PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

Yuflyma® 10mg/0.1ml solution for injection in pre-filled pen (40mg and 80mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Yuflyma 40 mg solution for injection in pre-filled pen

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

Yuflyma 80 mg solution for injection in pre-filled pen

Each 0.8 ml single dose pre-filled pen contains 80 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)

Clear to slightly opalescent, colourless to pale brown solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Yuflyma 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.
Yuflyma can be used alone or in combination with methotrexate or other disease modifying anti-rheumatic drugs (DMARDs).

Psoriatic Arthritis

Yuflyma 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.

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

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

Non-radiographic Axial spondyloarthritis (Axial Spondyloarthritis without radiographic evidence of AS)
Yuflyma 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

Yuflyma 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

Yuflyma is indicated for the treatment of moderately to severely active Crohn's Disease in adult patients who have inadequate response to conventional therapy. Yuflyma 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

Yuflyma 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

Yuflyma 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

Yuflyma 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

Yuflyma 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). Yuflyma can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enthesitis-Related Arthritis

Yuflyma 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

Yuflyma 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

Yuflyma 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

Yuflyma 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

Yuflyma 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.

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

Plaque Psoriasis
The recommended dose of Yuflyma 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 Yuflyma 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 Yuflyma 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 Yuflyma and signs and symptoms of disease recur, Yuflyma 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 Yuflyma 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 Yuflyma 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 Yuflyma. 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 Yuflyma 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 Yuflyma 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 Yuflyma if necessary.

Should treatment need to be interrupted, Yuflyma 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 Yuflyma 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 Yuflyma alone. Treatment with Yuflyma 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 Yuflyma.

Paediatric
Juvenile idiopathic arthritis
Polyarticular juvenile idiopathic arthritis
The recommended dose of Yuflyma for patients from 2 years of age with polyarticular juvenile idiopathic arthritis (JIA) is based on body weight (Table 1). Yuflyma is administered every other week via subcutaneous injection.

Table 1. Adalimumab dose for patients with Polyarticular Juvenile Idiopathic Arthritis

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

Note: Yuflyma is available as 40 mg presentations or 80 mg presentations. Thus, it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose.

Adalimumab 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 adalimumab in patients aged less than 2 years for this indication.

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

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

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

Note: Yuflyma is available as 40 mg presentations or 80 mg presentations. Thus, it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose.

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

Paediatric Crohn's disease

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

Table 3. Adalimumab Dose for Paediatric Patients with Crohn's Disease

Patient weight	Induction dose	Maintenance dose starting at week 4
< 40 kg	• 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	–
≥ 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

* Note: Yuflyma is available as 40 mg presentations or 80 mg presentations. Thus,it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose.

Patients who experience insufficient response may benefit from an increase in dosage:

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

Continued therapy should be carefully considered in a subject not responding by week 12. There is no relevant use of adalimumab in children aged less than 6 years for this indication.

Paediatric plaque psoriasis

The recommended Yuflyma dose for patients from 4 to 17 years of age with plaque psoriasis is based on body weight (Table 4). Yuflyma is administered via subcutaneous injection.

Table 4. Adalimumab Dose for Paediatric Patients with Plaque Psoriasis

Patient Weight	Dosing Regimen
15 kg to < 30 kg	-
≥ 30 kg	Initial dose of 40 mg, followed by 40 mg given every other week starting one week after the initial dose

Note: Yuflyma is available as 40 mg presentations or 80 mg presentations. Thus, it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose.

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

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

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

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

Paediatric uveitis

The recommended dose of Yuflyma for paediatric patients 2 years of age and older with chronic non-infectious uveitis is based on body weight (Table 5). Yuflyma is administered via subcutaneous injection.

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

Table 5. Adalimumab Dose for Paediatric Patients with Uveitis

Patient Weight	Dosing Regimen
< 30 kg	-
≥ 30 kg	40 mg every other week in combination with methotrexate

Note: Yuflyma is available as 40 mg presentations or 80 mg presentations. Thus, it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose.

