PROFESSIONAL INFORMATION

HYRIMOZ® 40 mg / 0,8 mL (Solution for Injection)

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HYRIMOZ are at increased risk for developing serious infections that may lead to hospitalisation or death (see section 4.4). Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HYRIMOZ if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HYRIMOZ use and during therapy. Initiate treatment for latent TB prior to HYRIMOZ use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection.**

  Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HYRIMOZ prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HYRIMOZ, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy (see sections 4.4 and 4.8).

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HYRIMOZ (see section 4.4). Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HYRIMOZ. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants [see section 4.4).

SCHEDULING STATUS: S4

1 NAME OF MEDICINE:

HYRIMOZ® 40 mg / 0,8 mL (solution for injection)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION:

HYRIMOZ 40 mg / 0,8 mL solution for injection in pre-filled syringe:

Each 0,8 mL single-dose pre-filled syringe contains 40 mg of adalimumab.

HYRIMOZ 40 mg / 0,8 mL solution for injection in pre-filled pen:

Each 0,8 mL single-dose pre-filled pen contains 40 mg of adalimumab.

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

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection.

Colourless to slightly yellowish solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

Rheumatoid arthritis:

HYRIMOZ 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. HYRIMOZ 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. HYRIMOZ 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:

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

HYRIMOZ 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.

HYRIMOZ can be used alone or in combination with disease modifying anti-rheumatic drugs (DMARD's).

Psoriasis:

HYRIMOZ 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.

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

Axial Spondyloarthritis including ankylosing spondylitis:

HYRIMOZ 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:

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

Crohn's disease:

HYRIMOZ 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.

HYRIMOZ 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:

HYRIMOZ is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had 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:

HYRIMOZ 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:

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

Paediatrics:

Polyarticular Juvenile Idiopathic Arthritis:

HYRIMOZ 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. HYRIMOZ can be used alone or in combination with methotrexate.

Paediatric Crohn's Disease:

HYRIMOZ 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:

HYRIMOZ 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:

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

4.2 Posology and method of administration

Posology:

***Adults*:**

Rheumatoid Arthritis:

The recommended dose of HYRIMOZ 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 HYRIMOZ.

In monotherapy, some patients who experience a decrease in their response may benefit from an increase in dose intensity to 40 mg of HYRIMOZ 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 HYRIMOZ for adult patients with psoriatic arthritis is 40 mg, administered every other week as a single dose via subcutaneous injection.

Glucocorticoids, salicylates, non-steroidal anti-inflammatory medicines, analgesics, or disease modifying anti-rheumatic drugs (DMARD's) can be continued during treatment with HYRIMOZ.

Axial spondyloarthritis including Ankylosing spondylitis:

The recommended dose of HYRIMOZ for patients with Axial spondyloarthritis including ankylosing spondylitis is 40 mg administered every other week as a single dose via subcutaneous injection. Glucocorticoids, salicylates, nonsteroidal anti-inflammatory medicines, analgesics, or disease modifying anti-rheumatic medicines can be continued during treatment with HYRIMOZ.

Crohn's Disease:

The recommended HYRIMOZ 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 injections 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 medicines (e.g., 6-mercaptopurine and azathioprine) may be continued during treatment with HYRIMOZ.

Some patients may derive additional benefit from increasing the dosing frequency of HYRIMOZ 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.

Ulcerative colitis:

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

Aminosalicylates, corticosteroids, and/or immunomodulatory medicines (e.g., 6-mercaptopurine and azathioprine) may be continued during treatment with HYRIMOZ.

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

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

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

Plaque Psoriasis:

The recommended dose of HYRIMOZ 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.

Beyond 16 weeks, patients with inadequate response may benefit from an increase in dosing frequency to 40 mg every week. The benefits and risks of continued weekly HYRIMOZ therapy should be carefully reconsidered in a patient with an inadequate response 24 weeks after the increase in dosing frequency.

Hidradenitis Suppurativa:

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

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

Uveitis:

The recommended dose of HYRIMOZ 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. HYRIMOZ can be used alone or in combination with corticosteroids, which may be tapered in accordance with clinical practice, or other non-biologic immunomodulatory medicines.

Paediatric:

There is no dosage form for HYRIMOZ that allows weight-based dosing for paediatric patients below 30 kg for Juvenile Idiopathic Arthritis, Paediatric Uveitis and Plaque Psoriasis and below 40 kg for Crohn's disease.

