1. NAME OF THE MEDICINAL PRODUCT

Hyrimoz 40mg/0.4ml Solution for Injection in Pre-Filled Pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.4 ml single-dose pre-filled pen contains 40 mg of adalimumab.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in pre-filled pen (SensoReady).

Clear to slightly opalescent, colourless or slightly yellowish solution.

Hyrimoz is a biosimilar medicinal product of Humira.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid Arthritis
Hyrimoz is indicated for reducing signs and symptoms, inducing major clinical response and clinical remission, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.

Hyrimoz can be used alone or in combination with methotrexate or other disease modifying antirheumatic drugs (DMARDs).

Psoriatic Arthritis
Hyrimoz is indicated for reducing the signs and symptoms of active arthritis in patients with psoriatic arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

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

Axial Spondyloarthritis
Ankylosing Spondylitis
Hyrimoz is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Non-radiographic Axial spondyloarthritis (Axial Spondyloarthritis without radiographic evidence of AS)
Hyrimoz is indicated for reducing signs and symptoms in patients with active non-radiographic axial spondyloarthritis (nr-axSpA) but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Plaque Psoriasis
Hyrimoz is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy and when other systemic therapies are medically less appropriate.

Crohn's Disease
Hyrimoz is indicated for the treatment of moderately to severely active Crohn's Disease in adult patients who have inadequate response to conventional therapy. Hyrimoz is also indicated for treatment in adult patients with moderately to severely active Crohn's Disease who 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 an inadequate response to conventional therapy including corticosteroids and 6- mercaptopurine (6-

MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Hidradenitis Suppurativa
Hyrimoz is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with an inadequate response to conventional systemic HS therapy.

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

Paediatrics
Juvenile idiopathic arthritis
Polyarticular Juvenile Idiopathic Arthritis
Hyrimoz in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients aged above 2 years old who had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). Hyrimoz can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enthesitis-Related Arthritis
Hyrimoz is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy.

Paediatric Crohn's Disease
Hyrimoz is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (6 to 17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and/or an immunomodulator, or who are intolerant to or have contraindication for such therapies.

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

Adolescent Hidradenitis Suppurativa
Hyrimoz is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adolescents from 12 years of age with an inadequate response to conventional systemic hidradenitis suppurativa (HS) therapy.

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

4.2 Posology and method of administration

Rheumatoid Arthritis, Psoriatic Arthritis and Axial Spondyloarthritis (Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis)
The recommended dose of Hyrimoz for adult patients with rheumatoid arthritis, psoriatic arthritis or axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) is 40 mg administered every other week as a single dose via subcutaneous injection. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, analgesics or other DMARDs may be continued during treatment with Hyrimoz.

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

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

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

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

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

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

Some patients who experience decrease in their response may benefit from an increase in dosage to 40 mg Hyrimoz 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 Hyrimoz induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at Week 0 (dose can be administered 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 agents (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 decrease in their response may benefit from an increase in dosage to 40 mg Hyrimoz every week or 80 mg every other week.

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

Hidradenitis Suppurativa
The recommended Hyrimoz 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 Hyrimoz if necessary.

Should treatment need to be interrupted, Hyrimoz may be re-introduced.

In patients without any benefit after 12 weeks of treatment, prescriber should consider to discontinue the treatment.

Uveitis

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

Paediatrics

Juvenile idiopathic arthritis

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). Hyrimoz is administered every other week via subcutaneous injection.

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

Patient Weight	Dosing Regimen
10 kg to < 30 kg	*20 mg every other week
≥ 30 kg	40 mg every other week

* Hyrimoz is only available as 40mg pre-filled pen. Thus, it is not possible to administer Hyrimoz to patients that require less than a full 40mg dose.

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 less than 2 years in this indication.

Enthesitis-Related Arthritis

The recommended dose of Hyrimoz for patients from 6 years of age with enthesitis-related arthritis is based on body weight (Table 2). Hyrimoz is administered every other week via subcutaneous injection.

Table 2. Hyrimoz Dose for Patients with Enthesitis-Related Arthritis

Patient Weight	Dosing Regimen
15 kg to < 30 kg	*20 mg every other week
≥ 30 kg	40 mg every other week

* Hyrimoz is only available as 40mg pre-filled pen. Thus, it is not possible to administer Hyrimoz to patients that require less than a full 40mg dose.

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

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 Peadiatric Patients with Crohn's disease

Patient Weight	Induction Dose	Maintenance Dose Starting at Week 4
< 40 kg * Hyrimoz is only available as 40mg pre-filled pen. Thus, it is not possible to administer Hyrimoz to patients that require less than a full 40mg dose.	• 40 mg at Week 0 and • *20 mg at Week 2 In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used: • 80 mg at week 0 and 40 mg at week 2	*20 mg every other week

≥ 40 kg	• 80 mg at week 0 and 40 mg at week 2 In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used: • 160 mg at week 0 (dose can be administered as 160 mg in one day or as 80 mg per day for two consecutive days) and 80 mg at week 2.	40 mg every other week

Patients who experience insufficient response may benefit from an increase in dosage:
• < 40 kg: *20 mg every week
• ≥ 40 kg: 40 mg every week or 80 mg every other week
* Hyrimoz is only available as 40mg pre-filled pen. Thus, it is not possible to administer Hyrimoz to patients that require less than a full 40mg dose.

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

There is no relevant use of Hyrimoz in children aged less than 6 years for 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 4). Hyrimoz is administered via subcutaneous injection.

Table 4. Hyrimoz Dose for Paediatric Patients with Plaque Psoriasis

Patient Weight	Dosing Regimen
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

* Hyrimoz is only available as 40mg pre-filled pen. Thus, it is not possible to administer Hyrimoz to patients that require less than a full 40mg 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.

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

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

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 5). Hyrimoz is administered via subcutaneous injection.

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

Table 5. Hyrimoz Dose for Paediatric Patients with Uveitis

Patient Weight	Dosing Regimen
< 30 kg	*20 mg every other week in combination with methotrexate

≥ 30 kg	40 mg every other week in combination with methotrexate

* Hyrimoz is only available as 40mg pre-filled pen. Thus, it is not possible to administer Hyrimoz to patients that require less than a full 40mg dose.

When Hyrimoz 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. No clinical data are available on the use of a Hyrimoz loading dose in children < 6 years of age (see Pharmacokinetic properties section).

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

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

Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)
There are no clinical trials with Hyrimoz in adolescent patients with hidradenitis suppurativa (HS). The posology of Hyrimoz in these patients has been determined from pharmacokinetic modeling and simulation.

The recommended Hyrimoz dose in adolescent patients from 12 years of age weighing at least 30 kg with hidradenitis suppurativa is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via subcutaneous injection.

In adolescent patients with inadequate response to Hyrimoz 40 mg every other week, an increase in dosage to 40 mg every week or 80 mg every other week may be considered.

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

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

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

The benefit and risk of continued long-term treatment should be periodically evaluated. There

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

Paediatric Ulcerative Colitis
The recommended dose of Hyrimoz for patients from 6 to 17 years of age with ulcerative colitis is based on body weight (Table 6). Hyrimoz is administered via subcutaneous injection.