When Yuflyma therapy 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 an adalimumab loading dose in children < 6 years of age (see section 5.2).

There is no relevant use of adalimumab 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 (see section 5.1).

Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)

There are no clinical trials with adalimumab in adolescent patients with hidradenitis suppurativa (HS). The posology of adalimumab in these patients has been determined from pharmacokinetic modeling and simulation.

The recommended Yuflyma 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.

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

In adolescent patients with inadequate response to Yuflyma 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 Yuflyma 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 Yuflyma.

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

Should treatment be interrupted, Yuflyma 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 Yuflyma in children aged less than 12 years in this indication.

Paediatric ulcerative colitis

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

Table 6. Adalimumab Dose for Paediatric Patients with Ulcerative Colitis

Patient weight	**Induction dose**	**Maintenance dose starting at week 4***
< 40 kg	• 80 mg at week 0 and • 40 mg at week 2	• 40 mg every other week
≥ 40 kg	• 160 mg at week 0 and • 80 mg at week 2	• 80 mg every other week

* Paediatric patients who turn 18 years of age while on Yuflyma should continue their prescribed maintenance dose.

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

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

Method of administration

Yuflyma is administered by subcutaneous injection.

Full instructions for use are provided in the Consumer Medication Information Leaflet (RiMUP).

4.3 Contraindications

Yuflyma should not be administered to patients with known hypersensitivity to adalimumab 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 adalimumab. 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 adalimumab 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 adalimumab 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 adalimumab.

Patients who develop a new infection while undergoing treatment with adalimumab, should be monitored closely and undergo a complete diagnostic evaluation. Administration of adalimumab 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 adalimumab 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 adalimumab. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated).
Before initiation of therapy with adalimumab, 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 adalimumab. 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, adalimumab therapy must not be initiated.

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylactic treatment before the initiation of adalimumab 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 adalimumab. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with adalimumab. Also, active tuberculosis has developed in patients receiving adalimumab 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 adalimumab 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 adalimumab.

+as permitted by local regulations.

Other Opportunistic Infections

Opportunistic infections, including invasive fungal infections, have been observed in patients receiving adalimumab. 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, adalimumab should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurologic Events

TNF antagonists, including adalimumab, 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 adalimumab in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of adalimumab 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 adalimumab 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 adalimumab, the overall rate of malignancies was similar to what would be expected for an age, gender and race matched general population. With the current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

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

Very rare postmarketing reports of hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with 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 adalimumab 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 adalimumab. Thus additional caution should be exercised in considering adalimumab 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 adalimumab.

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

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 adalimumab were rare during clinical trials. Reports of serious allergic reactions including anaphylaxis have been received following adalimumab administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of adalimumab 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 adalimumab. The causal relationship of these reports to adalimumab 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 adalimumab. Discontinuation of adalimumab 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 adalimumab, 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 adalimumab, 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 adalimumab group compared to 82% in the placebo group. A total of 37% of adalimumab-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 adalimumab group and 95% in the placebo group achieved protective antibody levels to the influenza antigens. A total of 52% of adalimumab- 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 adalimumab therapy.

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

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

Adalimumab 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 adalimumab. Physicians should exercise caution when using adalimumab in patients who have heart failure and monitor them carefully.

Autoimmune processes

Treatment with adalimumab may result in the formation of autoimmune antibodies.

The impact of long-term treatment with adalimumab on the development of autoimmune diseases is unknown.

If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with adalimumab, treatment should be discontinued (see ADVERSE REACTIONS- Autoantibodies).

Geriatric Use

The frequency of serious infection among adalimumab 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 adalimumab, 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

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 adalimumab 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.

4.6 Pregnancy, lactation and nursing mothers

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 non-randomized 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.

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 on the breastfed child from adalimumab or from the underlying maternal condition.

