

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Hulio 20 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.4 ml single dose pre-filled syringe contains 20 mg of adalimumab.

Adalimumab is a recombinant human monoclonal antibody produced in Chinese hamster ovary cells.

Excipient with known effect

Each pre-filled syringe contains 19.1 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

Clear or slightly opalescent, colourless to pale brownish-yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis

Hulio in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Hulio can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Hulio 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 (see section 5.1).

Paediatric plaque psoriasis

Hulio 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 phototherapies.

Paediatric Crohn's disease

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

Paediatric Uveitis

Hulio 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.

4.2 Posology and method of administration

Hulio treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which Hulio is indicated. Ophthalmologists are advised to consult with an appropriate specialist before initiation of treatment with Hulio (see section 4.4). Patients treated with Hulio should be given the patient reminder card.

After proper training in injection technique, patients may self-inject with Hulio if their physician determines that it is appropriate and with medical follow-up as necessary.

During treatment with Hulio, other concomitant therapies (e.g., corticosteroids and/or immunomodulatory agents) should be optimised.

Posology

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis from 2 years of age

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

Table 1. Hulio 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

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.

Hulio may be available in other strengths and/or presentations depending on the individual treatment needs.

Enthesitis-related arthritis

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

Table 2. Hulo 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

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

Hulo may be available in other strengths and/or presentations depending on the individual treatment needs.

Paediatric plaque psoriasis

The recommended Hulo dose for patients with plaque psoriasis from 4 to 17 years of age is based on body weight (Table 3). Hulo is administered via subcutaneous injection.

Table 3. Hulo 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

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

If retreatment with Hulo 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.

Hulio may be available in other strengths and/or presentations depending on the individual treatment needs.

Paediatric Crohn's disease

The recommended dose of Hulio for patients with Crohn's disease from 6 to 17 years of age is based on body weight (Table 4). Hulio is administered via subcutaneous injection.

Table 4. Hulio dose for paediatric patients with crohn's disease

Patient weight	Induction dose	Maintenance dose starting at week 4
< 40 kg	<ul style="list-style-type: none"> • 40 mg at week 0 and 20 mg at week 2 <p>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:</p> <ul style="list-style-type: none"> • 80 mg at week 0 and 40 mg at week 2 	20 mg every other week
≥ 40 kg	<ul style="list-style-type: none"> • 80 mg at week 0 and 40 mg at week 2 <p>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:</p> <ul style="list-style-type: none"> • 160 mg at week 0 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

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.

Hulio may be available in other strengths and/or presentations depending on the individual treatment needs.

Paediatric uveitis

The recommended dose of Hulo for paediatric patients with uveitis from 2 years of age is based on body weight (Table 5). Hulo is administered via subcutaneous injection.

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

Table 5. Hulo 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

When Hulo 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 a Hulo 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).

Hulo may be available in other strengths and/or presentations depending on the individual treatment needs.

Renal and/or hepatic impairment

Adalimumab has not been studied in these patient populations. No dose recommendations can be made.

Method of administration

Hulo is administered by subcutaneous injection. Full instructions for use are provided in the package leaflet.

Hulo is available in other strengths and presentations.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active tuberculosis or other severe infections such as sepsis and opportunistic infections (see section 4.4).

Moderate to severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

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

Infections

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

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

Patients who develop a new infection while undergoing treatment with adalimumab should be monitored closely and undergo a complete diagnostic evaluation. Administration of Hulio should be discontinued if a patient develops a new serious infection or sepsis and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of adalimumab in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications.

Serious infections

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

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

Tuberculosis

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

Before initiation of therapy with Hulio, all patients must be evaluated for both active or inactive (“latent”) tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients (local recommendations may apply). It is recommended that the conduct and results of these tests are recorded in the patient reminder card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Hulio therapy must not be initiated (see section 4.3).

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

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

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

Use of anti-tuberculosis prophylaxis treatment should also be considered before the initiation of Hulio 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.

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

Patients should be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (e.g., persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with Hulio.

Other opportunistic infections

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

For patients who develop the signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock an invasive fungal infection should be suspected and administration of Hulio should be promptly discontinued. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections.

Hepatitis B reactivation

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

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

Neurological events

TNF-antagonists including adalimumab have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of

central nervous system demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of adalimumab in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of Hulio 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 Hulio therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Allergic reactions

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

Immunosuppression

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

Malignancies and lymphoproliferative disorders

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

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy \leq 18 years of age), including adalimumab in the post marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

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

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

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

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

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.

Haematologic reactions

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF-antagonists. Adverse events of the haematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been reported with adalimumab. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor) while on adalimumab. Discontinuation of Hulio therapy should be considered in patients with confirmed significant haematologic abnormalities.

Vaccinations

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

It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating adalimumab therapy.

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

Congestive heart failure

In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving adalimumab. Adalimumab should be used with caution in patients with mild heart failure (NYHA class I/II). Adalimumab is contraindicated in moderate to severe heart failure (see section 4.3). Treatment with Hulio must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes

Treatment with Hulio 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 Hulio and is positive for antibodies against double-stranded DNA, further treatment with Hulio should not be given (see section 4.8).

Concurrent administration of biologic DMARDs or TNF-antagonists

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-antagonist, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF-antagonists. Therefore, the combination of adalimumab and anakinra is not recommended. (see section 4.5).

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, including serious infections and other potential pharmacological interactions. (see section 4.5).

Surgery

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

Small bowel obstruction

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

Elderly

The frequency of serious infections among adalimumab-treated subjects over 65 years of age (3.7%) was higher than for those under 65 years of age (1.5%). Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly.

Paediatric population

See vaccinations above.

Excipients with known effect

Sorbitol

This medicinal product contains sorbitol (E420). Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Sodium

This medicinal product contains less than 1 mmol of sodium (23 mg) per 0.4 ml dose, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

The combination of adalimumab and anakinra is not recommended (see section 4.4 “Concurrent administration of biologic DMARDs or TNF-antagonists”).

The combination of adalimumab and abatacept is not recommended (see section 4.4 “Concurrent administration of biologic DMARDs or TNF-antagonists”).

4.6 Fertility, Pregnancy and lactation

Women of child bearing potential

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

Pregnancy

A large number (approximately 2,100) of prospectively collected pregnancies exposed to adalimumab resulting in live birth with known outcomes, including more than 1,500 exposed during the first trimester, does not indicate an increase in the rate of malformation in the newborn.

In a prospective cohort registry, 257 women with rheumatoid arthritis (RA) or Crohn’s disease (CD) treated with adalimumab at least during the first trimester and 120 women with RA or CD not treated with adalimumab were enrolled. The primary endpoint was the birth prevalence of major birth defects. The rate of pregnancies ending with at least one live born infant with a major birth defect was 6/69 (8.7%) in the adalimumab-treated women with RA and 5/74 (6.8%) in the untreated women with RA (unadjusted OR 1.31, 95% CI 0.38-4.52) and 16/152 (10.5%) in the adalimumab-treated women with CD and 3/32 (9.4%) in the untreated women with CD (unadjusted OR 1.14, 95% CI 0.31-4.16). The adjusted OR (accounting for baseline differences) was 1.10 (95% CI 0.45-2.73) with RA and CD combined. There were no distinct differences between adalimumab-treated and untreated women for the secondary endpoints spontaneous abortions, minor birth defects, preterm delivery, birth size and serious or opportunistic infections and no stillbirths or malignancies

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

In a developmental toxicity study conducted in monkeys, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. Preclinical data on postnatal toxicity of adalimumab are not available (see section 5.3).