Polyarticular Juvenile Idiopathic Arthritis:

The recommended dose of HYRIMOZ for patients from 2 years of age with polyarticular juvenile idiopathic arthritis (JIA) is based on body weight (Table 1). Methotrexate, glucocorticoids, NSAIDS and/or analgesics may be continued during treatment with HYRIMOZ.

Table 1: HYRIMOZ Dose for Patients with Polyarticular Juvenile Idiopathic Arthritis

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

HYRIMOZ 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 HYRIMOZ in children aged < 2 years in this indication.

Paediatric Plaque Psoriasis:

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

Table 2: HYRIMOZ Dose for Paediatric Patients with Plaque Psoriasis

Patient Weight	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 HYRIMOZ is indicated, the above guidance on dose and treatment duration should be followed.

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

Paediatric Crohn's Disease:

The recommended dose of HYRIMOZ for patients from 6 to 17 years of age with Crohn's disease is based on body weight (Table 3). HYRIMOZ is administered via subcutaneous injection.

Table 3: HYRIMOZ Dose for Paediatric Patients with Crohn's disease

Patient Weight	Induction Dose	Maintenance Dose Starting at Week 4
≥ 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 frequency to weekly if a disease flare or an inadequate response is experienced during maintenance dosing. HYRIMOZ has not been studied in children with Crohn's disease aged less than 6 years.

Paediatric Uveitis:

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

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

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

When HYRIMOZ is initiated as a loading dose of 80 mg for patients ≥ 30 kg, it may be administered one week prior to the start of maintenance therapy.

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

Preparation of HYRIMOZ

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

HYRIMOZ 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.

Full instructions for use are provided in the Patient Information Leaflet.

Paediatric Use

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

Use in Elderly

Of the total number of subjects in clinical studies with HYRIMOZ, 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

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Active tuberculosis or other severe infections such as sepsis, and opportunistic infections, see section 4.4. Moderate to severe heart failure (NYHA class III/IV), see section 4.4.

4.4 Special warnings and precautions for use

Traceability:

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

Infections:

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

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

Patients who develop a new infection while undergoing treatment with HYRIMOZ should be monitored closely and undergo a complete diagnostic evaluation. Administration of HYRIMOZ 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 HYRIMOZ in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications.

Serious infections:

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

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

Tuberculosis:

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

Invasive fungal infections, and other opportunistic infections have been observed in patients receiving HYRIMOZ. Some of these infections, including tuberculosis, have been fatal.

Before initiation of therapy with HYRIMOZ, all patients must 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 (i.e., tuberculin skin test and chest X-ray) should be performed in all patients in accordance with local recommendations. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

Treatment of latent tuberculosis infection should be initiated prior to therapy with HYRIMOZ. 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, HYRIMOZ therapy must not be initiated, see section 4.3.

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

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

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

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

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

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 HYRIMOZ.

Other opportunistic infections:

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

For patients who develop the signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnoea, and / or pulmonary infiltrates or other serious systemic illness with or without concomitant shock, an invasive fungal infection should be suspected and administration of HYRIMOZ should be

promptly discontinued. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections.

Hepatitis B reactivation:

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

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

Neurological events:

TNF-antagonists including adalimumab have been associated in rare instances with new onset or exacerbation of clinical symptoms and / or radiographic evidence of central nervous system demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of HYRIMOZ in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of HYRIMOZ should be considered if any of these disorders develop. There is known association between intermediate uveitis and central demyelinating disorders; discontinuation of HYRIMOZ 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 HYRIMOZ

therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Allergic reactions:

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

Immunosuppression:

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

Malignancies and lymphoproliferative disorders:

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

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including adalimumab in the post marketing setting. Approximately, half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with

immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

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

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

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

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

With the current data, it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk of dysplasia or colon carcinoma (for example, patients with long standing ulcerative colitis or primary sclerosing cholangitis),

or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.

Haematologic reactions:

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF-antagonists. Adverse events of the haematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been reported with adalimumab. 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 HYRIMOZ. Discontinuation of HYRIMOZ therapy should be considered in patients with confirmed significant haematologic abnormalities.

Vaccinations:

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

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 HYRIMOZ therapy.

Patients on HYRIMOZ may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to adalimumab *in utero* is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Congestive heart failure:

In a clinical trial with another TNF-antagonist, worsening congestive heart failure and increased mortality due to congestive heart failure have been observed.