4.7 Effects on ability to drive and use machines

Yuflyma may have a minor influence on the ability to drive and use machines. Vertigo and visual impairment may occur following administration of Yuflyma (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 2 below. The highest frequency seen among the various indications has been included. An asterisk (*) appears in the SOC column if further information is found elsewhere in sections Contraindications, Warnings and Precautions and Adverse Reactions.

Table 7 Undesirable effects

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), 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 neoplasms (including breast cancer, lung neoplasm and thyroid neoplasm) melanoma*

System Organ Class	Frequency	Adverse Reaction
Blood and the lymphatic system disorders*	Very common	leucopenia (including neutropenia and agranulocytosis), anemia
	Common	thrombocytopenia, leucocytosis
	Uncommon	idiopathic thrombocytopenic purpura
	Rare	pancytopenia
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, hyperglycemia, hypophosphotemia, dehydration
Psychiatric disorders	Common	mood alterations (including depression), anxiety, insomnia
Nervous system disorders*	Very Common	headache
	Common	paraesthesias (including hypoasthesia), 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

System Organ Class	Frequency	Adverse Reaction
Gastrointestinal disorders	Very common	abdominal pain, nausea and vomiting
	Common	GI hemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	pancreatitis, dysphagia, face edema
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 tests 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 found elsewhere in Contraindications, Warnings & Precautions and Adverse Reactions

** 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 non-infectious uveitis treated with adalimumab 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, haemorrhage, pain or swelling), compared to 7.2% of patients receiving placebo or active control. 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 placebo and active 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 infection, and sinusitis. Most patients continued on adalimumab after the infection resolved.

In controlled and open label adult and paediatric studies with adalimumab, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extra-pulmonary locations) and invasive opportunistic infections (e.g. disseminated or extrapulmonary histoplasmosis, blastomycosis, coccidioidomycosis, pneumocystis, candidiasis, aspergillosis and listeriosis).

Malignancies and lymphoproliferative disorders

No malignancies were observed in 249 paediatric patients with an exposure of 655.6 patient years during adalimumab trials in patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis).

In addition, no malignancies were observed in 192 paediatric patients with an exposure of 498.1 patient years during adalimumab trials in paediatric patients with Crohn's disease.

No malignancies were observed in 93 paediatric patients with an exposure of 65.3 patient years during an adalimumab trial in paediatric patients with ulcerative colitis.

During the controlled portions of pivotal adalimumab trials in adults of at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, 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 non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.8 (4.4, 10.5) per 1,000 patient-years among 5,291 adalimumab-treated patients *versus* a rate of 6.3 (3.4, 11.8) per 1,000 patient-years among 3,444 control patients (median duration of treatment was 4.0 months for adalimumab and 3.8 months for control-treated patients).

The rate (95% confidence interval) of non-melanoma skin cancers was 8.8 (6.0, 13.0) per 1,000 patient-years among adalimumab-treated patients and 3.2 (1.3, 7.6) per 1,000 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 1,000 patient-years among adalimumab-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients.

The rate (95% confidence interval) of lymphomas was 0.7 (0.2, 2.7) per 1,000 patient-years among adalimumab-treated patients and 0.6 (0.1, 4.5) per 1,000 patient-years among control patients.

The observed rate of malignancies, other than lymphoma and non-melanoma skin cancers, is approximately 8.5 per 1,000 patient years. The observed rate of non-melanoma skin cancers is approximately 9.6 per 1,000 patient years, and the observed rate of lymphomas is approximately 1.3 per 1,000 patient years. The median duration of these studies is approximately 3.3 years and included 6427 patients who were on adalimumab for at least 1 year or who developed a malignancy within a year of starting therapy, representing 26439.6 patient-years of therapy.

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis studies I − V. In these adequate and well-controlled trials, 11.9% of patients treated with adalimumab and 8.1% of placebo and active control−treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at week 24.