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

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

Breast-feeding

Limited information from the published literature indicates that adalimumab is excreted in breast milk at very low concentrations with the presence of adalimumab in human milk at concentrations of 0.1% to 1% of the maternal serum level. Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breastfed newborns/infants are anticipated. Consequently, adalimumab can be used during breastfeeding.

Fertility

Preclinical data on fertility effects of adalimumab are not available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

The proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of pivotal studies was 5.9% for patients taking adalimumab and 5.4% for control-treated patients.

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

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

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

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

Paediatric population

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

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on postmarketing experience and are displayed by system organ class and frequency in Table 6 below: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The highest frequency seen among the various indications has been included. An asterisk (*) appears in the

System Organ Class (SOC) column if further information is found elsewhere in sections 4.3, 4.4 and 4.8.

Table 6: 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	Neurological infections (including viral meningitis), opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), bacterial infections, eye infections, diverticulitis ¹⁾
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Common	Skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma), benign neoplasm
	Uncommon	Lymphoma**, solid organ neoplasm (including breast

System organ class	Frequency	Adverse reaction
		cancer, lung neoplasm and thyroid neoplasm), melanoma**
	Rare	Leukaemia ¹⁾
	Not known	Hepatosplenic T-cell lymphoma ¹⁾ , Merkel cell carcinoma (neuroendocrine carcinoma of the skin) ¹⁾ , Kaposi's sarcoma
Blood and the lymphatic system disorders*	Very common	Leukopenia (including neutropenia and agranulocytosis), anaemia
	Common	Leucocytosis, thrombocytopenia
	Uncommon	Idiopathic thrombocytopenic purpura
	Rare	Pancytopenia
Immune system disorders*	Common	Hypersensitivity, allergies (including seasonal allergy)
	Uncommon	Sarcoidosis ¹⁾ , vasculitis
	Rare	Anaphylaxis ¹⁾
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,

System organ class	Frequency	Adverse reaction
		insomnia
Nervous system disorders*	Very common	Headache
	Common	Paraesthesias (including hypoesthesia), migraine, nerve root compression
	Uncommon	Cerebrovascular accident ¹⁾ , tremor, neuropathy
	Rare	Multiple sclerosis, demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome) ¹⁾
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	Myocardial infarction ¹⁾ , arrhythmia, congestive heart failure
	Rare	Cardiac arrest
Vascular disorders	Common	Hypertension, flushing, haematoma
	Uncommon	Aortic aneurysm, vascular arterial occlusion,

System organ class	Frequency	Adverse reaction
		thrombophlebitis
Respiratory, thoracic and mediastinal disorders*	Common	Asthma, dyspnoea, cough
	Uncommon	Pulmonary embolism ¹⁾ , interstitial lung disease, chronic obstructive pulmonary disease, pneumonitis, pleural effusion ¹⁾
	Rare	Pulmonary fibrosis ¹⁾
Gastrointestinal disorders	Very common	Abdominal pain, nausea and vomiting
	Common	GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	Pancreatitis, dysphagia, face oedema
	Rare	Intestinal perforation ¹⁾
Hepato-biliary disorders*	Very Common	Elevated liver enzymes
	Uncommon	Cholecystitis and cholelithiasis, hepatic steatosis, bilirubin increased
	Rare	Hepatitis reactivation of hepatitis B ¹⁾ , autoimmune hepatitis ¹⁾
	Not known	Liver failure ¹⁾
Skin and subcutaneous tissue disorders	Very Common	Rash (including exfoliative rash)
	Common	Worsening or new onset of psoriasis (including palmoplantar pustular

System organ class	Frequency	Adverse reaction
		psoriasis) ¹⁾ , urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasia, hyperhidrosis, alopecia ¹⁾ , pruritus
	Uncommon	Night sweats, scar
	Rare	Erythema multiforme ¹⁾ , Stevens-Johnson syndrome ¹⁾ , angioedema ¹⁾ , cutaneous vasculitis ¹⁾ lichenoid skin reaction ¹⁾
	Not known	Worsening of symptoms of dermatomyositis ¹⁾
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain
	Common	Muscle spasms (including blood creatine phosphokinase increased)
	Uncommon	Rhabdomyolysis, systemic lupus erythematosus
	Rare	Lupus-like syndrome ¹⁾
Renal and urinary disorders	Common	Renal impairment, haematuria
	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, oedema, pyrexia ¹⁾

System organ class	Frequency	Adverse reaction
	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
Injury, poisoning and procedural complications	Common	Impaired healing

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

** including open label extension studies

¹⁾ including spontaneous reporting data

Uveitis

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

Description of selected adverse reactions

Injection site reactions

In the pivotal controlled trials in adults and children, 12.9% of patients treated with adalimumab developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 7.2% of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Infections

In the pivotal controlled trials in adults and children, the rate of infection was 1.51 per patient year in the adalimumab-treated patients and 1.46 per patient year in the placebo and active control-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, and sinusitis. Most patients continued on adalimumab after the infection resolved.

The incidence of serious infections was 0.04 per patient year in adalimumab-treated patients and 0.03 per patient year in placebo and active control-treated patients.

In controlled and open label adult and paediatric studies with adalimumab, serious infections (including fatal infections, which occurred rarely) have been reported,

which include reports of tuberculosis (including miliary and extra-pulmonary locations) and invasive opportunistic infections (e.g. disseminated or extrapulmonary histoplasmosis, blastomycosis, coccidioidomycosis, pneumocystis, candidiasis, aspergillosis and listeriosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

Malignancies and lymphoproliferative disorders

No malignancies were observed in 249 paediatric patients with 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 77 paediatric patients with an exposure of 80.0 patient years during an adalimumab trial in paediatric patients with chronic plaque psoriasis. No malignancies were observed in 60 paediatric patients with an exposure of 58.4 patient years during an adalimumab trial in paediatric patients with uveitis.

During the controlled portions of pivotal adalimumab trials in adults of at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.8 (4.4, 10.5) per 1,000 patient-years among 5,291 adalimumab-treated patients versus a rate of 6.3 (3.4, 11.8) per 1,000 patient-years among 3,444 control patients (median duration of treatment was 4.0 months for adalimumab and 3.8 months for control-treated patients). The rate (95% confidence interval) of 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.

When combining controlled portions of these trials and ongoing and completed open label extension studies with a median duration of approximately 3.3 years including 6,427 patients and over 26,439 patient-years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 8.5 per 1,000 patient years. The observed rate of non-melanoma skin cancers is approximately 9.6 per 1,000 patient years, and the observed rate of lymphomas is approximately 1.3 per 1,000 patient years.

In post-marketing experience from January 2003 to December 2010, predominantly in patients with rheumatoid arthritis, the reported rate of malignancies is approximately 2.7 per 1,000 patient treatment years. The reported rates for non-melanoma skin cancers and lymphomas are approximately 0.2 and 0.3 per 1,000 patient treatment years, respectively (see section 4.4).

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

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis studies I – V. In these trials, 11.9% of patients treated with adalimumab and 8.1% of placebo and active control-treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at week 24. Two patients out of 3,441 treated with adalimumab in all rheumatoid arthritis and psoriatic arthritis studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms.

Hepato-biliary events

In controlled Phase 3 trials of adalimumab in patients with rheumatoid arthritis and psoriatic arthritis with a control period duration ranging from 4 to 104 weeks, ALT elevations $\geq 3 \times$ ULN occurred in 3.7% of adalimumab-treated patients and 1.6% of control-treated patients.

In controlled Phase 3 trials of adalimumab in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations $\geq 3 \times$ 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 $\geq 3 \times$ ULN occurred in the Phase 3 trial of adalimumab in patients with polyarticular juvenile idiopathic arthritis who were 2 to < 4 years.