Cases of worsening congestive heart failure have also been reported in patients receiving adalimumab. HYRIMOZ should be used with caution in patients with mild heart failure, see section 4.3. Treatment

with HYRIMOZ must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes:

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

Concurrent administration of biologic DMARDs or TNF-antagonists:

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-antagonist, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF-antagonists. Therefore, the combination of adalimumab with other biologic DMARDs (e.g., anakinra and abatacept) or other TNF-antagonists is not recommended based upon the possible increased risk for infections, including serious infections and other potential pharmacological interactions, see section 4.5.

Surgery:

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

Small bowel obstruction:

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

Elderly:

The frequency of serious infections among adalimumab-treated subjects over 65 years of age (3,7 %) was higher than for those under 65 years of age (1,5 %). Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly.

Paediatric population:

See “Vaccinations” above.

Sodium content:

This medicine contains less than 1 mmol sodium (23 mg) per 0,8 ml dose, that is to say, essentially “sodium-free”.

4.5 Interaction with other medicines and other forms of interaction

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

The combination of adalimumab and anakinra is not recommended, see section 4.4. The combination of adalimumab and abatacept is not recommended, see section 4.4.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential:

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 HYRIMOZ treatment.

Pregnancy:

A large number (approximately 2100) of prospectively collected pregnancies exposed to adalimumab 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 adalimumab at least during the first trimester and 120 women with RA or CD not treated with adalimumab 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 with secondary endpoints spontaneous abortions, minor birth defects, pre-term delivery, birth size and serious 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, see section 5.3.

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

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

Breastfeeding:

Limited information from the published literature indicates that adalimumab is excreted in breast milk at very low concentrations with the presence of adalimumab 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, HYRIMOZ can be used during breastfeeding.

Fertility:

Preclinical data on fertility effects of adalimumab are not available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile:

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

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

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

Serious adverse reactions have been reported for adalimumab. TNF-antagonists, such as adalimumab affect the immune system and their use may affect the body's defence against infection and cancer.

Fatal and life-threatening infections (including sepsis, opportunistic infections and TB), HBV reactivation and various malignancies (including leukaemia, lymphoma and HSTCL) have also been reported with use of adalimumab.

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

Tabulated summary of adverse reactions

System Organ Class	Frequent	Less Frequent	Frequency unknown
Infections and infestations*	Respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral) Systemic infections (including sepsis,	Neurological infections (including viral meningitis), Opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection),	

	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	Bacterial infections, Eye infections, Diverticulitis[1)]	
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma), Benign neoplasm	Lymphoma**, Solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), Melanoma**, Leukaemia[1)], Hepatosplenic T-cell lymphoma[1)],	

		Merkel cell carcinoma (neuroendocrine carcinoma of the skin)[1)], Kaposi's sarcoma	
Blood and the lymphatic system disorders*	Leucopaenia (including neutropaenia and agranulocytosis), Anaemia, Leucocytosis, Thrombocytopaenia	Idiopathic thrombocytopaenic purpura, Pancytopaenia	
Immune system disorders*	Hypersensitivity, Allergies (including seasonal allergy)	Sarcoidosis[1)], Vasculitis, Anaphylaxis[1)]	
Metabolism and nutrition disorders	Lipids increased, Hypokalaemia, Uric acid increased, Blood sodium abnormal, Hypocalcaemia, Hyperglycaemia, Hypophosphataemia, Dehydration		
Psychiatric disorders	Mood alterations (including depression), Anxiety, Insomnia		
Nervous system disorders*	Headache, Paraesthesias (including hypoaesthesia), Migraine, Nerve root compression	Cerebrovascular accident[1)], Tremor, Neuropathy, Multiple sclerosis, Demyelinating disorders	

		(e.g., optic neuritis, Guillain-Barré syndrome)[1)]	
Eye disorders	Visual impairment, Conjunctivitis, Blepharitis, Eye swelling	Diplopia	
Eye and labyrinth disorders	Vertigo	Deafness, Tinnitus	
Cardiac Disorders*	Tachycardia	Myocardial infarction[1)], Arrhythmia, Congestive heart failure	
Vascular disorders	Hypertension, Flushing, Haematoma	Aortic aneurysm, Vascular arterial occlusion, Thrombophlebitis	
Respiratory, thoracic, and mediastinal disorders*	Asthma, Dyspnoea, Cough	Pulmonary embolism[1)], Interstitial lung disease, Chronic obstructive pulmonary disease, Pneumonitis, Pleural effusion[1)], Pulmonary fibrosis[1)]	
Gastrointestinal disorders	Abdominal pain, Nausea and vomiting, GI haemorrhage, Dyspepsia, Gastroesophageal reflux disease, Sicca syndrome	Pancreatitis, Dysphagia, Face oedema, Intestinal perforation[1)]	