Two patients out of 3,989 treated with adalimumab in all rheumatoid arthritis and psoriatic arthritis studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with adalimumab 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 a. 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

In controlled Phase 3 trials of adalimumab (40 mg SC every other week), in patients with rheumatoid arthritis and psoriatic arthritis with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.7% of adalimumab-treated patients and 1.6% of control-treated patients. Since many of the patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between adalimumab and the liver enzyme elevations is not clear. In controlled Phase 3 trials of adalimumab (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 adalimumab -treated patients and 0.9% of control-treated patients. In controlled Phase 3 trials of adalimumab (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 adalimumab adalimumab -treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of adalimumab (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 adalimumab-treated patients and 1.8% of control-treated patients.

In controlled trials of adalimumab (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in patients with hidradenitis suppurativa with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of adalimumab-treated patients and 0.6% of control-treated patients.

In controlled Phase 3 trials of adalimumab (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 adalimumab-treated patients and 0.8% of control-treated patients.

In controlled Phase 3 trials of adalimumab in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations ≥ 3 x ULN occurred in 6.1% of adalimumab-treated patients and 1.3% of control-treated patients. Most ALT elevations occurred with concomitant methotrexate use. No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial of adalimumab in patients with polyarticular juvenile idiopathic arthritis who were 2 to < 4 years.

In the Phase 3 trial of adalimumab in patients with paediatric Crohn's disease which evaluated efficacy and safety of two body weight adjusted maintenance dose regimens following body weight adjusted induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients of whom 4 were receiving concomitant immunosuppressants at baseline.

In controlled trials of adalimumab (initial doses of 80 mg at week 0 followed by 40 mg every other week starting at week 1) in adult patients with uveitis up to 80 weeks with a median exposure of 166.5 days and 105.0 days in adalimumab-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of adalimumab-treated patients and 2.4% of control-treated patients.

In the controlled Phase 3 trial of adalimumab in patients with paediatric ulcerative colitis (N=93) which evaluated efficacy and safety of a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every other week (N=31) and a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every week (N=32), following body weight adjusted induction dosing of 2.4 mg/kg (maximum of 160 mg) at week 0 and week 1, and 1.2 mg/kg (maximum of 80 mg) at week 2 (N=63), or an induction dose of 2.4 mg/kg (maximum of 160 mg) at week 0, placebo at week 1, and 1.2 mg/kg (maximum of 80 mg) at week 2 (N=30), ALT elevations ≥ 3 X ULN occurred in 1.1% (1/93) of patients.

No ALT elevations ≥ 3 X ULN occurred in the Phase 3 trial of adalimumab 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 rate 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.

<u>Concurrent treatment with azathioprine/6-mercaptopurine</u>
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.

<u>Additional Adverse Reactions from Post marketing Surveillance or Phase IV Clinical Trials</u>

Adverse events have been reported during post-approval use of adalimumab. 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 adalimumab exposure.

Table 8: Additional Adverse Reactions from Postmarketing 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 adalimumab	

4.9 Overdose

The maximum tolerated dose of adalimumab has not been established in humans. No dose-limiting toxicities have been observed during clinical trials with adalimumab. 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 General

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).

5.2 Pharmacodynamic properties

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

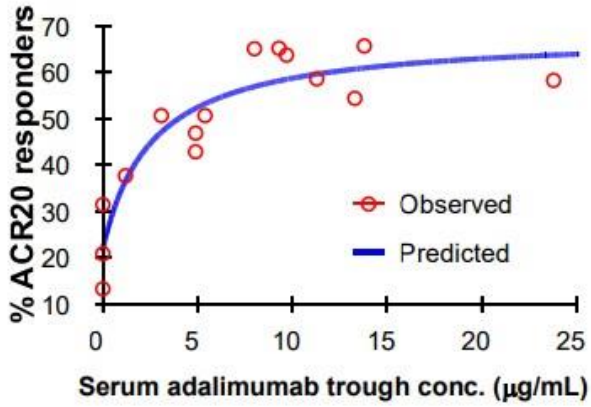
Yuflyma is a biosimilar medicinal product.