In controlled Phase 3 trials of adalimumab in patients with Crohn's disease and ulcerative colitis with a control period ranging from 4 to 52 weeks. ALT elevations $\geq 3 \times$ ULN occurred in 0.9% of adalimumab-treated patients and 0.9% of controlled-treated patients.

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

In controlled Phase 3 trials of adalimumab in patients with plaque psoriasis with a control period duration ranging from 12 to 24 weeks, ALT elevations $\geq 3 \times$ ULN occurred in 1.8% of adalimumab-treated patients and 1.8% of control-treated patients.

No ALT elevations $\geq 3 \times$ ULN occurred in the Phase 3 trial of adalimumab in paediatric patients with plaque psoriasis.

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 $\geq 3 \times$ ULN occurred in 2.4% of adalimumab-treated patients and 2.4% of control-treated patients.

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

Concurrent treatment with azathioprine/6-mercaptopurine

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Hulio is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

Mechanism of action

Adalimumab binds specifically to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

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 IC₅₀ of 0.1-0.2 nM).

Pharmacodynamic effects

After treatment with adalimumab, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL-6) was observed, compared to baseline in patients with rheumatoid arthritis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after adalimumab administration. Patients treated with adalimumab usually experienced improvement in haematological signs of chronic inflammation.

A rapid decrease in CRP levels was also observed in patients with polyarticular juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis and hidradenitis suppurativa after treatment with adalimumab. In patients with Crohn's disease, a reduction of the number of cells expressing inflammatory markers in the colon including a significant reduction of expression of TNF α was seen. Endoscopic studies in intestinal mucosa have shown evidence of mucosal healing in adalimumab-treated patients.

Clinical efficacy and safety

Juvenile idiopathic arthritis (JIA)

Polyarticular juvenile idiopathic arthritis (pJIA)

The safety and efficacy of adalimumab was assessed in two studies (pJIA I and II) in children with active polyarticular or polyarticular course juvenile idiopathic arthritis, who had a variety of JIA onset types (most frequently rheumatoid-factor negative or positive polyarthritis and extended oligoarthritis).

pJIA I

The safety and efficacy of adalimumab were assessed in a multicentre, randomised, double-blind, parallel – group study in 171 children (4-17 years old) with polyarticular JIA. In the open-label lead in phase (OL LI) patients were stratified into two groups, MTX (methotrexate)-treated or non-MTX-treated. Patients who were in the non-MTX stratum were either naïve to or had been withdrawn from MTX at least two weeks prior to study drug administration. Patients remained on stable doses of non-steroidal anti-inflammatory drugs (NSAIDs) and or prednisone (≤ 0.2 mg/kg/day or 10 mg/day maximum). In the OL LI phase all patients received 24 mg/m² up to a maximum of 40 mg adalimumab every other week for 16 weeks. The distribution of patients by age and minimum, median and maximum dose received during the OL LI phase is presented in Table 7.

Table 7: Distribution of patients by age and adalimumab dose received during the OL LI phase

Age group	Number of patients at baseline n (%)	Minimum, median and maximum dose
4 to 7 years	31 (18.1)	10, 20 and 25 mg
8 to 12 years	71 (41.5)	20, 25 and 40 mg
13 to 17 years	69 (40.4)	25, 40 and 40 mg

Patients demonstrating a Pediatric ACR 30 response at week 16 were eligible to be randomised into the double blind (DB) phase and received either adalimumab 24 mg/m² up to a maximum of 40 mg, or placebo every other week for an additional 32 weeks or until disease flare. Disease flare criteria were defined as a worsening of $\geq 30\%$ from baseline in ≥ 3 of 6 Pediatric ACR core criteria, ≥ 2 active joints, and improvement of $> 30\%$ in no more than 1 of the 6 criteria. After 32 weeks or at disease flare, patients were eligible to enrol into the open label extension phase.

Table 8: Ped ACR 30 responses in the JIA study

Stratum	MTX		Without MTX	
Phase				
OL-LI 16 weeks				
Ped ACR 30 response (n/N)	94.1% (80/85)		74.4% (64/86)	
Efficacy outcomes				
Double Blind 32 weeks	Adalimumab/MTX (N = 38)	Placebo/MTX (N = 37)	Adalimumab (N = 30)	Placebo (N = 28)
Disease flares at the end of	36.8% (14/38)	64.9% (24/37) ^b	43.3% (13/30)	71.4% (20/28) ^c

32 weeks ^a (n/N)				
Median time to disease flare	>32 weeks	20 weeks	>32 weeks	14 weeks

^a Ped ACR 30/50/70 responses week 48 significantly greater than those of placebo-treated patients

^b p = 0.015

^c p = 0.031

Amongst those who responded at week 16 (n=144), the Pediatric ACR 30/50/70/90 responses were maintained for up to six years in the OLE phase in patients who received adalimumab throughout the study. Over all 19 subjects, of which 11 of the baseline age group 4 to 12 and 8 of the baseline age group 13 to 17 years were treated 6 years or longer.

Overall responses were generally better and, fewer patients developed antibodies when treated with the combination of adalimumab and MTX compared to adalimumab alone. Taking these results into consideration, adalimumab is recommended for use in combination with MTX and for use as monotherapy in patients for whom MTX use is not appropriate (see section 4.2).

pJIA II

The safety and efficacy of adalimumab was assessed in an open-label, multicentre study in 32 children (2 - < 4 years old or aged 4 and above weighing < 15 kg) with moderately to severely active polyarticular JIA. The patients received 24 mg/m² body surface area (BSA) of adalimumab up to a maximum of 20 mg every other week as a single dose via SC injection for at least 24 weeks. During the study, most subjects used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs.

At week 12 and week 24, PedACR30 response was 93.5% and 90.0%, respectively, using the observed data approach. The proportions of subjects with PedACR50/70/90 at week 12 and week 24 were 90.3%/61.3%/38.7% and 83.3%/73.3%/36.7%, respectively. Amongst those who responded (Pediatric ACR 30) at week 24 (n=27 out of 30 patients), the Pediatric ACR 30 responses were maintained for up to 60 weeks in the OLE phase in patients who received adalimumab throughout this time period. Overall, 20 subjects were treated for 60 weeks or longer.

Enthesitis-related arthritis

The safety and efficacy of adalimumab were assessed in a multicentre, randomised, double-blind study in 46 paediatric patients (6 to 17 years old) with moderate enthesitis-related arthritis. Patients were randomised to receive either 24 mg/m² body surface area (BSA) of adalimumab up to a maximum of 40 mg, or placebo every other week for 12 weeks. The double-blind period is followed by an open-label (OL)

period during which patients received 24 mg/m² BSA of adalimumab up to a maximum of 40 mg every other week subcutaneously for up to an additional 192 weeks. The primary endpoint was the percent change from baseline to week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with loss of motion plus pain and/or tenderness), which was achieved with mean percent decrease of -62.6% (median percent change -88.9%) in patients in the adalimumab group compared to -11.6% (median percent change -50.0%) in patients in the placebo group. Improvement in number of active joints with arthritis was maintained during the OL period through week 156 for the 26 of 31 (84%) patients in the adalimumab group who remained in the study. Although not statistically significant, the majority of patients demonstrated clinical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count (TJC), swollen joint count (SJC), Pediatric ACR 50 response, and Pediatric ACR 70 response.

Adults with rheumatoid arthritis

adalimumab was evaluated in over 3,000 patients in all rheumatoid arthritis clinical trials. The efficacy and safety of adalimumab were assessed in five randomised, double-blind and well-controlled studies. Some patients were treated for up to 120 months duration.

