weekly HUMIRA therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosing frequency. If adequate response is achieved with an increased dosage, the dose may subsequently be reduced to 40 mg every other week.

Hidradenitis Suppurativa

The recommended HUMIRA dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at Day 1 (given as 160 mg in one day or as 80 mg per day for two consecutive days), followed by 80 mg two weeks later at Day 15. Two weeks later (Day 29) continue with a dose of 40 mg every week or 80 mg every other week. Antibiotics may be continued during treatment with HUMIRA if necessary.

Should treatment need to be interrupted, HUMIRA may be re-introduced. In patients without any benefit after 12 weeks of treatment, continued therapy should be reconsidered.

Uveitis

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

HUMIRA can be used alone or in combination with corticosteroids, which may be tapered in accordance with clinical practice, or other non-biologic immunomodulatory medicines.

Paediatrics

Polyarticular Juvenile Idiopathic Arthritis

The recommended dose of HUMIRA for patients from 2 years of age with polyarticular juvenile idiopathic arthritis (JIA) is based on body weight (Table1). Methotrexate, glucocorticoids, NSAIDs and/or analgesics may be continued during treatment with HUMIRA. HUMIRA may be available in other strengths and/or presentations.

Table 1. HUMIRA Dose for Patients with Polyarticular Juvenile Idiopathic Arthritis

Patients Weight	**DOSE**
10 kg to <30 kg	20 mg every other week
≥30 kg	40 mg every other week

HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

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

There is no relevant use of HUMIRA in children aged <2 years in this indication.

Paediatric Plaque Psoriasis:

The recommended HUMIRA dose for patients from 4 to 17 years of age with plaque psoriasis is based on body weight (Table 2). HUMIRA is administered via subcutaneous injection. HUMIRA may be available in other strengths and/or presentations.

Table 2: HUMIRA Dose for Paediatric Patients with Plaque Psoriasis

Patients Weight	**DOSE**
15 kg to < 30 kg	Initial dose of 20 mg, followed by 20 mg given every other week starting one week after the initial dose
≥ 30 kg	Initial dose of 40 mg, followed by 40 mg given every other week starting one week after the initial dose

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

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

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

Paediatric Crohn's Disease

The recommended dose of HUMIRA for patients from 6 to 17 years of age with Crohn's disease is based on body weight (Table 3). HUMIRA is administered via subcutaneous injection. HUMIRA may be available in other strengths and/or presentations depending on the individual treatment needs.

Table 3. HUMIRA Dose for Paediatric Patients with Crohn's disease

Patient Weight	**Induction Dose**	**Maintenance Dose Starting at Week 4**
< 40 kg	• 80 mg at Week 0 and • 40 mg at Week 2	20 mg every other week
≥ 40 kg	• 160 mg at Week 0 and • 80 mg at Week 2	40 mg every other week

Some patients may benefit from increasing the dosage if a disease flare or an inadequate response is experienced during maintenance dosing.

- < 40 kg: 20 mg every week
- ≥ 40 kg: 40 mg every week or 80 mg every other week

HUMIRA has not been studied in children with Crohn's disease aged less than 6 years.

Paediatric Uveitis

The recommended dose of HUMIRA for paediatric patients 2 years of age and older with chronic non-infectious uveitis is based on body weight (Table 4). HUMIRA is administered via subcutaneous injection. HUMIRA may be available in different strengths and/or presentations. HUMIRA may be used in combination with methotrexate or other non-biologic immunomodulatory agents based on clinical judgment**.**

Table 4: HUMIRA Dose by Weight for Patients with Paediatric Uveitis

Patients Weight	**DOSE**
< 30 kg	20 mg every other week
≥ 30 kg	40 mg every other week

When HUMIRA is initiated a loading dose of 40 mg for patients <30 kg or 80 mg for patients ≥30 kg may be administered one week prior to the start of maintenance therapy.

HUMIRA has not been studied in patients with chronic non-infections uveitis less than 2 years of age.

Paediatric Ulcerative Colitis

The recommended dose of HUMIRA for patients from 5 to 17 years of age with ulcerative colitis is based on body weight (Table 5). HUMIRA is administered via subcutaneous injection.

HUMIRA may be available in different strengths and/or presentations.