Table 6. Hyrimoz Dose for Paediatric Ulcerative Colitis

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

#Paediatric patients who turn 18 years of age while on Hyrimoz should continue their prescribed maintenance dose.
* Hyrimoz is only available as 40mg pre-filled pen. Thus, it is not possible to administer Hyrimoz to patients that require less than a full 40mg dose.

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

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

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

Sites for self-injection include 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 discoloration 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.

Paediatric Use
Hyrimoz is only available as 40 mg pre-filled pen. Thus, it is not possible to administer Hyrimoz to paediatric patients that require less than a full 40 mg dose.

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

The safety and efficacy of Hyrimoz in paediatric patients for indications other than juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis), paediatric Crohn's disease, paediatric plaque psoriasis, paediatric uveitis, adolescent hidradenitis suppurativa and paediatric ulcerative colitis have not been established.

Geriatric Use
Of the total number of subjects in clinical studies of Hyrimoz, 9.4% were 65 years 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

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

4.4 Special warnings and precautions for use

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

Infections

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

Treatment with 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 traveled 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 Opportunistic Infections).

As with other TNF antagonists, patients should be monitored closely for infections, including tuberculosis before, during and after treatment with Hyrimoz.

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 infections are 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.

Tuberculosis

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

Before initiation of therapy with Hyrimoz, 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 infections 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 traveled to countries with a high prevalence of tuberculosis or who had close contact with a person with active tuberculosis.

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

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylactic treatment before the initiation of Hyrimoz and in accordance with local recommendations. Use of antituberculosis prophylactic treatment should also be considered 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 physician with expertise in the treatment of tuberculosis.

Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with Hyrimoz. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with Hyrimoz. Also, active tuberculosis has developed in patients receiving Hyrimoz whose screening for latent tuberculosis infection was negative, and some patients who have been successfully treated for active tuberculosis have redeveloped active tuberculosis while being treated with TNF blocking agents.

Patients receiving Hyrimoz 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.

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) occur during or after therapy with Hyrimoz.
[+]as permitted by local regulations.

Other Opportunistic Infections

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

Patients taking TNF-blockers are more susceptible to serious fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, aspergillosis, candidiasis, and other opportunistic infections. Those who develop fever, malaise, weight loss, sweats, cough, dyspnea, and/or pulmonary infiltrates, or other serious systemic illness with or without concomitant shock should promptly seek medical attention for a diagnostic evaluation.

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infections should be suspected if they develop the signs and symptoms of possible systemic fungal infection. Patients are at risk of histoplasmosis and other invasive fungal infections and hence clinicians should consider empiric antifungal treatment until the pathogen(s) are identified. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in

these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy. Patients who develop a severe fungal infection are also advised to stop the TNF-blocker until infections are controlled.

Hepatitis B Reactivation

Use of TNF blockers has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers 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 or 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, Hyrimoz should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurologic Events

TNF antagonists, including Hyrimoz, have been associated in rare cases 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 preexisting or recent-onset central or peripheral nervous system 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 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 conclusions. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. During the long-term open label trials with Hyrimoz, the overall rate of malignancies was similar to what would be expected for an age, gender and race matched general population. With the current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

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

Very rare post-marketing reports of hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with adalimumab. Most of the patients had prior infliximab therapy as well as concomitant azathioprine or 6-mercaptopurine use for inflammatory bowel disease. The potential risk with the combination of azathioprine or 6– mercaptopurine and Hyrimoz should be carefully considered. The causal association of HSTCL with adalimumab is not clear.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving Hyrimoz. Thus additional caution should be exercised in considering Hyrimoz treatment of these patients.

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.

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

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

Allergic

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

Hematologic Events

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse events of the hematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been reported with Hyrimoz. The causal relationship of these reports to Hyrimoz remains unclear. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor) while on Hyrimoz. Discontinuation of Hyrimoz therapy should be considered in patients with confirmed significant hematologic abnormalities.

Concurrent administration of biologic DMARDS or TNF-antagonists

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

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

Immunosuppression

In a study of 64 patients with RA that were treated with Hyrimoz, 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 randomized, double-blind, placebo-controlled study in 226 adult rheumatoid arthritis patients treated with Hyrimoz, 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 Hyrimoz group compared to 82% in the placebo group. A total of 37% of Hyrimoz-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 Hyrimoz group and 95% in the placebo group achieved protective antibody levels to the influenza antigens. A total of 52% of Hyrimoz-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 immunizations in

agreement with current immunization guidelines prior to initiating Hyrimoz therapy.

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

Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Congestive Heart Failure

Hyrimoz has not been formally studied in patients with congestive heart failure (CHF), however, in clinical studies with another TNF antagonist, a higher rate of serious CHF-related adverse events including worsening CHF and new onset CHF have been reported. Cases of worsening CHF have also been reported in patients receiving Hyrimoz. Physicians should exercise caution when using Hyrimoz in patients who have heart failure and monitor them carefully.

Autoimmune Processes

Treatment with Hyrimoz may result in the formation of autoimmune antibodies. The impact of long-term treatment with Hyrimoz on the development of autoimmune diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Hyrimoz, treatment should be discontinued (see Undesirable Effects - Autoantibodies).

Geriatric Use

The frequency of serious infection among Hyrimoz 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 Hyrimoz, 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.

4.5 Interaction with other medicinal products and other forms of interaction

Information provided below is based on the Humira data
When adalimumab was administered to 21 RA patients on stable MTX therapy, there were no statistically significant changes in the serum MTX concentration profiles. In contrast, after single and multiple dosing, MTX reduced adalimumab apparent clearances by 29% and 44% respectively. The data do not suggest the need for dose adjustment of either Hyrimoz or MTX.

Interactions between adalimumab and drugs other than MTX have not been evaluated in formal pharmacokinetic studies. In clinical trials, no interactions have been observed when adalimumab was administered with commonly used DMARDs (sulfasalazine, hydrochloroquine, leflunomide and parenteral gold), glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs or analgesics.

Drug/Laboratory Test Interaction
There is no known interference between adalimumab and laboratory tests.

4.6 Pregnancy and lactation

Information provided below is based on the Humira data
Pregnancy and lactation
An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (373 times human AUC when given 40 mg SC) and has revealed no evidence of harm to the fetuses due to adalimumab.

In a prospective cohort pregnancy exposure registry, 257 women with RA or CD treated with adalimumab at least during the first trimester and 120 women with RA or CD not treated with adalimumab were enrolled.

There were no significant differences in the overall rates for the primary endpoint of major birth defects (adjusted Odds Ratio 0.84, 95% Confidence Interval (CI) 0.34, 2.05) as well as the secondary endpoints which included minor birth defects, spontaneous abortion, preterm delivery, low birth weight, and serious or opportunistic infections. No stillbirths or malignancies were reported.

Although the registry has methodological limitations, including small sample size and nonrandomized study

design, the data show no increased risk of adverse pregnancy outcomes in women with RA or CD treated with adalimumab in comparison to women with RA or CD not treated with adalimumab. In addition, data from post-marketing surveillance does not establish the presence of a drug-associated risk.

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

Labor and delivery
There are no known effects of Hyrimoz on labor or delivery.