RA study I evaluated 271 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had failed therapy with at least one disease-modifying, anti rheumatic drug and had insufficient efficacy with methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 10 to 25 mg every week. Doses of 20, 40 or 80 mg of adalimumab or placebo were given every other week for 24 weeks.

RA study II evaluated 544 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old and had failed therapy with at least one disease-modifying, anti-rheumatic drugs. Doses of 20 or 40 mg of adalimumab were given by subcutaneous injection every other week with placebo on alternative weeks or every week for 26 weeks; placebo was given every week for the same duration. No other disease-modifying anti-rheumatic drugs were allowed.

RA study III evaluated 619 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, and who had an ineffective response to methotrexate at doses of 12.5 to 25 mg or have been intolerant to 10 mg of methotrexate every week. There were three groups in this study. The first received placebo injections every week for 52 weeks. The second received 20 mg of adalimumab every week for 52 weeks. The third group received 40 mg of adalimumab every other week with placebo injections on alternate weeks. Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of adalimumab/MTX was administered every other week up to 10 years.

RA study IV primarily assessed safety in 636 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old. Patients were permitted to be either disease-modifying, anti-rheumatic drug-naïve or to remain on their pre-existing

rheumatologic therapy provided that therapy was stable for a minimum of 28 days. These therapies include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine and/or gold salts. Patients were randomised to 40 mg of adalimumab or placebo every other week for 24 weeks.

RA study V evaluated 799 methotrexate-naïve, adult patients with moderate to severely active early rheumatoid arthritis (mean disease duration less than 9 months). This study evaluated the efficacy of adalimumab 40 mg every other week/methotrexate combination therapy, adalimumab 40 mg every other week monotherapy and methotrexate monotherapy in reducing the signs and symptoms and rate of progression of joint damage in rheumatoid arthritis for 104 weeks. Upon completion of the first 104 weeks, 497 patients enrolled in an open-label extension phase in which 40 mg of adalimumab was administered every other week up to 10 years.

The primary end point in RA studies I, II and III and the secondary endpoint in RA study IV was the percent of patients who achieved an ACR 20 response at week 24 or 26. The primary endpoint in RA study V was the percent of patients who achieved an ACR 50 response at week 52. RA studies III and V had an additional primary endpoint at 52 weeks of retardation of disease progression (as detected by X-ray results). RA study III also had a primary endpoint of changes in quality of life.

ACR response

The percent of adalimumab-treated patients achieving ACR 20, 50 and 70 responses was consistent across RA studies I, II and III. The results for the 40 mg every other week dose are summarised in Table 9.

Table 9: ACR responses in placebo-controlled trials (percent of patients)

Response	RA study I ^{a**}		RA study II ^{a**}		RA study III ^{a**}	
	Placebo/ MTX ^c n=60	Adalimumab ^b / MTX ^c n=63	Placebo n=110	Adalimumab ^b n=113	Placebo/ MTX ^c n=200	Adalimumab ^b / MTX ^c n=207
ACR 20						
6 months	13.3%	65.1%	19.1%	46.0%	29.5%	63.3%
12 months	NA	NA	NA	NA	24.0%	58.9%
ACR 50						
6 months	6.7%	52.4%	8.2%	22.1%	9.5%	39.1%
12 months	NA	NA	NA	NA	9.5%	41.5%
ACR 70						
6 months	3.3%	23.8%	1.8%	12.4%	2.5%	20.8%
12 months	NA	NA	NA	NA	4.5%	23.2%

^a RA study I at 24 weeks, RA study II at 26 weeks, and RA study III at 24 and 52 weeks

^b 40 mg adalimumab administered every other week

^c MTX = methotrexate

**p < 0.01, adalimumab *versus* placebo

In RA studies I-IV, all individual components of the ACR response criteria (number of tender and swollen joints, physician and patient assessment of disease activity and pain, disability index (HAQ) scores and CRP (mg/dl) values) improved at 24 or 26 weeks compared to placebo. In RA study III, these improvements were maintained throughout 52 weeks.

In the open-label extension for RA study III, most patients who were ACR responders maintained response when followed for up to 10 years. Of 207 patients who were randomised to adalimumab 40 mg every other week, 114 patients continued on adalimumab 40 mg every other week for 5 years. Among those, 86 patients (75.4%) had ACR 20 responses; 72 patients (63.2%) had ACR 50 responses; and 41 patients (36%) had ACR 70 responses. Of 207 patients, 81 patients continued on adalimumab 40 mg every other week for 10 years. Among those, 64 patients (79.0%) had ACR 20 responses; 56 patients (69.1%) had ACR 50 responses; and 43 patients (53.1%) had ACR 70 responses.

In RA study IV, the ACR 20 response of patients treated with adalimumab plus standard of care was statistically significantly better than patients treated with placebo plus standard of care (p < 0.001).

In RA studies I-IV, adalimumab-treated patients achieved statistically significant ACR 20 and 50 responses compared to placebo as early as one to two weeks after initiation of treatment.

In RA study V with early rheumatoid arthritis patients who were methotrexate naïve, combination therapy with adalimumab and methotrexate led to faster and

significantly greater ACR responses than methotrexate monotherapy and adalimumab monotherapy at week 52 and responses were sustained at week 104 (see Table 10).

Table 10: ACR responses in RA study V (percent of patients)

Response	MTX n=257	Adalimumab n=274	Adalimumab /MTX n=268	p-value ^a	p-value ^b	p-value ^c
ACR 20						
Week 52	62.6%	54.4%	72.8%	0.013	< 0.001	0.043
Week 104	56.0%	49.3%	69.4%	0.002	< 0.001	0.140
ACR 50						
Week 52	45.9%	41.2%	61.6%	< 0.001	< 0.001	0.317
Week 104	42.8%	36.9%	59.0%	< 0.001	< 0.001	0.162
ACR 70						
Week 52	27.2%	25.9%	45.5%	< 0.001	< 0.001	0.656
Week 104	28.4%	28.1%	46.6%	< 0.001	< 0.001	0.864
a. p-value is from the pairwise comparison of methotrexate monotherapy and adalimumab /methotrexate combination therapy using the Mann-Whitney U test. b. p-value is from the pairwise comparison of adalimumab monotherapy and adalimumab/methotrexate combination therapy using the Mann-Whitney U test c. p-value is from the pairwise comparison of adalimumab monotherapy and methotrexate monotherapy using the Mann-Whitney U test						

In the open-label extension for RA study V, ACR response rates were maintained when followed for up to 10 years. Of 542 patients who were randomised to adalimumab 40 mg every other week, 170 patients continued on adalimumab 40 mg every other week for 10 years. Among those, 154 patients (90.6%) had ACR 20 responses; 127 patients (74.7%) had ACR 50 responses; and 102 patients (60.0%) had ACR 70 responses.

At week 52, 42.9% of patients who received adalimumab/methotrexate combination therapy achieved clinical remission (DAS28 (CRP) < 2.6) compared to 20.6% of patients receiving methotrexate monotherapy and 23.4% of patients receiving adalimumab monotherapy. Adalimumab/methotrexate combination therapy was clinically and statistically superior to methotrexate ($p < 0.001$) and adalimumab monotherapy ($p < 0.001$) in achieving a low disease state in patients with recently diagnosed moderate to severe rheumatoid arthritis. The response for the two monotherapy arms was similar ($p = 0.447$). Of 342 subjects originally randomized to adalimumab monotherapy or adalimumab/methotrexate combination therapy who entered the open-label extension study, 171 subjects completed 10 years of adalimumab treatment. Among those, 109 subjects (63.7%) were reported to be in remission at 10 years.

Radiographic response

In RA study III, where adalimumab-treated patients had a mean duration of rheumatoid arthritis of approximately 11 years, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score. adalimumab/methotrexate patients demonstrated significantly less radiographic progression than patients receiving methotrexate alone at 6 and 12 months (see Table 11).