Table 5. HUMIRA Dose for Paediatric Ulcerative Colitis

Patient Weight	**Induction Dose**	**Maintenance Dose Starting at Week 4***
< 40 kg	• 80 mg at Week 0 and • 40 mg at Week 2	• 40 mg every other week or • 20 mg every week
≥ 40 kg	• 160 mg at Week 0 and • 80 mg at Week 2	• 80 mg every other week or • 40 mg every week
* Paediatric patients who turn 18 years of age while on HUMIRA should continue their prescribed maintenance dose.		

Continued therapy beyond 8 weeks should be carefully considered in patients not showing signs of response within this time period.

Patients who experience a disease flare after beginning maintenance therapy may benefit from a one-time re-induction dose of 80 mg (<40 kg) or 160 mg (≥40 kg), followed by maintenance dosing.

There is no relevant use of HUMIRA in children aged less than 5 years in this indication.

Method of administration

Preparation of HUMIRA

HUMIRA is intended for use under the guidance and supervision of a medical practitioner. Patients may self-inject HUMIRA if their medical practitioner 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.

Paediatric Use

HUMIRA has not been studied in children less than 2 years of age.

The safety and efficacy of HUMIRA in paediatric patients for indications other than polyarticular juvenile idiopathic arthritis, paediatric Crohn's disease, paediatric plaque psoriasis, paediatric uveitis and paediatric ulcerative colitis have not been established.

Use in Elderly

Of the total number of subjects in clinical studies with HUMIRA, 9,4 % were 65 and over, while approximately 2,0 % 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.

4.3 Contraindications

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

HUMIRA is contraindicated in:

- Moderate to severe cardiac failure (NYHA class III/IV)
- Active tuberculosis or other severe infections
- Concomitant use with live vaccines

4.4 Special warnings and precautions for use

Traceability

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

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 medicines. Sepsis, rare cases of tuberculosis, candidiasis, listeriosis, legionellosis 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. Hospitalisation 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.

Medical practitioner 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.

Tuberculosis

Tuberculosis including reactivation and new onset of tuberculosis, has been reported in patients receiving HUMIRA. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated). Invasive fungal infections, and other opportunistic infections have been observed in patients receiving HUMIRA. Some of these infections, including tuberculosis, have been fatal.

Before initiation of therapy with HUMIRA, all patients should be evaluated for both active and inactive ("latent") tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy.

Appropriate screening tests (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 travelled 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 treatment must be started with anti-tuberculosis prophylactic treatment before the initiation of HUMIRA and in accordance with local recommendations. Use of anti-tuberculosis prophylactic treatment should also be considered before the initiation of HUMIRA in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. 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 medical practitioner 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. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA.

Also, active tuberculosis has developed in patients receiving HUMIRA whose screening for latent tuberculosis infection was negative, and some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with TNF blocking medicines.

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 suggestive of a tuberculosis infection (e.g. persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with HUMIRA. Extra care should be taken with HIV positive patients where the clinical course of tuberculosis may be particularly aggressive.

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, dyspnoea, 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 medical practitioner 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 HUMIRA 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 HUMIRA therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medicines 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 HUMIRA 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 with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis, optic neuritis, and peripheral demyelinating disease, including Guillain Barré syndrome. Prescribers should exercise caution in considering the use of HUMIRA in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders, discontinuation of HUMIRA should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of HUMIRA therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

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.

Malignancies, some fatal, have been reported among children and adolescents who received treatment with TNF-blocking medicines. 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.

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 immunosuppressive therapy as well as concomitant azathioprine or 6-mercaptopurine use for inflammatory bowel disease.

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.

Acute and chronic leukaemia 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 leukaemia, even in the absence of HUMIRA therapy.

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

Allergy

Serious allergic reactions associated with HUMIRA were reported during clinical trials. Reports of serious allergic reactions, including anaphylaxis have been received following HUMIRA

administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of HUMIRA should be discontinued immediately and appropriate therapy initiated. The needle cover of the syringe contains natural rubber (latex). This may cause severe allergic reactions in patients sensitive to latex.

Haematologic Events

Reports of pancytopenia including aplastic anaemia have been reported with TNF blocking medicines, including HUMIRA. Adverse events of the haematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been reported with HUMIRA. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor) while on HUMIRA.

Discontinuation of HUMIRA therapy should be considered in patients with confirmed significant haematologic abnormalities.

Concurrent administration of biologic disease modifying anti-rheumatic drugs (DMARDS) or TNF-antagonists

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

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

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 paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating HUMIRA therapy.

Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines (see Section 4.3). No data is available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

In the event that a woman becomes pregnant during HUMIRA therapy, administration of live vaccines to the infant is not recommended for 5 months following the mother's last HUMIRA injection during pregnancy.

Congestive Heart Failure

Cases of worsening congestive heart failure have 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 (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, treatment should be discontinued.

Drug/Laboratory Test Interaction

There is no known interference between HUMIRA and laboratory tests.

Elderly

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, 9,4 % were 65 years and over, while approximately 2,0 % 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.

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.

In patients with moderately to severely active UC, the rate of anti-adalimumab antibody development in patients treated with adalimumab was 5, 0 %.

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.

In plaque psoriasis patients on long term adalimumab without concomitant methotrexate who participated in a withdrawal and retreatment study, the rate of anti-adalimumab antibodies after retreatment was 2,3 %, and was similar to the rate observed prior to withdrawal 1,9 %.

In patients with moderate to severe hidradenitis suppurativa, anti-adalimumab antibodies were identified in 10,1 % (10/99) of patients treated with adalimumab.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4,8 % (12/249) of patients treated with adalimumab.

4.5 Interaction with other medicinal products and other forms of interaction

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 medicines 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 medicines or analgesics.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

A large number (approximately 2100) of prospectively collected pregnancies exposed to HUMIRA resulting in live birth with known outcomes, including more than 1500 exposed during the first trimester, does not indicate an increase in the rate of malformation in the newborn.

In a prospective cohort registry, 257 women with rheumatoid arthritis (RA) or Crohn's disease (CD) treated with HUMIRA at least during the first trimester and 120 women with RA or CD not treated with HUMIRA were enrolled. The primary endpoint was the birth prevalence of major birth defects. The rate of pregnancies ending with at least one live born infant with a major birth defect was 6/69 (8,7 %) in the adalimumab-treated women with RA and 5/74 (6,8 %) in the untreated women with RA (unadjusted OR 1,31; 95 % CI 0,38 - 4,52) and 16/152 (10,5 %) in the adalimumab-treated women with CD and 3/32 (9,4 %) in the untreated women with CD (unadjusted OR 1,14; 95 % CI 0,31 – 4,16). The adjusted OR (accounting for baseline differences) was 1,10 (95 % CI 0,45 – 2,73) with RA and CD combined. There were no distinct differences between adalimumab-treated and untreated women for the secondary endpoints spontaneous abortions, minor birth defects, preterm delivery, birth size and serious or opportunistic infections and no stillbirths or malignancies

were reported. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomized design.

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

Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect normal immune responses in the newborn. HUMIRA should only be used during pregnancy if clearly needed.

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

Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least five months after the last HUMIRA treatment.

Labour and Delivery

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

Breastfeeding Mothers

Limited information from the published literature indicates that HUMIRA is excreted in breast milk at very low concentrations with the presence of HUMIRA in human milk at concentrations of 0,1 % to 1% of the maternal serum level. Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breastfed newborns/infants are anticipated. Consequently, HUMIRA can be used during breastfeeding.

4.7 Effects on ability to drive and use machines

HUMIRA may influence the ability to drive and use of machines. Vertigo and visual impairment may occur following the administration of HUMIRA (see Section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions from clinical trials

HUMIRA was studied in 9506 patients in pivotal controlled and open label trials for up to 60 months. These trials included rheumatoid arthritis patients with short term and long term standing disease, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis) as well as psoriatic arthritis, ankylosing spondylitis, axial spondyloarthritis including ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients. The controlled pivotal studies involve 6089 patients receiving HUMIRA and 3801 patients receiving placebo or active comparator during the controlled period.

The proportion of patients who discontinued treatment due to adverse events during the double blind, controlled portion of pivotal studies was 5,9 % for patients taking HUMIRA and 5,4 % for control treated patients.

Approximately 13 % of patients can be expected to experience injection site reactions, based on one of the most common adverse events with HUMIRA in controlled clinical studies.

b. Tabulated summary of adverse reactions

Adverse events at least possibly causally-related to HUMIRA, 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 6 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 Special Precautions and Adverse Reactions.