Hepato-biliary disorders*	Elevated liver enzymes	Cholecystitis and cholelithiasis, Hepatic steatosis, Bilirubin increased, Hepatitis, Reactivation of hepatitis B[1)], Autoimmune hepatitis	Liver failure[1)]
Skin and subcutaneous tissue disorders	Rash (including exfoliative rash), Worsening or new onset of psoriasis (including palmoplantar pustular psoriasis)[1)], Urticaria, Bruising (including purpura), Dermatitis (including eczema), Onychoclasis, Hyperhidrosis, Alopecia[1)], Pruritus	Night sweats, scar, Erythema multiforme[1)], Stevens-Johnson syndrome[1)], Angioedema[1)], Cutaneous vasculitis[1)], Lichenoid skin reaction[1)]	Worsening of symptoms of dermatomyositis[1)]
Musculoskeletal and connective tissue disorders	Musculoskeletal pain, Muscle spasms (including blood creatine phosphokinase increased)	Rhabdomyolysis, Systemic lupus erythematosus, Lupus-like syndrome[1)]	
Renal and urinary disorders	Renal impairment, Haematuria	Nocturia	

Reproductive system and breast disorders	Erectile dysfunction		
General disorders and administration site conditions*	Injection site reaction (including injection site erythema), Chest pain, Oedema, Pyrexia[1)]		
Investigations*	Coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), Autoantibody test positive (including double stranded DNA antibody), Blood lactate dehydrogenase increased.	Weight increased[2]	
Injury, poisoning and procedural complications	Impaired healing		

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

** including open label extension studies

1) including spontaneous reporting data
2) the mean weight change from baseline for adalimumab ranged from 0.3 kg to 1.0 kg across adult indications compared to (minus) -0.4 kg to 0.4 kg for placebo over a treatment period of 4-6 months. Weight increase of 5 - 6 kg has also been observed in long-term extension studies with mean exposures of approximately 1 - 2 years without control group, particularly in patients with Crohn's disease and

ulcerative colitis. The mechanism behind this effect is unclear but could be associated with the anti-inflammatory effect of adalimumab.

Paediatric population:

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

Hidradenitis suppurativa:

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

Uveitis:

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

Description of selected adverse reactions*:*

Injection site reactions:

In the pivotal controlled trials in adults and children, 12,9 % of patients treated with adalimumab developed injection site reactions (erythema and / or itching, haemorrhage, pain or swelling), compared to 7,2 % of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicine.

Infections:

In the pivotal controlled trials in adults and children, the rate of infection was 1,51 per patient year in the adalimumab-treated patients and 1,46 per patient year in the placebo and active control treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, and sinusitis. Most patients continued on adalimumab after the infection resolved.

The incidence of serious infections was 0,04 per patient year in adalimumab-treated patients and 0,03 per patient year in placebo and active control-treated patients.

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

Malignancies and lymphoproliferative disorders:
No malignancies were observed in 249 paediatric patients with exposure of 655,6 patient years during adalimumab 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 Crohn's disease. No malignancies were observed in 77 paediatric patients with an exposure of 80,0 patient years during an adalimumab trial in paediatric patients with chronic plaque psoriasis. No malignancies were observed in 60 paediatric patients with an exposure of 58,4 patient years during an adalimumab trial in paediatric patients with uveitis.

During the controlled portions of pivotal adalimumab trials in adults of at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95 % confidence interval) of 6,8 (4,4 ; 10,5) per 1,000 patient years among 5,291 adalimumab-treated patients versus a rate of 6,3 (3,4 ; 11,8) per 1,000 patient years among 3,444 control patients (median duration of treatment was 4,0 months for adalimumab and 3,8 months for control-treated patients). The rate (95 % confidence interval) of lymphomas was 0,7 (0,2 ; 2,7) per 1,000 patient years among adalimumab-treated patients and 0,6 (0,1 ; 4,5) per 1,000 patient years among control patients.