In the open-label extension of RA Study III, the reduction in rate of progression of structural damage is maintained for 8 and 10 years in a subset of patients. At 8 years, 81 of 207 patients originally treated with 40 mg adalimumab every other week were evaluated radiographically. Among those, 48 patients showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less. At 10 years, 79 of 207 patients originally treated with 40 mg adalimumab every other week were evaluated radiographically. Among those, 40 patients showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less.

Table 11: Radiographic mean changes over 12 months in RA study III

	Placebo/MTX ^a	Adalimumab/MTX 40 mg every other week	Placebo/MTX- Adalimumab/MTX (95% Confidence Interval ^b)	p-value
Total Sharp Score	2.7	0.1	2.6 (1.4, 3.8)	< 0.001 ^c
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	< 0.001
JSN ^d score	1.0	0.1	0.9 (0.3, 1.4)	0.002

^amethotrexate

^b95% confidence intervals for the differences in change scores between methotrexate and adalimumab.

^cBased on rank analysis

^dJoint Space Narrowing

In RA study V, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (see Table 12).

Table 12: Radiographic mean changes at week 52 in RA study V

	MTX n=257 (95% confidence interval)	Adalimumab n=274 (95% confidence interval)	Adalimumab /MTX n=268 (95% confidence interval)	p- value ^a	p- value ^b	p- value ^c
Total Sharp Score	5.7 (4.2-7.3)	3.0 (1.7-4.3)	1.3 (0.5-2.1)	< 0.001	0.0020	< 0.001
Erosion score	3.7 (2.7-4.7)	1.7 (1.0-2.4)	0.8 (0.4-1.2)	< 0.001	0.0082	< 0.001
JSN score	2.0 (1.2-2.8)	1.3 (0.5-2.1)	0.5 (0-1.0)	< 0.001	0.0037	0.151

^a p-value is from the pairwise comparison of methotrexate monotherapy and adalimumab/methotrexate combination therapy using the Mann-Whitney U test.

^b p-value is from the pairwise comparison of adalimumab monotherapy and adalimumab/methotrexate combination therapy using the Mann-Whitney U test

^c p-value is from the pairwise comparison of adalimumab monotherapy and methotrexate monotherapy using the Mann-Whitney U test

Following 52 weeks and 104 weeks of treatment, the percentage of patients without progression (change from baseline in modified Total Sharp Score \leq 0.5) was significantly higher with adalimumab/methotrexate combination therapy (63.8% and 61.2% respectively) compared to methotrexate monotherapy (37.4% and 33.5% respectively, $p < 0.001$) and adalimumab monotherapy (50.7%, $p < 0.002$ and 44.5%, $p < 0.001$ respectively).

In the open-label extension of RA study V, the mean change from baseline at Year 10 in the modified Total Sharp Score was 10.8, 9.2 and 3.9 in patients originally randomized to methotrexate monotherapy, adalimumab monotherapy and adalimumab/methotrexate combination therapy, respectively. The corresponding proportions of patients with no radiographic progression were 31.3%, 23.7% and 36.7% respectively.

Quality of life and physical function

Health-related quality of life and physical function were assessed using the disability index of the Health Assessment Questionnaire (HAQ) in the four original adequate and well-controlled trials, which was a pre-specified primary endpoint at week 52 in RA study III. All doses/schedules of adalimumab in all four studies showed statistically significantly greater improvement in the disability index of the HAQ from baseline to Month 6 compared to placebo and in RA study III the same was seen at week 52. Results from the Short Form Health Survey (SF 36) for all doses/schedules of adalimumab in all four studies support these findings, with statistically significant physical component summary (PCS) scores, as well as statistically significant pain and vitality domain scores for the 40 mg every other week dose. A statistically significant decrease in fatigue as measured by functional assessment of chronic illness therapy (FACIT) scores was seen in all three studies in which it was assessed (RA studies I, III, IV).

In RA study III, most subjects who achieved improvement in physical function and continued treatment maintained improvement through week 520 (120 months) of open-label treatment. Improvement in quality of life was measured up to week 156 (36 months) and improvement was maintained through that time.

In RA study V, the improvement in the HAQ disability index and the physical component of the SF 36 showed greater improvement ($p < 0.001$) for adalimumab/methotrexate combination therapy versus methotrexate monotherapy and adalimumab monotherapy at week 52, which was maintained through week 104. Among the 250 subjects who completed the open-label extension study, improvements in physical function were maintained through 10 years of treatment.

Paediatric plaque psoriasis

The efficacy of adalimumab was assessed in a randomised, double-blind, controlled study of 114 paediatric patients from 4 years of age with severe chronic plaque psoriasis (as defined by a Physician's Global Assessment (PGA) ≥ 4 or $> 20\%$ BSA involvement or $> 10\%$ BSA involvement with very thick lesions or Psoriasis Area and Severity Index (PASI) ≥ 20 or ≥ 10 with clinically relevant facial, genital, or hand/ foot involvement) who were inadequately controlled with topical therapy and heliotherapy or phototherapy.

Patients received adalimumab 0.8 mg/kg eow (up to 40 mg), 0.4 mg/kg eow (up to 20 mg), or methotrexate 0.1-0.4 mg/kg weekly (up to 25 mg). At week 16, more patients randomised to adalimumab 0.8 mg/kg had positive efficacy responses (e.g., PASI 75) than those randomised to 0.4 mg/kg eow or MTX.

Table 13: Paediatric plaque psoriasis efficacy results at 16 weeks

	MTX ^a N=37	Adalimumab 0.8 mg/kg eow N=38
PASI 75 ^b	12 (32.4%)	22 (57.9%)
PGA: Clear/minimal ^c	15 (40.5%)	23 (60.5%)
^a MTX = methotrexate ^b P=0.027, adalimumab 0.8 mg/kg versus MTX ^c P=0.083, adalimumab 0.8 mg/kg versus MTX		

Patients who achieved PASI 75 and PGA clear or minimal were withdrawn from treatment for up to 36 weeks and monitored for loss of disease control (i.e. a worsening of PGA by at least 2 grades). Patients were then re-treated with adalimumab 0.8 mg/kg eow for an additional 16 weeks and response rates observed during retreatment were similar to the previous double-blind period: PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects).

In the open label period of the study, PASI 75 and PGA clear or minimal responses were maintained for up to an additional 52 weeks with no new safety findings.

Adult plaque psoriasis

The safety and efficacy of adalimumab were studied in adult patients with chronic plaque psoriasis ($\geq 10\%$ BSA involvement and PASI ≥ 12 or ≥ 10) who were candidates for systemic therapy or phototherapy in randomised, double-blind studies. 73% of patients enrolled in psoriasis studies I and II had received prior systemic therapy or phototherapy. The safety and efficacy of adalimumab were also studied in adult patients with moderate to severe chronic plaque psoriasis with concomitant hand and/or foot psoriasis who were candidates for systemic therapy in a randomised double-blind study (psoriasis study III).

Psoriasis study I (REVEAL) evaluated 1,212 patients within three treatment periods. In period A, patients received placebo or adalimumab at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. After 16 weeks of therapy, patients who achieved at least a PASI 75 response (PASI score improvement of at least 75% relative to baseline), entered period B and received open-label 40 mg adalimumab every other week. Patients who maintained \geq PASI 75 response at week 33 and were originally randomised to active therapy in Period A, were re-randomised in period C to receive 40 mg adalimumab every other week or placebo for an additional 19 weeks. Across all treatment groups, the mean baseline PASI score was 18.9 and the baseline PGA score ranged from “moderate” (53% of subjects included) to “severe” (41%) to “very severe” (6%).