TABLE 6: ADVERSE REACTIONS IN CLINICAL STUDIES		
SYSTEM ORGAN CLASS	**FREQUENCY**	**SYSTEM ORGAN CLASS**
Infections and infestations	Very Common	respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections, joint infections.
	Uncommon	opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), neurological infections (including viral meningitis), eye infections, bacterial infections.
Neoplasms benign, malignant and unspecified	Common	benign neoplasm, skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma)

(including cysts and polyps) *	Uncommon	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), anaemia thrombocytopenia, leucocytosis idiopathic thrombocytopenic purpura pancytopenia
Immune system disorders *	Common	hypersensitivity (including seasonal allergy)
Metabolism and nutrition disorders	Very common Common	lipids increased hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia, hyperglycaemia, hypophosphotaemia, dehydration
Psychiatric disorders	Common	mood alterations (including depression) anxiety, insomnia
Nervous system disorders	Very Common Common Uncommon Rare	headache paraesthesias (including hypoasthesia), migraine, nerve root compression tremor, neuropathy 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, dysrhythmia, congestive heart failure cardiac arrest
Vascular disorders	Common Uncommon	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 and connective tissue disorders	Very Common Common Uncommon	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, poisoning and procedural complications	Common	impaired healing

Further information found elsewhere in Section 4.3, 4.4 and 4.8

****Includes open label extension studies***

c. Description of selected adverse reactions

Injection Site Reaction

In the pivotal controlled trials in adults and children, 12,9 % of patients treated with HUMIRA developed injection site reactions (erythematic and/or itching, haemorrhage, pain or swelling), compared with 7,2 % 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 in adults and children, the rate of infection was 1,51 per patient year in the HUMIRA treated patients and 1,46 per patient year in the 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 nasopharyngitis, upper respiratory tract infections and sinusitis. Most patients continued on HUMIRA after the infection resolved.

In the controlled and open label adult and paediatric studies with HUMIRA, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extrapulmonary locations) at an overall rate of approximately 0,026/1000 patient years and invasive opportunistic infections (e.g. disseminated histoplasmosis, pneumocystis jirovecii pneumonia, aspergillosis and listeriosis) at an overall rate of approximately 0,0075/1000 patient years.

Malignancies and lymphoproliferative disorders

No malignancies were observed in 249 paediatric patients with an exposure of 655,6 patient years during Humira trials in patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis).

In addition, no malignancies were observed in 192 paediatric patients with an exposure of 498,1 patient years during a Humira trial in paediatric patients with Crohn's disease.

No malignancies were observed in 77 paediatric patients with an exposure of 80,0 patient years during a Humira trial in paediatric patients with plaque psoriasis.

No malignancies were observed in 60 paediatric patients with an exposure of 58,4 patient years during a Humira trial in paediatric patients with uveitis.

No malignancies were observed in 93 paediatric patients with an exposure of 65,3 patient years during a Humira trial in paediatric patients with ulcerative colitis.

During the controlled portions of pivotal HUMIRA trials in adults at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, axial spondyloarthritis including ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, psoriasis and uveitis , malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95 % confidence interval) of 6,8 (4,4; 10,5) per 1000 patient-years among 5291 HUMIRA treated patients versus a rate of 6,3 (3,4; 11,8) per 1000 patient-years among 3444 control patients (median duration of treatment was 4,0 months for HUMIRA and 3,8 months for control-treated patients).

The rate (95 % confidence interval) of non-melanoma skin cancers was 8,8 (6,0; 13,0) per 1000 patient-years among HUMIRA treated patients and 3,2 (1,3; 7,6) per 1000 patient-years among control patients.

Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) of 2,7 (1,4; 5,4) per 1000 patient years among HUMIRA treated patients and 0,6 (0,1; 4,5) per 1000 patient years among control patients.

The rate (95 % confidence interval) of lymphomas was 0,7 (0,2; 2,7) per 1000 patient-years among HUMIRA treated patients and 0,6 (0,1; 4,5) per 1000 patient-years among control patients.

The observed rate of malignancies, other than lymphoma and non-melanoma skin cancers, is approximately 8,5 per 1000 patient years in the controlled portion of clinical trials and in ongoing and completed open label extension studies. The observed rate of non-melanoma skin cancers is approximately 9,6 per 1000 patient years, and the observed rate of lymphomas is approximately 1,3 per 1000 patient years. The median duration of these studies is approximately 3,3 years and included 6427 patients who were on HUMIRA for at least 1 year or who developed a malignancy within a year of starting therapy, representing over 26439,6 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 hospitalisation. 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 controlled Phase 3 trials of HUMIRA (40 mg SC every other week), in patients with RA and PsA with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3,7 % of HUMIRA-treated patients and 1,6 % of control-treated patients. Since many of the patients in these trials were also taking medications that cause liver enzyme elevations (e.g. NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week), in patients with Crohn's

disease with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0,9 % of HUMIRA-treated patients and 0,9 % of control-treated patients.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week), in patients with ulcerative colitis with a control period duration ranging from 1 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 1,5 % of HUMIRA-treated patients and 1,0 % of control-treated patients.