Nursing mothers
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 ingested immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability, systemic effects of adalimumab in a breast fed infant are unlikely. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for adalimumab and any potential adverse effects the breastfed child from adalimumab or from the underlying maternal condition.

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

Rheumatoid Arthritis, Juvenile Idiopathic Arthritis (Polyarticular Juvenile Idiopathic Arthritis and Enthesitis-Related Arthritis), Psoriatic Arthritis, Axial Spondyloarthritis (Ankylosing Spondylitis, and Non-radiographic Axial Spondyloarthritis), Crohn's Disease, Ulcerative Colitis, Psoriasis, Hidradenitis Suppurativa and Uveitis Clinical Trials

Adalimumab was studied in 9506 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 disease, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis) as well as psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis), Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients.

The controlled pivotal studies involved 6089 patients receiving adalimumab 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 adalimumab 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 adalimumab in controlled clinical studies.

Adverse events at least possibly causally-related to adalimumab, both clinical and laboratory, are displayed by system organ class and frequency (very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1000 to <1/100; rare ≥ 1/10,000 to <1/1000) in Table 7 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, Special warnings and precautions for use and Undesirable Effects.

Table 7
Undesirable effects
Information provided below is based on the Humira data

System Organ Class	Frequency	Adverse Reaction

Infections and infestations*	Very common	Respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	Systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections, joint infections
	Uncommon	Opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), bacterial infections, neurological infections (including viral meningitis), eye infections, bacterial infections.
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Common	Benign neoplasm, skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma)
	Uncommon	Lymphoma**, solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma**
Blood and the lymphatic system disorders*	Very common	Leucopaenia (including neutropaenia and agranulocytosis), anaemia
	Common	Thrombocytopaenia, leucocytosis
	Uncommon	Idiopathic thrombocytopaenic purpura
	Rare	Pancytopaenia
Immune system disorders*	Common	Hypersensitivity, allergies (including seasonal allergy)
Metabolism and nutrition disorders	Very common	Lipids increased
	Common	Hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia, hyperglycaemia, hypophosphataemia, dehydration
Psychiatric disorders	Common	Mood alterations (including depression), anxiety, insomnia
Nervous system disorders*	Very common	Headache
	Common	Paraesthesias (including hypoaesthesia), migraine, nerve root compression
	Uncommon	Tremor, neuropathy
	Rare	Multiple sclerosis

Eye disorders	Common	Visual impairment, conjunctivitis, blepharitis, eye swelling
	Uncommon	Diplopia
Ear and labyrinth disorders	Common	Vertigo
	Uncommon	Deafness, tinnitus
Cardiac disorders*	Common	Tachycardia
	Uncommon	Arrhythmia, congestive heart failure
	Rare	Cardiac arrest
Vascular disorders	Common	Hypertension, flushing, haematoma
	Uncommon	Vascular arterial occlusion, thrombophlebitis, aortic aneurysm
Respiratory, thoracic and mediastinal disorders*	Common	Cough, asthma, dyspnoea
	Uncommon	Chronic obstructive pulmonary disease, interstitial lung disease, pneumonitis
Gastrointestinal disorders	Very common	Abdominal pain, nausea and vomiting
	Common	GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	Pancreatitis, dysphagia, face oedema
Hepato-biliary disorders*	Very common	Liver enzymes elevated
	Uncommon	Cholecystitis and cholelithiasis, bilirubin increased, hepatic steatosis,
Skin and subcutaneous tissue disorders	Very common	Rash (including exfoliative rash)
	Common	Pruritus, urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis, hyperhydrosis
	Uncommon	Night sweats, scar
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain
	Common	Muscle spasms (including blood creatine phosphokinase increased)
	Uncommon	Rhabdomyolysis, systemic lupus erythematosus
Renal and urinary disorders	Common	Haematuria, renal impairment
	Uncommon	Nocturia
Reproductive system and breast disorders	Uncommon	Erectile dysfunction
General disorders and administration site conditions*	Very common	Injection site reaction (including injection site erythema)

	Common	Chest pain, edema
	Uncommon	Inflammation
Investigations*	Common	Coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), autoantibody test positive (including double stranded DNA antibody), blood lactate dehydrogenase increased
	Not known	Weight increased[1)]
Injury, poisoning and procedural complications	Common	Impaired healing

* further information is found elsewhere in Contraindication, Special warnings and precautions for use and Undesirable Effects

** includes open label extension studies

[1)] 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.

Hidradenitis suppurativa

The safety profile for patients with hidradenitis suppurativa 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.

Paediatric Population

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

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, hemorrhage, pain or swelling), compared to 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 adalimumab 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 adalimumab 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 adalimumab after the infection resolved.

In the 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 extrapulmonary locations) and invasive opportunistic infections (e.g., disseminated histoplasmosis, pneumocystis carinii pneumonia, aspergillosis and listeriosis).

Malignancies and lymphoproliferative disorders

Information provided below is based on the Humira data

No malignancies were observed in 249 paediatric patients with an exposure of 655.6 patient years during adalimumab trial 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 93 pediatric patients with an exposure of 65.3 patient years during a Humira trial in pediatric 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, axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis), Crohn's disease, ulcerative colitis, hidradenitis suppurativa, psoriasis, and uveitis, malignancies, other than lymphoma and nonmelanoma 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 26439.6 patient-years of therapy.

Autoantibodies
Information provided below is based on the Humira data
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 patients 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 diseases 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 adalimumab. Many of these patients were taking concomitant immunosuppressants (e.g.,MTX, corticosteroids). Some of these patients required hospitalization. Most patients had improvement of their psoriasis following discontinuation of their TNF blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF blocker. Discontinuation of adalimumab should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Liver Enzyme Elevations
Information provided below is based on the Humira data
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 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 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 (40 mg every other week), in patients with axial spondyloarthritis (ankylosing spondylitis and non-radiographic 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 80mg at Week 0 followed by 40mg 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 pediatric 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 adalimumab. The causal relationship to adalimumab 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 adalimumab and azathioprine/6–mercaptopurine compared with adalimumab alone.

Information provided below is based on the Humira data

Additional Adverse Reactions from Post-marketing Surveillance or Phase IV Clinical Trials

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

Additional Adverse Reactions from Post-marketing Surveillance or Phase IV Clinical Trials	
System Organ Class	**Adverse Reaction**
Infections and infestations	diverticulitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)*	hepatosplenic T-cell lymphoma, leukemia, Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin), Kaposi's sarcoma**
Immune system disorders*	Anaphylaxis, sarcoidosis

Nervous system disorders*	demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome), cerebrovascular accident.
Respiratory, thoracic and mediastinal disorders	pulmonary embolism, pleural effusion, pulmonary fibrosis
Gastrointestinal disorders*	intestinal perforation
Hepatobiliary disorders*	reactivation of hepatitis B, 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**
Musculoskeletal and connective tissue disorders	lupus-like syndrome
Cardiac disorders	myocardial infarction
General disorders and administrative site conditions	pyrexia
* further information is found elsewhere in Contraindications, Warnings & Precautions and Adverse Reactions. ** occurring in patients receiving a TNF-antagonist including Humira	

CLINICAL STUDY ON NAIL PSORIASIS

Psoriasis Study IV compared the efficacy and safety of Humira versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg Humira followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open-label Humira treatment for an additional 26 weeks. Nail psoriasis was assessed using the Modified Nail Psoriasis Severity Index (mNAPSI) and the Physician's Global Assessment of Fingernail Psoriasis (PGA-F). A statistically significantly higher proportion of patients randomized to Humira achieved at least a 75% improvement in mNAPSI (mNAPSI 75) at Week 26, as compared with patients randomized to placebo (see Table 8. The percent improvement in NAPSI was statistically significantly greater in Humira patients compared with placebo at Week 16 (44.2% vs 7.8%) and at Week 26 (56.2% vs 11.5%).