After treatment with adalimumab, a rapid decrease in levels of acute phase reactants of inflammation C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) and serum cytokines (IL-6) was observed compared to baseline in patients with RA. A 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 adalimumab 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 adalimumab 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:

Figure 1: Concentration-Efficacy Relationship



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.

5.3 Pharmacokinetic properties

Absorption

Following a single 40 mg 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 (Vss) ranged from 4.7 to 6.0 L, indicating that adalimumab distributes approximately equally between the vascular and extravascular fluids. Adalimumab is slowly eliminated, with clearances typically under 12 mL/h. The mean terminal phase half-life was approximately two weeks, ranging from 10 to 20 days across studies. The clearance and half-life were relatively unchanged over the studied dose range, and the terminal half-life was similar after IV and SC administration. Adalimumab concentrations in the synovial fluid from several RA patients ranged from 31 to 96% of those in serum.

Steady-state pharmacokinetics

Accumulation of adalimumab was predictable based on the half-life following SC administration of 40 mg of adalimumab every other week to patients with RA, with mean steady-state trough concentrations of approximately 5 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) (see DRUG INTERACTIONS). 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 7mcg/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/m2 (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 ≥30 kg 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 w a s 6.0 ± 6.1μg/ml (101% CV) for adalimumab without concomitant methotrexate and 7.9 ± 5.6 μg/ml (71.2% CV) with concomitant methotrexate.
Following the administration of 24 mg/m2 (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 40 mg) 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.

5.4 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. COMPARATIVE CLINICAL TRIALS

6.1 Comparative Trial Design and Study Demographics

Clinical Studies conducted to support similarity between Yuflyma and the reference biologic drug included:

- A comparative pharmacokinetic (PK) clinical Phase I study CT-P17 1.1 in healthy subjects
- A comparative efficacy and safety clinical Phase III study CT-P17 3.1 in patients with moderate to severe RA

An overview of the study design and demographic characteristics of patients enrolled in each clinical study are presented in Table 9.

Table 9 Summary of Trial Design and Patient Demographics (Subjects in Intent-to-treat Population)

Study Number	Study Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (years; range)	Gender
CT-P17 1.1	Phase 1, randomized, double-blind, three-arm, parallel group, single-dose study in healthy male and female subjects	Yuflyma, EU-Humira, or US-Humira; Single dose 40 mg, Subcutaneous injection; Total duration 10 weeks	312 healthy subjects Yuflyma (n=103) EU-Humira (n=106) US-Humira (n=103)	Overall 28.3 (19, 54) Yuflyma 27.0 (19, 51) EU-Humira 28.9 (19, 54) US-Humira 29.0 (19, 53)	Overall M 267 (85.6%), F 45 (14.4%) Yuflyma M 88 (85.4%) F 15 (14.6%) EU-Humira M 90 (84.9%) F 16 (15.1%) US-Humira M 89 (86.4%) F 14 (13.6%)
CT-P17 3.1	Phase 3, randomized, active-controlled, double-blind , multicenter study in patients with moderate to severe active RA	Yuflyma or EU-Humira; 40 mg every other week; Subcutaneous injection; Total duration 52 weeks	648 RA patients Yuflyma (n=324) EU-Humira (n=324)	Overall 51.9 (18, 75) Yuflyma 52.0 (18, 75) EU-Humira 51.8 (19, 75)	Overall M 134 (20.7%), F 514 (79.3%) Yuflyma M 75 (23.1%) F 249 (76.9%) EU-Humira M 59 (18.2%) F 265 (81.8%)

Abbreviations: EU, European Union; US, United States; RA, Rheumatoid arthritis; M, Male; F, Female