When combining controlled portions of these trials and ongoing and completed open label extension studies with a median duration of approximately 3,3 years including 6,427 patients and over 26,439 patient years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 8,5 per 1,000 patient years. The observed rate of non-melanoma skin cancers is approximately 9,6 per 1,000 patient years, and the observed rate of lymphoma is approximately 1,3 per 1,000 patient years.

In post-marketing experience from January 2003 to December 2010, predominantly in patients with rheumatoid arthritis, the reported rate of malignancies is approximately 2,7 per 1,000 patient treatment years. The reported rates for non-melanoma skin cancers and lymphomas are approximately 0,2 and 0,3 per 1,000 patient treatment years, respectively, see section 4.4.

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

Autoantibodies:

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis studies I-V. In these trials, 11,9 % of patients treated with adalimumab and 8,1 % of placebo and active control-treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at week 24. Two patients out of 3,441 treated with adalimumab in all rheumatoid arthritis and psoriatic arthritis studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms.

Hepato-biliary events:

In controlled Phase 3 trials of adalimumab in patients with rheumatoid arthritis and psoriatic arthritis with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3,7 % of adalimumab-treated patients and 1,6 % of control-treated patients.

In controlled Phase 3 trials of adalimumab 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 adalimumab-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 adalimumab in patients with polyarticular juvenile idiopathic arthritis who were 2 to < 4 years.

In controlled Phase 3 trials of adalimumab in patients with Crohn's disease and ulcerative colitis with a control period ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0,9 % of adalimumab-treated patients and 0,9 % of controlled-treated patients.

In the Phase 3 trial of adalimumab in patients with paediatric Crohn's disease which evaluated efficacy and safety of two body weight adjusted maintenance dose regimens following body weight adjusted induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2,6 % (5/192) of patients of whom 4 were receiving concomitant immunosuppressants at baseline.

In controlled Phase 3 trials of adalimumab 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 adalimumab-treated patients and 1,8 % of control-treated patients.

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

In controlled trials of adalimumab (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 adalimumab treated patients and 0,6 % of control-treated patients.

In controlled trials of adalimumab (initial doses of 80 mg at week 0 followed by 40 mg every other week starting at week 1) in adult patients with uveitis up to 80 weeks with median exposure of 166,5 days and

105,0 days in adalimumab-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2,4 % of adalimumab-treated patients and 2,4 % of control-treated patients.

In controlled Phase 3 trial of adalimumab 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.

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

Concurrent treatment with azathioprine/6-mercaptopurine:

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

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Suspected adverse reactions can also be reported directly to the HCR via the website: https://pvi1j.solutions.iqvia.com or the e-mail address, adverse.event.sac@sandoz.com.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 30.1 Antibodies

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

HYRIMOZ is a biosimilar medicine.

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 pharmacodynamics 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.

5.2 Pharmacokinetic properties

Absorption and Distribution:

After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64 %. After single intravenous doses ranging from 0,25 to 10 mg/kg, concentrations were dose proportional. After doses of 0,5 mg/kg (~40 mg), clearances ranged from 11 to 15 mL/hour, the distribution volume (V_{ss}) ranged from 5 to 6 litres and the mean terminal phase half-life was approximately two weeks. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31 - 96 % of those in serum.

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

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with polyarticular juvenile idiopathic arthritis (JIA) who were 4 to 17 years the mean trough steady-state (values measured from week 20 to 48) serum adalimumab concentration was 5,6 ± 5,6 µg/ml (102 % CV) for adalimumab without concomitant methotrexate and 10,9 ± 5,2 µg/ml (47,7 % CV) with concomitant methotrexate.

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with enthesitis-related arthritis who were 6 to 17 years, the mean trough steady-state (values measured at week 24) serum adalimumab concentrations were 8,8 ± 6,6 µg/ml for adalimumab without concomitant methotrexate and 11,8 ± 4,3 µg/ml with concomitant methotrexate.

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

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

Following subcutaneous administration of 40 mg of adalimumab every other week in adult non-radiographic axial spondyloarthritis patients, the mean (± SD) trough steady-state concentration at week 68 was 8,0 ± 4,6 µg/ml.

In adult 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.