A statistically significant higher proportion of patients in the Humira group achieved a PGA-F of "clear" or "minimal" with at least a 2-grade improvement from Baseline at Week 26 compared with placebo. In this study, Humira demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement (BSA=10% and BSA<10% and =5%) and a statistically significant improvement in scalp psoriasis compared with placebo.

Table 8
Efficacy Results at 26 Weeks

Endpoint	Placebo N=108	Humira 40 mg eow N=109
≥ mNAPSI 75 (%)	3.4	46.6[a]
PGA-F clear/minimal and ≥2-grade improvement (%)	6.9	48.9[a]
Percent Change in Total Fingernail NAPSI (%)	-11.5	-56.2[a]
mNAPSI = 0 (%)	0	6.6[b]
Change in Nail Pain Numeric Rating Scale	-1.1	-3.7[a]
Change in Nail Psoriasis Physical Functioning Severity score	-0.8	-3.7[a]
B-SNIPI 50 Scalp (%)	N=12 0.4	N=18 58.3[b]
[a]p<0.001, Humira vs. placebo [b]p<0.05, Humira vs. placebo B-SNIPI 50: At least a 50% reduction in scalp component of Brigham Scalp Nail Inverse Palmo- Plantar Psoriasis index (B-SNIPI) among subjects with Baseline scalp score of 6 or greater)		

Of those who continued to receive Humira treatment until Week 52, 65.0% achieved mNAPSI 75 response and 61.3% achieved PGA-F response.

Humira treated patients showed statistically significant improvements at Week 26 from baseline compared with placebo in the DLQI (Dermatology Life Quality Index). The mean decrease (improvement) from baseline at Week 26 was 8.0 in the Humira group (N=94) and 1.9 in the placebo group (N=93).

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

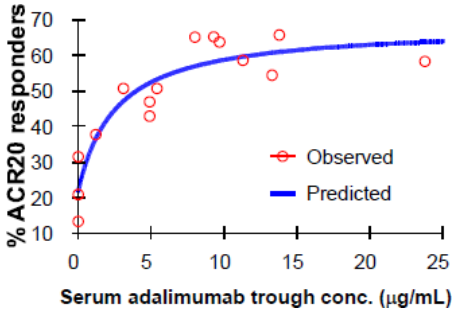
Mechanism of action
Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis, including juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis (Ps) plaques. In plaque psoriasis, treatment with Humira may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which Humira exerts its clinical effects is unknown.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1-2 X 10^{-10}M).

Pharmacodynamics
Clinical efficacy and safety
Information below refer to Humira
After treatment with Humira, a rapid decrease in levels of acute phase reactants of inflammation C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) and serum cytokines (IL-6) was observed compared to baseline in patients with RA. A decrease in CRP levels was also observed in patients with JIA, Crohn's disease, ulcerative colitis and hidradenitis suppurativa as well as a significant reduction in the expression of TNF and inflammatory markers such as human leucocyte antigen (HLA-DR) and myeloperoxidase (MPO) in the colon of patients with Crohn's disease.

Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after Humira administration. Patients with RA, PsA and AS often experience mild to moderate anemia and decreased lymphocyte counts, as well as elevated neutrophil and platelet counts. Patients treated with Humira usually experienced improvement in these hematological signs of chronic inflammation.

The serum adalimumab concentration-efficacy relationship as measured by the American College of Rheumatology response criteria (ACR 20) appears to follow the Hill E_{max} equation as shown below:



EC_{50} estimates ranging from 0.8 to 1.4 mcg/mL were obtained through pharmacokinetic/ pharmacodynamic modeling of swollen joint count, tender joint count and ACR 20 response from patients participating in Phase II and III trials.

Comparability of Hyrimoz to Humira
Information below refer to biosimilar Hyrimoz
Clinical studies conducted to support similarity between Hyrimoz and the reference biologic drug included:

- A comparative pharmacokinetic (PK) clinical Phase I study in healthy male subjects comparing HYRIMOZ® with EU-Humira and EU-Humira with US-Humira (GP17-104).
- A comparative efficacy and safety clinical Phase III in patients with chronic plaque-type psoriasis comparing HYRIMOZ® with Humira (GP17-301).

An overview of the study design(s) and demographic characteristics of patients enrolled in each clinical study are presented in table below.

Study#	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Sex
GP17- 104 (pivotal PK study)	Single-center, randomized, double-blind, single-dose, three-arm, parallel-group study Objective: To demonstrate PK comparability for Hyrimoz and EU-Humira, and for EU-Humira and US-Humira after a single s.c. injection of 40 mg of adalimumab	Hyrimoz: 40 mg/0.8 mL, PFS, single s.c. injection Hyrimoz: 40 mg/0.8 mL, PFS, single s.c. injection US-Humira: 40 mg/0.8 mL, PFS, single s.c. injection	Healthy male subjects	Overall study population: 37.2 years (18 – 55 years) Hyrimoz: 37.6 years (21 – 55 years) EU-Humira: 36.5 years (19 – 55 years) US-Humira: 37.5 years (18 – 55 years)	Male; N=318m Hyrimoz: N=107m EU-Humira: N=106m US-Humira: N=105m
GP17- 301 (pivotal comparative efficacy and safety study)	Multi-center, randomized, double-blind, comparator-controlled study with treatment switches	Hyrimoz: 40 mg/0.8 mL, PFS EU-Humira: 40 mg/0.8 mL, PFS US-Humira: 40 mg/0.8 mL, PFS Hyrimoz and Humira were administered as s.c. injections with a loading dose of 80 mg on Day 1 and 40 mg every other week starting with Week 1 and up to Week 49	Male and female patients with moderate to severe chronic plaque-type psoriasis	Overall study population: 46.3 years (18 – 84 years) Hyrimoz: 45.6 years (18 – 81 years) Humira: 46.9 years (18 – 84 years) US-Humira: 46.9 years (19 – 84 years) EU-Humira: 46.9 years (18 – 79 years)	Male and female; N=465 (284m, 181f) Hyrimoz: N=231 (142m, 89f) EU-Humira: N=44 (28m, 16f) US-Humira: N=190 (114m, 76f)

Comparative pharmacokinetic study GP17-104

Study GP17-104: Statistical analysis of primary pharmacokinetic parameters for the comparison of Hyrimoz with EU-Humira

Adalimumab injection (1 x 40mg) From measured data Geometric Mean Arithmetic Mean (CV%)

Parameter	**Hyrimoz[2]**	**EU-Humira[3]**	**% Ratio of Geometric Means[4]**	**90% Confidence Interval**
AUC_T (mcg•h/mL)	2261 2489 (42.0)	2163 2326 (37.5)	104.6	94.7 – 115.4
AUC_I (mcg•h/mL)	2728 2952 (41.5)	2557 2719 (35.1)	106.7	97.6 – 116.6
C_{MAX} (mcg/mL)	3.67 3.84 (29.0)	3.54 3.70 (29.9)	103.8	96.7 – 111.5
T_{MAX} (h)[1]	167.6 (40.1)	154.4 (50.4)	n.a.	n.a.
$T_{½}$ (h)[1]	405.6 (45.5)	404.0 (41.4)	n.a.	n.a.