Study CT-P17 3.1 was a phase 3, randomized, active-controlled, double-blind, multicenter study designed to evaluate efficacy, PK, PD, usability, overall safety and immunogenicity of multiple single-doses (40 mg) of either Yuflyma or EU-Humira administered via PFS in combination with MTX in patients with moderate to severe active RA. The study period for up to 52 weeks after 1st randomization includes 48 weeks of treatment and 4 weeks of safety follow-up. Prior to dosing at Week 26, all patients underwent the 2nd

randomization process. Patients who were initially randomly assigned to EU-Humira were randomized again in a ratio of 1:1 to either continue EU-Humira or undergo transition to Yuflyma. The primary endpoint, ACR20 at Week 24, met with 95% CI falling within the margin of -15% to +15%.

6.2 Comparative Study Results

6.2.1 Comparative Bioavailability Studies

6.2.1.1 Pharmacokinetics

Comparative Pharmacokinetic Study CT-P17 1.1

Table 10 ANCOVA for C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}last}$ for Yuflyma, US-Humira, and EU-Humira in Study CT-P17 1.1 (PK Population)

(a) Yuflyma to EU-Humira

PK Parameters (Units)	Treatment	Mean (%CV)	Geometric LS Means[1]	Ratio (%) of Geometric LS Means	90% CIs[1]
C_{max} (μg/mL)	Yuflyma	3.619 (37.4)	3.008	100.05	(93.69, 106.85)
	EU-Humira	3.660 (33.4)	3.006		
$AUC_{0\text{-}inf}$ (h•μg/mL)	Yuflyma	2656.5 (43.3)	2165.0	98.00	(90.06, 106.63)
	EU-Humira	2690.6 (35.1)	2209.3		
$AUC_{0\text{-}last}$ (h•μg/mL)	Yuflyma	2372.7 (40.2)	1949.2	100.79	(92.42, 109.92)
	EU-Humira	2394.7 (36.2)	1933.9		

(b) Yuflyma to US-Humira

PK Parameters (Units)	Treatment	Mean (%CV)	Geometric LS Means[1]	Ratio (%) of Geometric LS Means	90% CIs[1]
C_{max} (μg/mL)	Yuflyma	3.619 (37.4)	3.008	101.89	(95.33, 108.89)
	US-Humira	3.556 (33.7)	2.952		
$AUC_{0\text{-}inf}$ (h•μg/mL)	Yuflyma	2656.5 (43.3)	2165.0	105.79	(97.19, 115.16)
	US-Humira	2469.7 (37.2)	2046.5		
$AUC_{0\text{-}last}$ (h•μg/mL)	Yuflyma	2372.7 (40.2)	1949.2	107.30	(98.29, 117.13)
	US-Humira	2185.0 (36.4)	1816.6		

[1] The LS mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of geometric LS means and 90% CIs for the ratios.
%CV: Percent coefficient of variation, ANCOVA: Analysis of covariance, CIs: Confidence intervals, LS: Least squares

6.2.2 Comparative Safety and Efficacy

6.2.2.1 Efficacy

Adult Rheumatoid Arthritis Study CT-P17 3.1

The number of patients who achieved ACR20 response at Week 24 was equal between the Yuflyma and EU-Humira treatment groups in the ITT population. A total of 268 (82.72%) patients achieved ACR20 response at Week 24 in each of the treatment groups. The 95% CI of the treatment difference was [-5.94, 5.94], which was within the pre-defined equivalence margin of [-15%, 15%] (Table 11).

Table 11 Exact Test for Proportion of Patients Achieving Response According to ACR20 Criteria in Study CT-P17 3.1 at Week 24 (ITT, PP Population)

Treatment	n/N	(%)	Estimated Difference (%)[1]	95% CI
ITT population				
Yuflyma	268/324	(82.72)	0.00	(-5.94, 5.94)
EU-Humira	268/324	(82.72)		
PP population				
Yuflyma	248/285	(87.02)	0.06	(-5.60, 5.78)
EU-Humira	240/276	(86.96)		

[1] Estimate of the difference in proportion and 95% confidence interval between the two treatment groups are estimated using the exact binomial method using a Farrington-Manning score method.