In controlled trials of HUMIRA (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in patients with hidradenitis suppurativa with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0,3% of HUMIRA -treated patients and 0,6% of control-treated patients

In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week), in patients with plaque psoriasis with a control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1,8 % of HUMIRA-treated patients and 1,8 % of control-treated patients.

In controlled Phase 3 trials of HUMIRA (40 mg every other week), in patients with ankylosing spondylitis and axial spondyloarthritis with a control period of 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 2,1 % of HUMIRA-treated patients and 0,8 % of control-treated patients.

In controlled Phase 3 trials of HUMIRA in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations ≥ 3 x ULN occurred in 6,1% of HUMIRA -treated patients and 1,3% of control-treated patients. Most ALT elevations occurred with concomitant methotrexate use. No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial of HUMIRA in patients with polyarticular juvenile idiopathic arthritis who were 2 to <4 years.

In the Phase 3 trial of HUMIRA in patients with paediatric Crohn's disease which evaluated efficacy and safety of two body weight adjusted maintenance dose regimens following body weight

adjusted induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 X ULN occurred in 2,6 % (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline.

In controlled trials of HUMIRA (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis with an exposure of 165,4 PYs and 119,8 PYs in HUMIRA -treated and control- treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2,4 % of HUMIRA -treated patients and 2,4 % of control-treated patients.

In the controlled Phase 3 trial of Humira in patients with paediatric ulcerative colitis (N=93) which evaluated efficacy and safety of a maintenance dose of 0,6 mg/kg (maximum of 40 mg) every other week (N=31) and a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every week (N=32), following body weight adjusted induction dosing of 2,4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1,2 mg/kg (maximum of 80 mg) at Week 2 (N=63), or an induction dose of 2.4 mg/kg (maximum of 160 mg) at Week 0, placebo at Week 1, and 1,2 mg/kg (maximum of 80 mg) at Week 2 (N=30), ALT elevations ≥ 3 X ULN occurred in 1,1 % (1/93) of patients.

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

Across all indications in clinical trials patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have been very rare post-marketing reports of severe hepatic reactions including liver failure in patients receiving TNF blockers, including HUMIRA. The causal relationship to HUMIRA treatment remains unclear.

Concurrent treatment with azathioprine / 6 mercaptopurine

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

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 possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

TABLE 7: ADDITIONAL ADVERSE REACTIONS FROM POSTMARKETING SURVEILLANCE OR PHASE IV CLINICAL TRIALS

BODY SYSTEM	**ADVERSE REACTION**
Immune system disorders *	anaphylaxis, sarcoidosis
Hepatobiliary disorders *	reactivation of hepatitis B, liver failure, hepatitis
Skin and subcutaneous tissue disorders	cutaneous vasculitis, Stevens Johnson Syndrome, angioedema, new onset or worsening of psoriasis (including palmoplantar pustular psoriasis), erythema multiforme, alopecia, lichenoid skin reaction**
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, leukaemia, Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)
Infections and Infestations	diverticulitis
Respiratory, thoracic and mediastinal disorders	pulmonary embolism, pleural effusion, pulmonary fibrosis
General disorders and administration site conditions	pyrexia

Further information found elsewhere in Section 4.3, 4.4 and 4.8

***** Occurring in patients receiving a TNF-antagonist including HUMIRA***

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions to SAHPRA via "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publication: https://www.sahpra.org.za/Publications/Index/8

Healthcare professionals, patients and caregivers are also asked to report any suspected adverse reaction to AbbVie (Pty) Ltd via this e-mail address: medicalcomplaints@abbvie.com

4.9 Overdose

The maximum tolerated dose of HUMIRA has not been established in humans. In overdose, side effects can be precipitated and / or be of increased severity. It is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic and supportive treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of Medicines: 30.1 - Antibodies

Adalimumab is a monoclonal antibody which binds specifically to TNF (Tumor Necrosis Factor) and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. The relationship between these pharmacodynamic activities and the mechanism(s) by which adalimumab exerts its clinical effects is unknown.