[1] Expressed as the arithmetic mean (CV%) only.
[2] n=104 for AUC_T, C_{MAX}, and T_{MAX}; n = 99 for AUC_I and $T_{1/2}$
[3] n=103 for AUC_T, C_{MAX}, and T_{MAX}; n = 101 for AUC_I and $T_{1/2}$
[4] Least square mean, estimated using analysis of variance with treatment as fixed effect.

Comparative safety and efficacy

Efficacy

Study GP17-301 (Chronic plaque type psoriasis)

The efficacy and safety of HYRIMOZ has been demonstrated in a multi-center, randomized, double-blind study (GP17-301) in which 465 patients with moderate to severe chronic plaque-type psoriasis were randomized 1:1 to HYRIMOZ or HUMIRA. The study was designed to rule out any clinically meaningful difference between HYRIMOZ and HUMIRA.

The patient population studied in study GP17-301 consisted of adult male and female patients with active, but clinically stable chronic plaque-type skin psoriasis involving a body surface area (BSA) of at least 10%, a minimal PASI of 12 (indicating moderate to-severe psoriasis), and an investigator global assessment (IGA) of at least moderate severity (score ≥3). Eligible patients had to have previously received at least one phototherapy or systemic therapy for psoriasis or were candidates to receive such therapy in the opinion of the investigator. Randomization at baseline was stratified by body weight (<90kg and ≥90kg), by prior systemic psoriasis therapy and by region (EU and US).

The primary efficacy endpoint was the PASI75 (defined as a 75% reduction of the Psoriasis Area Severity Index)* response rate measured at Week 16.

The 95% CI of the adjusted treatment difference remained within the predefined equivalence margin of [-18%, 18%].

Table 9

Treatment	N	n	Adjusted response rate[1] (SE) [%]	Adjusted response rate difference (SE) [%]	95% CI	Equivalence interval
Hyrimoz	231	134	58.1 (3.23)	2.2 (4.56)	[-6.79,11.10]	[-18%, 18%]
Humira	234	131	55.9 (3.23)			

CI=confidence intervals; N=number of patients per treatment group; n=number of patients per treatment group achieving PASI75 response; PASI=psoriasis area and severity index; SE=standard error.
[1] Adjusted response rates were estimated using a logistic regression model including treatment, body weight strata, region and prior systemic therapy. The 95% CI for the rate difference was derived based on the normal approximation and standard error computed using the delta method (method details and code were adopted from Ge et al 2011).
Patients with missing PASI scores at Week 16 regardless of reason (e.g. missing visit, early discontinuation) are considered non-responders for the analysis.

Table 10 Adjusted treatment difference with US-Humira

Treatment	N	n	Adjusted response rate[1] (SE) [%]	Adjusted response rate difference (SE) [%]	95% CI	Equivalence interval
Hyrimoz	231	134	58.1 (3.23)	5.1 (4.85)	[-4.39,14.61]	[-18%, 18%]
US-Humira	190	101	53.0 (3.61)			

CI=confidence intervals; N=number of patients per treatment group; n=number of patients per treatment group achieving PASI75 response; PASI=psoriasis area and severity index; SE=standard error.
[1] Adjusted response rates were estimated using a logistic regression model including treatment, body weight strata, region and prior systemic therapy. The 95% CI for the rate difference was derived based on the normal approximation and standard error computed using the delta method (method details and code were adopted from Ge et al 2011).
Patients with missing PASI scores at Week 16 regardless of reason (e.g. missing visit, early discontinuation) are considered non-responders for the analysis.

The 95% CI of the adjusted treatment difference for both HUMIRA and US-HUMIRA remained within the predefined equivalence margin of [-18%, 18%].

Safety
The types, frequency and severity of adverse events were comparable between the biosimilar and the reference biologic drug.

Immunogenicity
The numbers and proportions of patients with positive ADA responses were similar between the HYRIMOZ and the reference medicine groups during TP1 and during the entire study in the continued treatment groups; NAbs were detected in similar proportions between groups.

Table 11 Summary of patients with confirmed positive ADA response by treatment group – study GP17- 301 – Randomization to Week 17 (SAF)

ADA response, overall from Week 1[a]	**HYRIMOZ N=231** **n/N' (%)**	**Reference medicine N=234** **n/N' (%)**
Negative	139/220 (63.2)	145/220 (65.9)
Positive	81/220 (36.8)	75/220 (34.1)
Neutralizing	65/81 (80.2)	60/75 (80.0)

ADA=anti-drug antibody; n=number of patients per treatment group with ADA response; N'=number of patients with evaluable data; N=number of randomized patients; SAF=safety analysis set
[a] Overall from Week 1' indicates that patients had at least one ADA positive result (recorded as positive) or had consistently negative results (recorded as negative) post-baseline.

Table 12 Summary of patients with confirmed positive ADA response during the entire study by continued group – study GP17-301 – Randomization to Week 51 (SAF)

ADA response, overall from Week 1[a]	**Continued HYRIMOZ N=168** **n/N' (%)**	**Continued reference medicine N=171** **n/N' (%)**
Negative	98/160 (61.3)	87/159 (54.7)
Positive	62/160 (38.8)	72/159 (45.3)
Neutralizing	55/62 (88.7)	61/72 (84.7)

Continued groups include patients who continued the same treatment throughout the study.
ADA=anti-drug antibody; n=number of patients per treatment group with ADA response; N'=number of patients with evaluable data; N=number of randomized patients; SAF=safety analysis set
[a] 'Overall from Week 1' indicates that patients had at least one ADA positive result (recorded as positive) or had consistently negative results (recorded as negative) post-baseline.

Comparability of Hyrimoz-high concentration formulation (HCF) and Hyrimoz-low concentration formulation (LCF) (CGPN017B12101)

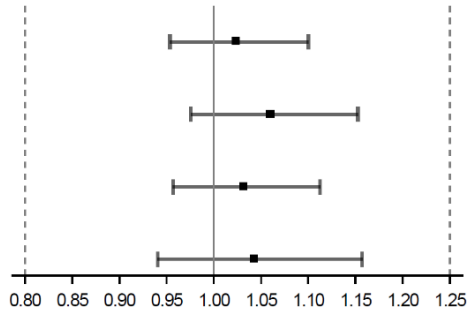
A clinical study was conducted to compare the pharmacokinetics (PK) of the newly developed Hyrimoz HCF (100mg/mL) to the currently approved Hyrimoz LCF (50mg/mL) following a single Hyrimoz s.c. dose.