Psoriasis study II (CHAMPION) compared the efficacy and safety of adalimumab versus methotrexate and placebo in 271 patients. Patients received placebo, an initial dose of MTX 7.5 mg and thereafter dose increases up to week 12, with a maximum dose of 25 mg or an initial dose of 80 mg adalimumab followed by 40 mg every other week (starting one week after the initial dose) for 16 weeks. There are no data available comparing adalimumab and MTX beyond 16 weeks of therapy. Patients receiving MTX who achieved a \geq PASI 50 response at week 8 and/or 12 did not receive further dose increases. Across all treatment groups, the mean baseline Pasi score was 19.7 and the baseline PGA score ranged from “mild” (<1%) to “moderate” (48%) to “severe” (46%) to “very severe” (6%).

Patients participating in all Phase 2 and Phase 3 psoriasis studies were eligible to enrol into an open-label extension trial, where adalimumab was given for at least an additional 108 weeks.

In psoriasis studies I and II, a primary endpoint was the proportion of patients who achieved a PASI 75 response from baseline at week 16 (see Tables 14 and 15).

Table 14: Ps study I (REVEAL) - efficacy results at 16 weeks

	Placebo N=398 n (%)	Adalimumab 40 mg eow N=814 n (%)
≥ PASI 75^a	26 (6.5)	578 (70.9) ^b
PASI 100	3 (0.8)	163 (20.0) ^b
PGA: Clear/minimal	17 (4.3)	506 (62.2) ^b

^a Percent of patients achieving PASI75 response was calculated as centre-adjusted rate
^b p < 0.001, adalimumab versus Placebo

Table 15: Ps study II (CHAMPION) efficacy results at 16 weeks

	Placebo N=53 n (%)	MTX N=110 n (%)	Adalimumab 40 mg eow N=108 n (%)
≥ PASI 75	10 (18.9)	39 (35.5)	86 (79.6) ^{a, b}
PASI 100	1 (1.9)	8 (7.3)	18 (16.7) ^{c, d}
PGA: Clear/minimal	6 (11.3)	33 (30.0)	79 (73.1) ^{a, b}

^a p < 0.001 adalimumab *versus* placebo
^b p < 0.001 adalimumab *versus* methotrexate
^c p < 0.01 adalimumab *versus* placebo
^d p < 0.05 adalimumab *versus* methotrexate

In psoriasis study I, 28% of patients who were PASI 75 responders and were re-randomised to placebo at week 33 compared to 5% continuing on adalimumab, p < 0.001, experienced “loss of adequate response” (PASI score after week 33 and on or before week 52 that resulted in a <PASI 50 response relative to baseline with a minimum of a 6-point increase in PASI score relative to week 33). Of the patients who lost adequate response after re-randomisation to placebo who then enrolled into the open-label extension trial, 38% (25/66) and 55% (36/66) regained PASI 75 response after 12 and 24 weeks of re-treatment, respectively.

A total of 233 PASI 75 responders at week 16 and week 33 received continuous adalimumab therapy for 52 weeks in psoriasis study I, and continued adalimumab in the open-label extension trial. PASI 75 and PGA of clear or minimal response rates in these patients were 74.7% and 59.0%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks). In an analysis in which all patients who dropped out of the study for adverse events or lack of efficacy, or who dose-escalated, were considered non-responders, PASI 75 and PGA of clear or minimal response rates in these patients were 69.6% and 55.7%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. During the withdrawal period, symptoms of psoriasis returned over time with a median time to relapse (decline to PGA “moderate” or worse) of approximately 5 months. None of these patients experienced

rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the retreatment period had a response of PGA “clear” or “minimal” after 16 weeks of retreatment, irrespective of whether they relapsed during withdrawal (69.1% [123/178] and 88.8% [95/107] for patients who relapsed and who did not relapse during the withdrawal period, respectively). A similar safety profile was observed during retreatment as before withdrawal.

Significant improvements at week 16 from baseline compared to placebo (Studies I and II) and MTX (Study II) were demonstrated in the DLQI (Dermatology Life Quality Index). In Study I, improvements in the physical and mental component summary scores of the SF-36 were also significant compared to placebo.

In an open-label extension study, for patients who dose escalated from 40 mg every other week to 40 mg weekly due to a PASI response below 50%, 26.4% (92/349) and 37.8% (132/349) of patients achieved PASI 75 response at week 12 and 24, respectively.

Psoriasis study III (REACH) compared the efficacy and safety of adalimumab versus placebo in 72 patients with moderate to severe chronic plaque psoriasis and hand and/or foot psoriasis. Patients received an initial dose of 80 mg adalimumab followed by 40 mg every other week (starting one week after the initial dose) or placebo for 16 weeks. At week 16, a statistically significantly greater proportion of patients who received adalimumab achieved PGA of 'clear' or 'almost clear' for the hands and/or feet compared to patients who received placebo (30.6% versus 4.3%, respectively [$P = 0.014$]).

Psoriasis study IV compared efficacy and safety of adalimumab versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg adalimumab followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open-label adalimumab treatment for an additional 26 weeks. Nail psoriasis assessments included the Modified Nail Psoriasis Severity Index (mNAPSI), the Physician’s Global Assessment of Fingernail Psoriasis (PGA-F) and the Nail Psoriasis Severity Index (NAPSI) (see Table 16). adalimumab demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement ($BSA \geq 10\%$ (60% of patients) and $BSA < 10\%$ and $\geq 5\%$ (40% of patients)).

Table 16: Ps study IV efficacy results at 16, 26 and 52 weeks

Endpoint	Week 16 Placebo-controlled		Week 26 Placebo-controlled		Week 52 Open-label
	Placebo N=108	Adalimumab 40 mg eow N=109	Placebo N=108	Adalimumab 40 mg eow N=109	Adalimumab 40 mg eow N=80
≥ mNAPSI 75 (%)	2.9	26.0 ^a	3.4	46.6 ^a	65.0
PGA-F clear/minimal and ≥2-grade improvement (%)	2.9	29.7 ^a	6.9	48.9 ^a	61.3
Percent Change in Total Fingernail NAPSI (%)	-7.8	-44.2 ^a	-11.5	-56.2 ^a	-72.2

^a p<0.001, adalimumab *versus* placebo

Adalimumab-treated patients showed statistically significant improvements at week 26 compared with placebo in the DLQI.

Paediatric Crohn's disease

Adalimumab was assessed in a multicentre, randomised, double-blind clinical trial designed to evaluate the efficacy and safety of induction and maintenance treatment with doses dependent on body weight (< 40 kg or ≥ 40 kg) in 192 paediatric subjects between the ages of 6 and 17 (inclusive) years, with moderate to severe Crohn's disease (CD) defined as Paediatric Crohn's Disease Activity Index (PCDAI) score > 30. Subjects had to have failed conventional therapy (including a corticosteroid and/or an immunomodulator) for CD. Subjects may also have previously lost response or been intolerant to infliximab.

All subjects received open-label induction therapy at a dose based on their baseline body weight: 160 mg at week 0 and 80 mg at week 2 for subjects ≥ 40 kg, and 80 mg and 40 mg, respectively, for subjects < 40 kg.

At week 4, subjects were randomised 1:1 based on their body weight at the time to either the Low Dose or Standard Dose maintenance regimens as shown in Table 17.

Table 17: Maintenance regimen

Patient Weight	Low dose	Standard dose
< 40 kg	10 mg eow	20 mg eow
≥ 40 kg	20 mg eow	40 mg eow

Efficacy results

The primary endpoint of the study was clinical remission at week 26, defined as PCDAI score ≤ 10 .