Note: Patients who were terminated from the study prior to the week of interest, who continued the study/study treatment but did not visit the site for the evaluation of ACR20 at the week of interest, and with incomplete data for evaluation of ACR20 criteria at the week of interest are considered as non-responder.

N: number of patients in the full analysis set, n: number of responders

6.2.2.2 Safety

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

6.3 Immunogenicity

Immunogenicity (Healthy Subjects)

The immunogenicity was evaluated in 308 healthy subjects in Study CT-P17 1.1. The blood samples were collected at Day 1 (pre-dose), Day 15, Day 29, Day 57 and Day 71. The proportions of subjects who had post-treatment ADA/NAb positive results up to Day 71 was similar amongst the three treatment groups.

Immunogenicity (RA)

The incidence of RA patients with ADA/NAb positive was comparable between the treatment groups up to Week 52 in Study CT-P17 3.1 (Table 12).

Table 12 Frequency of Positive ADA/NAb in Study CT-P17 3.1

Visit	Parameter	Yuflyma (N=324)	EU-Humira (N=324)
		n/N (%)	
Treatment Period I (Safety population)			
Week 0 (Pre-dose)	ADA	11/324 (3.4%)	6/324 (1.9%)
	NAb	4/11 (36.4%)	1/6 (16.7%)
Week 24	ADA	93/324 (28.7%)	116/324 (35.8%)
	NAb	83/93 (89.2%)	103/116 (88.8%)

Visit	Parameter	Yuflyma Maintenance (N=303)	EU-Humira Maintenance (N=152)	Switched to Yuflyma (N=152)
Treatment Period II (Safety population – Treatment Period II Subset)				
Week 26	ADA	74/303 (24.4%)	44/152 (28.9%)	52/152 (34.2%)
	NAb	71/74 (95.9%)	42/44 (95.5%)	47/52 (90.4%)
Week 52	ADA	86/303 (28.4%)	41/152 (27.0%)	43/152 (28.3%)
	NAb	75/86 (87.2%)	37/41 (95.5%)	40/43 (93.0%)
Post-treatment				
Up to Week 52	ADA	148/303 (48.8%)	89/152 (58.6%)	96/152 (63.2%)
	NAb	123/148 (83.1%)	71/89 (79.8%)	70/96 (72.9%)

Note: The proportion of ADA positive patients was calculated using the number of patients in the safety population.
The proportion of NAb positive patients was re-calculated using ADA positive patients as a denominator.
n: number of patients with the event, N: number of patients in each treatment group

7. PHARMACEUTICAL PARTICULARS

7.1 List of excipients

Acetic acid
Sodium acetate trihydrate Glycine
Polysorbate 80 Water
for injections

7.2 Incompatibilities

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

7.3 Shelf life

3 years

7.4 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 Yuflyma pre-filled pen may be stored at temperatures up to a maximum of 25°C for a period of up to 31 days. The pre-filled pen must be protected from light, and discarded if not used within the 31-day period.

7.5 Nature and contents of container

Yuflyma 40 mg solution for injection in pre-filled pen

Packs of:
- 1 pre-filled pen (0.4 ml sterile solution), with 2 alcohol pads.
- 2 pre-filled pens (0.4 ml sterile solution), with 2 alcohol pads.

Yuflyma 80 mg solution for injection in pre-filled pen

Packs of:
- 1 pre-filled pen (0.8 ml sterile solution), with 2 alcohol pads.
- 3 pre-filled pens (0.8 ml sterile solution), with 4 alcohol pads.

Solution for injection in a pre-filled pen for patient use containing a pre-filled syringe. The syringe inside the pen is made from type 1 glass with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

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Medicine: keep out of reach of children

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