An overview of the study design and demographic characteristics of patients enrolled in the clinical study are presented in the table below.

Study Number	Title of Study	Dosage, route of administration and duration	Study subjects (n)	Demographics and other baseline characteristics
CGPN017B12101	A randomized, double-blind, parallel, two-arm study to compare pharmacokinetics, safety and immunogenicity of GPN017B1 (Hyrimoz high concentration formulation; 100 mg/mL) with GP2017 (Hyrimoz low concentration formulation; 50 mg/mL) after a single dose of 40 mg subcutaneous injection in healthy male subjects	Hyrimoz HCF (100mg/mL): PFS, single s.c. injection. Hyrimoz LCF (50mg/mL): PFS, single s.c. injection	Healthy male subjects	Most subjects were White (79.4%); the mean age was 37.3 years (range 18-55 years), and the mean BMI was 26.79 kg/m^2 (range 20.5-29.9 kg/m^2)

The 90% CIs of the ratios (Hyrimoz-HCF / Hyrimoz-LCF) of geometric least square (LS) means for the primary parameters C_{max}, AUC_{inf}, and AUC_{0-360} and for the secondary PK parameter AUC_{last} were all contained within the predefined limits of 0.80 to 1.25. Therefore, PK comparability of Hyrimoz-HCF and Hyrimoz-LCF was concluded.

Table 13 Forest plot of primary and secondary PK endpoints (PKS)

Parameter (unit)	n	Geometric LS_{means}		Ratio Test/Reference		Comparison Hyrimoz-HCF vs Hyrimoz-LCF
		Test	Reference	Point estimate	90% CI (Lower, Upper)	
C_{max} (ng/mL)	300	3247	3170	1.0242	(0.9536, 1.1001)	
$AUC_{0\text{-}inf}$ (h*ng/mL)	285	2334410	2201267	1.0605	(0.9758, 1.1525)	
$AUC_{0\text{-}360}$ (h*ng/mL)	300	904669	876775	1.0318	(0.9568, 1.1127)	
$AUC_{0\text{-}last}$ (h*ng/mL)	300	1859656	1782651	1.0432	(0.9404, 1.1572)	

n=number of subjects by treatment group with evaluable PK parameter data
Test: Hyrimoz-HCF; Reference: Hyrimoz-LCF
ANCOVA analysis performed for PK parameter including treatment as a fixed effect and baseline body weight (at Day -1) as a covariate.

The 90% CIs of the ratios (Hyrimoz-HCF / Hyrimoz-LCF) of geometric LS means for C_{max}, AUC_{inf}, $AUC_{0\text{-}360}$, and AUC_{last} in anti-drug antibodies (ADA)-positive and in ADA-negative subjects were also contained within 0.80 to 1.25. These results underline PK comparability of Hyrimoz-HCF and Hyrimoz-LCF in both subpopulations and provide evidence for similar immunogenicity of both formulations.

In the pre-specified sensitivity analyses of primary and secondary PK comparability analyses using an analysis of variance (ANOVA) model including treatment as a fixed effect only; including study site as an additional fixed effect; using the PK parameters adjusted for individual subject protein content; in subjects who did not receive concomitant medication known to influence immune response; and in subjects who were pre-dose adalimumab negative, the 90% CIs of the ratios (Hyrimoz-HCF / Hyrimoz-LCF) of geometric LS means for C_{max}, AUC_{inf}, $AUC_{0\text{-}360}$, and AUC_{last} were also contained within 0.80 to 1.25. These results underline the robustness of the primary and secondary PK comparability analyses.

No clinically relevant differences in the safety and tolerability were observed between the Hyrimoz-HCF and Hyrimoz-LCF treatment groups. Single dose administrations of 40 mg s.c. Hyrimoz-HCF and Hyrimoz-LCF were safe and well tolerated by healthy male subjects.

The overall numbers and proportions of subjects with positive ADA responses (Hyrimoz-HCF: 112 subjects, 69.1%; Hyrimoz-LCF: 109 subjects, 64.9%) were comparable between the 2 treatment groups. ADA titers were low, and onset of ADA formation was on Day 16 or later in most ADA-positive subjects except in 7 subjects with onset of ADA formation on Day 7 or 10; ADA titers were > 1000 in 5 of these subjects.

PK comparability of Hyrimoz-HCF and Hyrimoz-LCF has been shown in the study.
Based on the study results, Hyrimoz-HCF and Hyrimoz-LCF are comparable also in terms of safety, tolerability, and immunogenicity.

5.2 Pharmacokinetic properties

Absorption

Following a single 40mg subcutaneous (SC) administration of adalimumab to 59 healthy adult subjects, absorption and distribution of adalimumab was 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 were determined in several studies with intravenous doses

ranging from 0.25 to 10 mg/kg. The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L, indicating that adalimumab distributes approximately equally between the vascular and extravascular fluids. Adalimumab is slowly eliminated, with clearances typically under 12 mL/h. The mean terminal phase half-life was approximately two weeks, ranging from 10 to 20 days across studies. The clearance and half-life were relatively unchanged over the studied dose range, and the terminal half-life was similar after IV and SC administration. Adalimumab concentrations in the synovial fluid from several RA patients ranged from 31 to 96% of those in serum.

Steady-state pharmacokinetics
Accumulation of adalimumab was predictable based on the half-life following SC administration of 40 mg of adalimumab every other week to patients with RA, with mean steady-state trough concentrations of approximately 5 mcg/mL (without concomitant methotrexate (MTX) and 8 to 9 mcg/mL (with concomitant MTX), 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 psoriasis, the mean steady-state trough concentration was 5 mcg/mL during adalimumab 40 mg eow without concomitant methotrexate 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 8mcg/mL at Week 2 and Week 4. The mean steady-state trough concentration at Week 12 through Week 36 were approximately 8 to 10 mcg/mL during adalimumab 40 mg every week treatment.

In patients with uveitis, a loading dose of 80mg adalimumab on Week 0 followed by 40mg adalimumab every other week starting at Week 1, result in mean steady-state concentrations of approximately 8 to 10 mcg/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 pediatric patients ≥ 40 kg with CD).

Population pharmacokinetic analyses with data from over 1200 patients revealed that coadministration of MTX had an intrinsic effect on adalimumab apparent clearance (CL/F). As expected, there was a trend toward higher apparent clearance of adalimumab with increasing body weight and in the presence of anti-adalimumab antibodies.

Other more minor factors were also identified; higher apparent clearance was predicted in patients receiving doses lower than the recommended dose, and in patients with high rheumatoid factor or CRP concentrations. These factors are not likely to be clinically important.

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 levels of approximately 12 mcg/mL at Week 2 and Week 4. Mean steady-state trough levels of approximately 7 mcg/mL were observed at Week 24 and Week 56 in Crohn's disease patients after receiving a maintenance dose of 40 mg adalimumab every other week.

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 mcg/mL during the induction period. Mean steady-state trough levels of approximately 8 mcg/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 pharmacokinetic analyses.