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 rheumatoid arthritis (RA). A decrease in CRP levels was also observed in patients with polyarticular juvenile idiopathic arthritis (JIA), Crohn's disease, ulcerative colitis and hidradenitis suppurativa. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after adalimumab administration. Patients with RA, psoriatic

arthritis (PsA) and ankylosing spondylitis (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.

Pharmacokinetic properties

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, 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 7µg/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.

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

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

Population pharmacokinetic and pharmacokinetic/pharmacodynamic modelling and simulation predicted comparable adalimumab exposure and efficacy in patients treated with 80 mg every other week when compared with 40 mg every week (including adult patients with RA, HS, UC, CD or Ps, adolescent patients with HS, and paediatric patients ≥ 40 kg with CD and UC).

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.

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

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) who were 4 to 17 years, the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5,6 ± 5,6 µg/mL (102 % CV) 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. In patients with polyarticular JIA who were 2 to <4 years old or aged 4 and above weighing <15 kg dosed with

adalimumab 24 mg/m^2, the mean trough steady-state serum adalimumab concentrations was 6,0 ± 6,1 µg/mL (101 % CV) for adalimumab without concomitant methotrexate and 7,9 ± 5,6 µg/mL (71,2 % CV) with concomitant methotrexate.

In paediatric patients with moderately to severely active Crohn's disease, the open-label adalimumab induction dose was 160/80 mg or 80/40 mg at Weeks 0 and 2, respectively, dependent on a body weight cut-off of 40 kg. At Week 4, subjects were randomized 1:1 to either the Standard Dose (40/20 mg eow) or Low Dose (20/10 mg eow) maintenance treatment groups based on their body weight. The mean (±SD) serum adalimumab trough concentrations achieved at Week 4 were 15,7 ± 6,6 µg/mL for subjects ≥40 kg (160/80 mg) and 10,6 ± 6,1 µg/mL for subjects < 40 kg (80/40 mg).

For subjects who stayed on their randomized therapy, the mean (±SD) adalimumab trough concentrations at Week 52 were 9,5 ± 5,6 µg/mL for the Standard Dose group and 3,5 ± 2,2 µg/mL for the Low Dose group. The mean trough concentrations were maintained in subjects who continued to receive adalimumab treatment eow for 52 weeks. For subjects whose dose escalated from eow to weekly regimen, the mean (±SD) serum concentrations of adalimumab at Week 52 were 15,3 ± 11,4 µg/mL (40/20 mg, weekly) and 6,7 ± 3,5 µg/mL (20/10 mg weekly).

Following the administration of 0,8 mg/kg (up to a maximum of 40 mg) subcutaneously every other week to paediatric patients with chronic plaque psoriasis, the mean ± SD steady-state adalimumab trough concentration was approximately 7,4 ± 5,8 µg/ mL (79 % CV).

Adalimumab exposure in adolescent hidradenitis suppurativa (HS) patients was predicted using population pharmacokinetic modeling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paaediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent HS dosing schedule of

40 mg every other week is predicted to provide serum adalimumab exposure similar to that observed in adult HS patients receiving the recommended adult dose of 40 mg every week.

Following the subcutaneous administration of body weight-based dosing of 0,6 mg/kg (maximum of 40 mg) every other week to paediatric patients with ulcerative colitis, the mean trough steady-state serum adalimumab concentration was 5,01± 3,28 µg/mL at Week 52. For patients who received 0,6 mg/kg (maximum of 40 mg) every week, the mean (±SD) trough steady-state serum adalimumab concentration was 15,7± 5,60 µg/mL at Week 52.

Elderly

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.

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.

Medicine 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 Section 4.5).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Polysorbate 80

Water for injection

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

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

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

DO NOT FREEZE. Discard any unused portions.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container and special equipment for use, administration or implantation

HUMIRA 20 mg is supplied as a sterile solution of 20 mg adalimumab per 0,2 mL for parenteral administration in the following packaging configurations:

- **HUMIRA 20 mg per 0,2 mL** solution for injection in a single-use, **pre-filled syringe**:

  Carton containing 2 pre-filled syringes, each with 1 alcohol pad, in a blister.

The pre-filled syringe is composed of a 1 mL colourless, type I glass barrel staked with a thin-walled 29 G needle, a latex free needle shield and a grey bromobutyl rubber plunger stopper.