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

In patients with Crohn's disease, the loading dose of 80 mg adalimumab on week 0 followed by 40 mg adalimumab on week 2 achieves serum adalimumab trough concentrations of approximately 5,5 µg/ml during the induction period. 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 7 µg/ml were observed in Crohn's disease patients who received a maintenance dose of 40 mg adalimumab every other week.

In paediatric patients with moderate to severe CD, the open-label adalimumab induction dose was 160/180 mg or 80/40 mg at weeks 0 and 2, respectively, dependent on a body weight cut-off of 40 kg. At

week 4, patients were randomised 1:1 to either the Standard Dose (40/20 mg every other week [eow]) or Low Dose (20/10 mg eow) maintenance treatment groups based on their body weight. The mean (± SD) serum adalimumab trough concentrations achieved at week 4 were 15,7 ± 6,6 µg/ml for patients ≥ 40 kg (160/80 mg) and 10,6 ± 6,1 µg/ml for patients < 40 kg (80/40 mg).

For patients who stayed on their randomised therapy, the mean (± SD) adalimumab trough concentrations at week 52 were 9,5 ± 5,6 µg/ml for Standard Dose group. The mean trough concentrations were maintained in patients who continued to receive adalimumab treatment eow for 52 weeks. For patients who dose-escalated from eow to weekly regimen, the mean (± SD) serum concentrations of adalimumab at week 52 were 15,3 ± 11,4 µg/ml (40/20 mg, weekly).

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.

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

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

Population pharmacokinetic and pharmacokinetic / pharmacodynamics 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, patients with adolescent HS, and paediatric patients ≥ 40 kg with CD.

Exposure-response relationship in paediatric population:

On the basis of clinical trial data in patients with JIA (pJIA and ERA), an exposure-response relationship was established between plasma concentrations and PedACR 50 response. The apparent adalimumab plasma concentration that produces half the maximum probability of PedACR 50 response (EC_{50}) was 3 µg/mL (95 % CI: 1 - 6 µg/mL).

Exposure-response relationships between adalimumab concentration and efficacy in paediatric patients with severe chronic plaque psoriasis were established for PASI 75 and PGA clear or minimal, respectively. PASI 75 and PGA clear or minimal increased with increasing adalimumab concentrations, both with a similar apparent EC_{50} of approximately 4,5 µg/mL (95 % CI 0,4-47,6 and 1,9 - 10,5, respectively).

Elimination:

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

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 28) serum adalimumab concentration was 5,6 ± 5,6 µg/mL (102 % CV) adalimumab monotherapy and 10,9 ± 5,2 mg/mL (47,7 % CV) with concomitant methotrexate. 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 paediatric patients with moderately to severely active Crohn's disease, the open-label adalimumab induction dose was 160/80 mg or 80 mg/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).

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. 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).

Following 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 modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent HS dosing schedule of 40 mg every 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.

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

Adipic acid, citric acid monohydrate, hydrochloric acid (for pH adjustment), mannitol, polysorbate 80, sodium chloride, sodium hydroxide (for pH adjustment), water for injection.

Sugar free.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

30 months

6.4 Special precautions for storage

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

A single HYRIMOZ pre-filled syringe / pre-filled pen may be stored at temperatures up to a maximum of 25 °C for a period of up to 21 days. The pre-filled syringe / pre-filled pen must be protected from light and discard if not used within the 21-day period.

6.5 Nature and contents of container

HYRIMOZ 40 mg solution for injection in a single-use pre-filled syringe:

HYRIMOZ 40 mg/0,8 mL solution for injection is supplied in a single-use clear type I glass syringe with a grey rubber stopper and a stainless-steel needle with an automatic needle guard with finger flange, rubber needle cap and plastic plunger, containing 0,8 mL solution.

Packs of 1 and 2 pre-filled syringes in a blister.

HYRIMOZ 40 mg / 0,8 mL solution for injection in a single-use pre-filled pen:

HYRIMOZ is supplied in a single-use pre-filled syringe assembled into a triangular-shaped pen with transparent window and label. The syringe inside the pen is made of type I glass with a stainless-steel needle, an inner rubber needle cap, and a grey rubber stopper, containing 0,8 mL solution.

Packs of 1 and 2 pre-filled pens.

Not all pack sizes or presentations may be marketed.

6.6 Special precautions for disposal

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

2090

[1]Comapany Reg No.: 1990/001979/07

8 REGISTRATION NUMBER

56/30.1/0665

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 October 2024