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

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) for adalimumab without concomitant methotrexate and 10.9 ± 5.2 µg/mL (47.7% CV) with concomitant methotrexate. The mean steady-state trough serum adalimumab concentrations for patients weighing <30 kg receiving 20 mg adalimumab subcutaneously every other week without concomitant methotrexate or with concomitant methotrexate were 6.8 µg/mL and 10.9 µg/mL, respectively. The mean steady-state trough serum adalimumab concentrations for patients weighing ≥30kg receiving 40 mg adalimumab subcutaneously every other week without concomitant methotrexate or with concomitant methotrexate were 6.6 µg/mL and 8.1 µg/mL, respectively. In patients with polyarticular juvenile idiopathic arthritis (JIA) who were 2 to <4 years old or aged 4 and above weighing <15kg 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 ± 5.6µg/ml (71.2% CV) with concomitant methotrexate.

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

In paediatric patients with 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, patients 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 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 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 patients who continued to receive adalimumab treatment eow for 52 weeks. For patients who dose escalated from eow to weekly regimen, the mean (±SD) serum concentrations of adalimumab at Week 52 were 15.3±11.4 µg/mL (40/20 mg, weekly) and 6.7±3.5 µg/mL (20/10 mg, weekly).

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

Adalimumab exposure in adolescent hidradenitis suppurativa (HS) patients was predicted using population pharmacokinetic modeling and simulation based on cross-indication pharmacokinetics in other pediatric patients (pediatric psoriasis, juvenile idiopathic arthritis, pediatric 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 40mg) every other week to pediatric 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.

Gender

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

Race

No differences in immunoglobulin clearance would be expected among races. From limited data in non- Caucasians, no important kinetic differences were observed for adalimumab.

Hepatic and renal insufficiency
No pharmacokinetic data are available in patients with hepatic or renal impairment.

Disease states
Healthy volunteers and patients with RA displayed similar adalimumab pharmacokinetics.

5.3 Preclinical safety data

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term animal studies of adalimumab have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

No clastogenic or mutagenic effects of adalimumab were observed in the in vivo mouse micronucleus test or the Salmonella-Escherichia coli (Ames) assay, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Adipic acid
Mannitol
Polysorbate 80
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

This medicine contains less than 1 mmol of sodium (23 mg) per 0.8 ml dose, that is to say essentially 'sodium-free'.

6.2 Incompatibilities

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

6.3 Shelf life

24 months

6.4 Special precautions for storage

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

A single Hyrimoz pre-filled pen may be stored at temperatures up to a maximum of **25°C** for a period of up to 42 days. The pre-filled pen must be protected from light, and discarded if not used within the 42-day period.

or

A single Hyrimoz pre-filled pen may be stored at temperatures up to a maximum of **30°C** for a period of up to 14 days. The pre-filled pen must be protected from light, and discarded if not used within the 14-day period.

Once removed from the refrigerator, the pre-filled pen must be used within the out-of-refrigerator period or

discarded, even if it had been subsequently returned to the refrigerator.

6.5 Nature and contents of container

Hyrimoz 40 mg solution for injection in single-use pre-filled SensoReady pen

Hyrimoz is supplied in a single-use pre-filled syringe assembled into a triangular-shaped pen with transparent window and label (SensoReady). The syringe inside the pen is made of type I glass with a stainless steel 29-gauge needle, an inner rubber needle cap (thermoplastic elastomer), and a rubber stopper (bromobutyl rubber), containing 0.4 ml solution.

Packs of 1 and 2 pre-filled pens

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

6.7 INSTRUCTIONS FOR USE

To help avoid possible infections and to ensure that you use Hyrimoz correctly, it is important that you follow these instructions.

Be sure that you read, understand, and follow these Instructions for use before injecting Hyrimoz. Your healthcare provider should show you how to prepare and inject Hyrimoz properly using the Hyrimoz single-dose pre-filled pen before you use it for the first time. Talk to your healthcare provider if you have any questions.

Your Hyrimoz single-use pre-filled pen

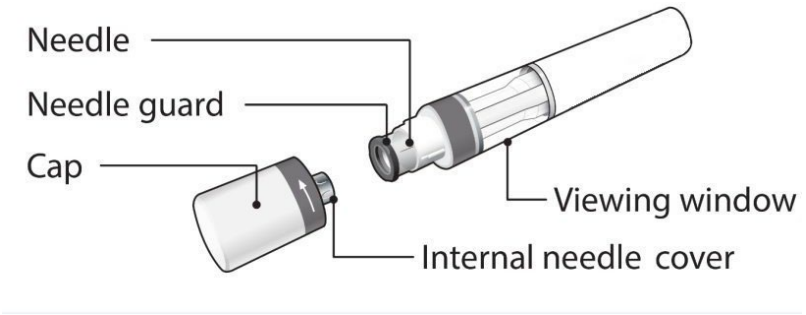


Figure A: Hyrimoz pen parts

In ***Figure A***, the pen is shown with the cap removed. **Do not remove** the cap until you are ready to inject.

It is important that you:
• **do not use** the pen if either the seal on the outer carton or the safety seal on the pen is broken. • keep your pen in the sealed outer carton until you are ready to use it. • **never leave** the pen unattended where others might tamper with it. • **do not use** your pen, if you dropped it, it looks damaged, or if you dropped it with the cap removed. • **inject** Hyrimoz 15–30 minutes after taking it out of the refrigerator for a more comfortable injection. • throw away the used pen right away after use. **Do not re-use the pen.** See **"8. Disposing of used pens"** at the end of this Instructions for Use.

How should you store your pen?

- Store your pen carton in a refrigerator, between 2°C to 8°C.
- When needed, for example when you are travelling, Hyrimoz may be stored at room temperature (up to 25°C) for a maximum period of 42 days. – be sure to protect it from light. Once removed from the refrigerator for room temperature storage, your pre-filled pen **must be used within 42 days or discarded**, even if it is later returned to the refrigerator.

  OR

  Hyrimoz may be stored at temperature up to 30°C for a maximum period of 14 days – be sure to protect it from light. Once removed from the refrigerator for room temperature storage, your pre-filled pen **must be used within 14 days or discarded**, even if it is later returned to the refrigerator.
- You should record the date when your pre-filled pen is first removed from the refrigerator, and the date after which it should be discarded.
- Keep your pen in the original carton until ready to use to protect from light.
- Do not store your pen in extreme heat or cold.
- Do not freeze your pen.

Keep Hyrimoz and all medicines out of the reach of children.

What do you need for your injection?

Place the following items on a clean, flat surface. Included

in your carton are:

- Hyrimoz pre-filled pen/s (see ***Figure A***). Each pen contains 40 mg/0.4 ml of adalimumab.

Not included in your pen carton are (see ***Figure B***):

- Alcohol wipe
- Cotton ball or gauze
- Sharps disposal container See "**8**. **Disposing of used pens**" at the end of these Instructions for Use
- Adhesive bandage.