Clinical remission and clinical response (defined as reduction in PCDAI score of at least 15 points from baseline) rates are presented in Table 18. Rates of discontinuation of corticosteroids or immunomodulators are presented in Table 19.

	Standard dose 40/20 mg eow N = 93	Low dose 20/10 mg eow N = 95	P value*
Week 26			
Clinical remission	38.7%	28.4%	0.075
Clinical response	59.1%	48.4%	0.073
Week 52			
Clinical remission	33.3%	23.2%	0.100
Clinical response	41.9%	28.4%	0.038

* p value for Standard Dose versus Low Dose comparison.

	Standard dose 40/20 mg eow	Low dose 20/10 mg eow	P value¹
Discontinued corticosteroids	N= 33	N=38	
Week 26	84.8%	65.8%	0.066
Week 52	69.7%	60.5%	0.420
Discontinuation of immunomodulators²	N=60	N=57	
Week 52	30.0%	29.8%	0.983
Fistula remission³	N=15	N=21	
Week 26	46.7%	38.1%	0.608
Week 52	40.0%	23.8%	0.303

¹ p value for Standard Dose versus Low Dose comparison.

² Immunosuppressant therapy could only be discontinued at or after week 26 at the investigator's discretion if the subject met the clinical response criterion

³ defined as a closure of all fistulas that were draining at baseline for at least 2 consecutive post-baseline visits

Statistically significant increases (improvement) from baseline to week 26 and 52 in Body Mass Index and height velocity were observed for both treatment groups.

Statistically and clinically significant improvements from baseline were also observed in both treatment groups for quality of life parameters (including IMPACT III).

One hundred patients (n=100) from the Paediatric CD Study continued in an open-label long-term extension study. After 5 years of adalimumab therapy, 74.0% (37/50) of the 50 patients remaining in the study continued to be in clinical remission, and 92.0% (46/50) of patients continued to be in clinical response per PDAI.

Adult Crohn's disease

The safety and efficacy of adalimumab were assessed in over 1,500 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomised, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 80% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies, CD Study I (CLASSIC I) and CD Study II (GAIN). In CD Study I, 299 TNF-antagonist naive patients were randomised to one of four treatment groups; placebo at weeks 0 and 2, 160 mg adalimumab at week 0 and 80 mg at week 2, 80 mg at week 0 and 40 mg at week 2, and 40 mg at week 0 and 20 mg at week 2. In CD Study II, 325 patients who had lost response or were intolerant to infliximab were randomised to receive either 160 mg adalimumab at week 0 and 80 mg at week 2 or placebo at weeks 0 and 2. The primary non-responders were excluded from the studies and therefore these patients were not further evaluated.

Maintenance of clinical remission was evaluated in CD study III (CHARM). In CD Study III, 854 patients received open-label 80 mg at week 0 and 40 mg at week 2. At week 4 patients were randomised to 40 mg every other week, 40 mg every week, or placebo with a total study duration of 56 weeks. Patients in clinical response (decrease in CDAI ≥ 70) at week 4 were stratified and analysed separately from those not in clinical response at week 4. Corticosteroid taper was permitted after week 8.

CD study I and CD study II induction of remission and response rates are presented in Table 20.

Table 20: Induction of clinical remission and response (percent of patients)

	CD study I: infliximab naive patients			CD study II: infliximab experienced patients	
	Placebo N=74	Adalimumab 80/40 mg N = 75	Adalimumab 160/80 mg N=76	Placebo N=166	Adalimumab 160/80 mg N=159
Week 4					
Clinical remission	12%	24%	36% *	7%	21% *
Clinical response (CR-100)	24%	37%	49% **	25%	38% **

All p-values are pairwise comparisons of proportions for adalimumab *versus* placebo

* p < 0.001

** p < 0.01

Similar remission rates were observed for the 160/80 mg and 80/40 mg induction regimens by week 8 and adverse events were more frequently noted in the 160/80 mg group.

In CD Study III, at week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. Of those in clinical response at week 4, 48% had been previously exposed to other TNF-antagonists. Maintenance of remission and response rates are presented in Table 21. Clinical remission results remained relatively constant irrespective of previous TNF-antagonist exposure.

Disease-related hospitalisations and surgeries were statistically significantly reduced with adalimumab compared with placebo at week 56.

Table 21: Maintenance of clinical remission and response (percent of patients)

	Placebo	40 mg adalimumab every other week	40 mg adalimumab every week
Week 26	N=170	N=172	N=157
Clinical remission	17%	40%*	47%*
Clinical response (CR-100)	27%	52%*	52%*
Patients in steroid-free remission for ≥ 90 days ^a	3% (2/66)	19% (11/58)**	15% (11/74)**
Week 56	N=170	N=172	N=157
Clinical remission	12%	36%*	41%*
Clinical response (CR-100)	17%	41%*	48%*
Patients in steroid-free remission for ≥ 90 days ^a	5% (3/66)	29% (17/58)*	20% (15/74)**

* p < 0.001 for adalimumab *versus* placebo pairwise comparisons of proportions

** p < 0.02 for adalimumab *versus* placebo pairwise comparisons of proportions

^a Of those receiving corticosteroids at baseline

Among patients who were not in response at week 4, 43% of adalimumab maintenance patients responded by week 12 compared to 30% of placebo maintenance patients. These results suggest that some patients who have not responded by week 4 benefit from continued maintenance therapy through week 12. Therapy continued beyond 12 weeks did not result in significantly more responses (see section 4.2).

117/276 patients from CD study I and 272/777 patients from CD studies II and III were followed through at least 3 years of open-label adalimumab therapy. 88 and 189 patients, respectively, continued to be in clinical remission. Clinical response (CR-100) was maintained in 102 and 233 patients, respectively.

Quality of life

In CD Study I and CD Study II, statistically significant improvement in the disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at week 4 in patients randomised to adalimumab 80/40 mg and 160/80 mg compared to placebo and was seen at weeks 26 and 56 in CD Study III as well among the adalimumab treatment groups compared to the placebo group.

Paediatric uveitis

The safety and efficacy of adalimumab was assessed in a randomized, double-masked, controlled study of 90 paediatric patients from 2 to < 18 years of age with active JIA-associated noninfectious anterior uveitis who were refractory to at least 12 weeks of methotrexate treatment. Patients received either placebo or 20 mg adalimumab (if < 30 kg) or 40 mg adalimumab (if \geq 30 kg) every other week in combination with their baseline dose of methotrexate.

The primary endpoint was 'time to treatment failure'. The criteria determining treatment failure were worsening or sustained non-improvement in ocular inflammation, partial improvement with development of sustained ocular co-morbidities or worsening of ocular co-morbidities, non-permitted use of concomitant medications, and suspension of treatment for an extended period of time.

Clinical response

Adalimumab significantly delayed the time to treatment failure, as compared to placebo (See Figure 1, $P < 0.0001$ from log rank test). The median time to treatment failure was 24.1 weeks for subjects treated with placebo, whereas the median time to treatment failure was not estimable for subjects treated with adalimumab because less than one-half of these subjects experienced treatment failure. Adalimumab significantly decreased the risk of treatment failure by 75% relative to placebo, as shown by the hazard ratio (HR = 0.25 [95% CI: 0.12, 0.49]).

Study UV II evaluated 226 patients with inactive uveitis requiring chronic corticosteroid treatment (oral prednisone 10 to 35 mg/day) at baseline to control their disease. Patients subsequently underwent a mandatory taper schedule, with complete corticosteroid discontinuation by week 19.

The primary efficacy endpoint in both studies was ‘time to treatment failure’. Treatment failure was defined by a multi-component outcome based on inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber (AC) cell grade, vitreous haze (VH) grade and best corrected visual acuity (BCVA).