The blister packaging for the pre-filled syringe is composed of a clear polymeric plastic with a white paper lidding material, with or without foil laminate.

HUMIRA 40 mg is supplied as a sterile solution of 40 mg adalimumab per 0,4 mL for parenteral administration in the following packaging configurations:

- **HUMIRA 40 mg per 0,4 mL** solution for injection in a single-use, **pre-filled syringe** (PFS):

  Carton containing 1 alcohol pad and 1 blister with 1 pre-filled syringe.

  Carton containing 2 alcohol pads and 2 blisters, each containing 1 pre-filled syringe.

  The pre-filled syringe is comprised of a 1 mL colourless, type I glass barrel staked with a thin-walled 29 G needle, a latex free needle shield and a grey rubber plunger stopper.

  The blister packaging for the pre-filled syringe is composed of clear polymeric plastic with a white paper lidding material, with or without foil laminate.

- **HUMIRA 40 mg per 0,4 mL** solution for injection in a single-use, **pre-filled Pen** (PFP):

  Carton containing 2 alcohol pads and 1 blister with 1 pre-filled Pen.

  Carton containing 2 alcohol pads and 2 blisters, each containing 1 pre-filled Pen.

  The pre-filled pen is composed of a pre-filled syringe, syringe housing sub-assembly and firing mechanism sub-assembly.

  The pre-filled syringe is composed of a 1 mL colourless type I glass barrel staked with a thin-walled 29 G needle, a latex free needle shield and a grey bromobutyl rubber plunger stopper.

  The syringe housing sub-assembly consists of a grey acrylonitrile butadiene styrene

(ABS) syringe housing with a white arrow printed on it and a grey ABS cap with a white numerical (1) printed on it.

The firing mechanism sub-assembly consists of a grey polypropylene (PP) firing body, plum PP firing button and a plum PP cap with a white numerical (2) printed on it.

The blister packaging for the pre-filled pen is composed of clear polymeric plastic with a white paper lidding material.

HUMIRA 80 mg is supplied as a sterile solution of 80 mg adalimumab per 0,8 mL for parenteral administration in the following packaging configurations:

- **HUMIRA 80 mg per 0,8 mL** solution for injection in a single-use, **pre-filled syringe**:

  Carton containing 1 alcohol pad and 1 blister with 1 pre-filled syringe.

  The pre-filled syringe is composed of a 1 mL colourless, type I glass barrel staked with a thin-walled 29 G needle, a latex free needle shield and a grey bromobutyl rubber plunger stopper.

  The blister packaging for the pre-filled syringe is composed of a clear polymeric plastic with a white paper lidding material, with or without foil laminate.

- **HUMIRA 80 mg per 0,8 mL** solution for injection in a single-use, **pre-filled Pen**: Carton containing 2 alcohol pads and 1 blister with 1 pre-filled Pen.

  The pre-filled pen is composed of a pre-filled syringe, syringe housing sub-assembly and firing mechanism sub-assembly.

  The pre-filled syringe is composed of a 1 mL colorless type I glass barrel staked with a thin-walled 29 G needle, a latex free needle shield and a grey bromobutyl rubber plunger stopper.

The syringe housing sub-assembly consists of a gray acrylonitrile butadiene styrene (ABS) syringe housing with a white arrow printed on it and a gray ABS cap with a white numerical (1) printed on it.

The firing mechanism sub-assembly consists of a gray polypropylene (PP) firing body, plum PP firing button and a plum PP cap with a white numerical (2) printed on it.

The blister packaging for the pre-filled pen is composed of clear polymeric plastic with a white paper lidding material.

6.6 Special precautions for disposal of the used medicine or waste derived from such medicine and other handling of product

Not applicable

7. HOLDER OF CERTIFICATE OF REGISTRATION

AbbVie (Pty) Ltd

Abbott Place, 219 Golf Club Terrace

1709, Constantia Kloof

Republic of South Africa

8. REGISTRATION NUMBER (S)

HUMIRA 20 mg / 0,2 mL: 53/30.1/0061

HUMIRA 40 mg / 0,4 mL: 50/30.1/1042

HUMIRA 80 mg / 0,8 mL: 53/30.1/0062

NAMIBIA Registration number:

HUMIRA 40 mg / 0,4 mL: 20/30.1/0071 (NS2)

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

12 May 2020

10. DATE OF REVISION OF THE TEXT

05 October 2020

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