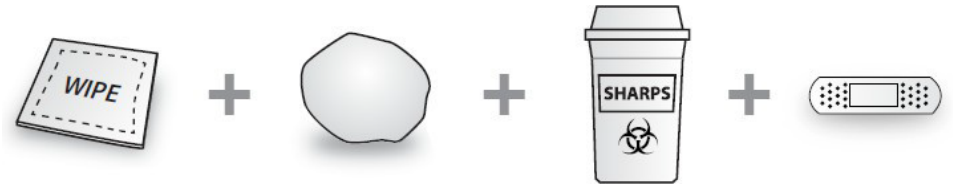
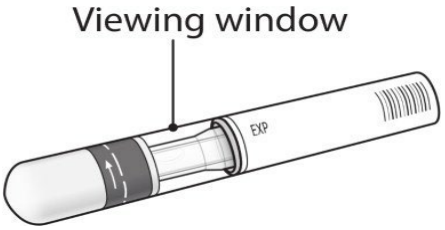
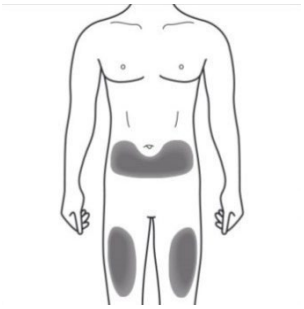
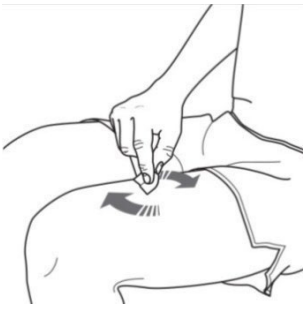
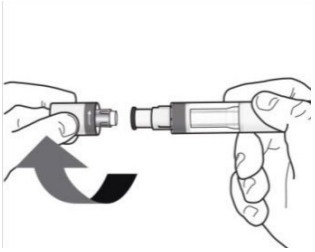


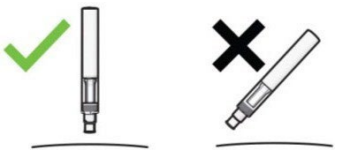
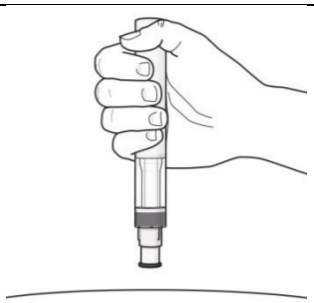
Figure B: items not included in the carton

Before your injection **Preparing the pen**	
• For a more comfortable injection, take your pen out of the refrigerator 15 to 30 minutes before injecting Hyrimoz to allow it to reach room temperature. • Look through the viewing window. The solution should be colourless or slightly yellowish as well as clear to slightly opalescent. **Do not use** if any particulates and / or discolorations are observed. You may see small air bubbles, which is normal. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance. • Look at the expiration date (EXP) on your pen (see ***Figure C*****).** Do not use your pen if the expiration date has passed. • Do not use if the safety seal has been broken. **Contact your pharmacist if the pen fails any of the above mentioned checks.**	 ***Figure C:*** Safety Checks before injection

1. Choosing your injection site:	
• The recommended injection site is the front of your thighs. You may also use the lower abdomen, but not the area 5 cm around your navel (belly button) (see ***Figure D***). • Choose a different site each time you give yourself an injection. • **Do not** inject into areas where the skin is tender, bruised, red, scaly, or hard. Avoid areas with scars or stretch marks. • If you have psoriasis, you should **NOT** inject directly into areas with psoriasis plaques.	 ***Figure D:*** choose your injection site

2. Cleaning your injection site:	
• Wash your hands well with soap and water. • Using a circular motion, clean the injection site with an alcohol wipe. Let it dry before injecting (see ***Figure E***). • **Do not** touch the cleaned area again before injecting.	 ***Figure E:*** clean your injection site

3.	**Removing the cap of your pen:**	
•	Only remove the cap when you are ready to use the pen.	
•	Twist off the cap in the direction of the arrows (see ***Figure F***).	***Figure F:*** remove the cap
•	Once removed, throw away the cap. **Do not** try to re-attach the cap.	
•	Use your pen within 5 minutes of removing the cap.	
•	You may see a few drops of liquid come out of the needle. This is normal.	

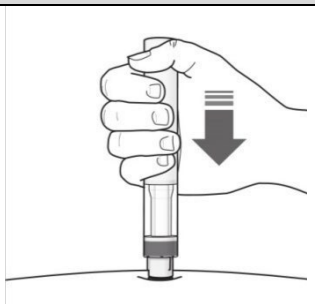
4.	**Holding the pen:**	
•	Hold your pen at 90 degrees to the cleaned injection site (see ***Figure G***).	
		 ***Figure G:*** hold your pen

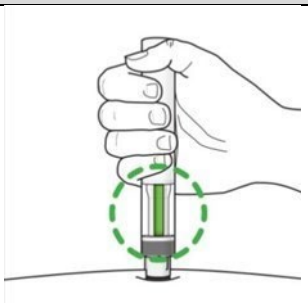
Your injection

You must read this before injecting
During the injection you will hear **2 loud clicks**:

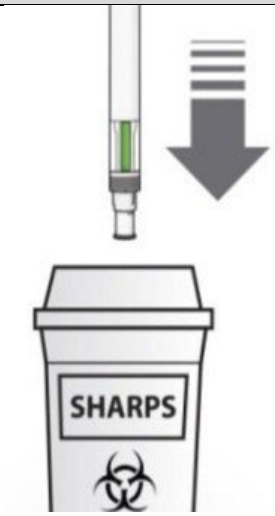
- The **first click** indicates that the injection has **started**.
- Several seconds later a **second click** will indicate that the injection is **almost** finished.

You **must** keep holding your pen firmly against your skin until you see a **green indicator** fill the window and stop moving.

5.	**Starting your injection:**	
•	Press your pen firmly against the skin to start the injection (see ***Figure H***).	
•	The first click indicates the injection has started.	***Figure H:*** start your injection
•	**Keep holding** your pen firmly against your skin.	
•	The green indicator shows the progress of the injection.	

6. Completing your injection:	
• Listen for the second click. This indicates the injection is almost complete. • Check the green indicator fills the window and has stopped moving (see ***Figure I***). • The pen can now be removed.	 ***Figure I:*** complete your injection

After your injection **7. Check the green indicator fills the window** (see ***Figure J***)**:**	
• This means the medicine has been delivered. Contact your doctor if the green indicator is not visible. • There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.	 ***Figure J:*** check the green indicator

8. Disposing of used pens:	
• Dispose of the used pens in a sharps container (closable, puncture-resistant container, see ***Figure K***). For the safety and health of you and others, the pens must never be re-used. • Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment. Any unused product or waste material should be disposed of in accordance with local requirements.	 ***Figure K*****:** dispose of your used pen

If you have any questions, please talk to a doctor, pharmacist or nurse who is familiar with Hyrimoz.

7. MANUFACTURER

Manufactured and released by:
Novartis Pharmaceutical Manufacturing GmbH
Biochemiestrasse 10
6336 Langkampfen
Austria

Note: “Adalimumab” refers to Humira, while “biosimilar” refers to Hyrimoz

8. DATE OF REVISION OF THE TEXT

Aug 2025

Package insert will be presented in font size 10, measure in Times New Roman