Patients who completed studies UV I and UV II were eligible to enroll in an uncontrolled long-term extension study with an originally planned duration of 78 weeks. Patients were allowed to continue on study medication beyond week 78 until they had access to adalimumab.

Clinical response

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with adalimumab versus patients receiving placebo (See Table 22). Both studies demonstrated an early and sustained effect of adalimumab on the treatment failure rate versus placebo (see Figure 2).

Table 22: Time to Treatment Failure in Studies UV I and UV II

Analysis Treatment	N	Failure N (%)	Median time to failure (months)	HR ^a	CI 95% for HR ^a	P value ^b
Time to treatment failure at or after week 6 in study UV I						
Primary analysis (ITT)						
Placebo	107	84 (78.5)	3.0	--	--	--
Adalimumab	110	60 (54.5)	5.6	0.50	0.36, 0.70	< 0.001
Time to treatment failure at or after week 2 in study UV II						
Primary analysis (ITT)						
Placebo	111	61 (55.0)	8.3	--	--	--
Adalimumab	115	45 (39.1)	NE ^c	0.57	0.39, 0.84	0.004

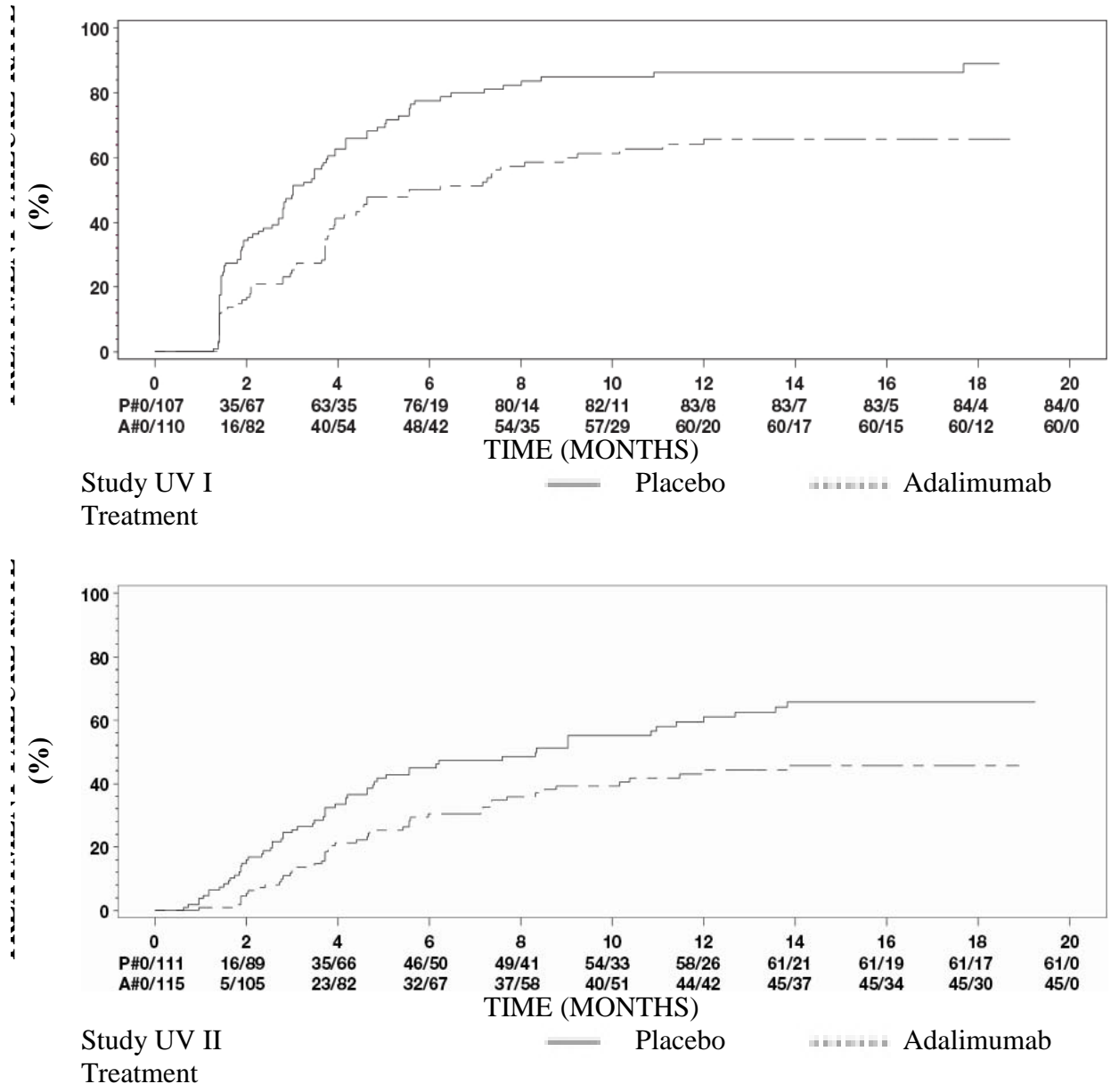
Note: Treatment failure at or after week 6 (Study UV I), or at or after week 2 (Study UV II), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

^a HR of adalimumab *versus* placebo from proportional hazards regression with treatment as factor.

^b 2-sided P value from log rank test.

^c NE = not estimable. Fewer than half of at-risk subjects had an event.

Figure 2: Kaplan-Meier curves summarizing time to treatment failure on or after week 6 (Study UV I) or week 2 (Study UV II)



Note: P# = Placebo (Number of Events/Number at Risk); A# = Adalimumab (Number of Events/Number at Risk).

In study UV I statistically significant differences in favour of adalimumab versus placebo were observed for each component of treatment failure. In study UV II, statistically significant differences were observed for visual acuity only, but the other components were numerically in favour of adalimumab.

Of the 424 subjects included in the uncontrolled long-term extension of studies UV I and UV II, 60 subjects were regarded ineligible (e.g. due to deviations or due to complications secondary to diabetic retinopathy, due to cataract surgery or vitrectomy) and were excluded from the primary analysis of efficacy. Of the 364 remaining patients, 269 evaluable patients (74%) reached 78 weeks of open-label

adalimumab treatment. Based on the observed data approach, 216 (80.3%) were in quiescence (no active inflammatory lesions, AC cell grade $\leq 0.5+$, VH grade $\leq 0.5+$) with a concomitant steroid dose ≤ 7.5 mg per day, and 178 (66.2%) were in steroid-free quiescence. BCVA was either improved or maintained (< 5 letters deterioration) in 88.6% of the eyes at week 78. Data beyond week 78 were generally consistent with these results but the number of enrolled subjects declined after this time. Overall, among the patients who discontinued the study, 18% discontinued due to adverse events, and 8% due to insufficient response to adalimumab treatment.

Quality of life

Patient reported outcomes regarding vision-related functioning were measured in both clinical studies, using the NEI VFQ-25. Adalimumab was numerically favoured for the majority of subscores with statistically significant mean differences for general vision, ocular pain, near vision, mental health, and total score in study UV I, and for general vision and mental health in study UV II. Vision related effects were not numerically in favour of adalimumab for colour vision in study UVI and for colour vision, peripheral vision and near vision in study UV II.

Immunogenicity

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

In patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years, anti-adalimumab antibodies were identified in 15.8% (27/171) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 25.6% (22/86) compared to 5.9% (5/85) when adalimumab was used as add-on to methotrexate. In patients with polyarticular juvenile idiopathic arthritis who were 2 to < 4 years old or aged 4 and above weighing < 15 kg, anti-adalimumab antibodies were identified in 7% (1/15) of patients, and the one patient was receiving concomitant methotrexate.

In patients with enthesitis-related arthritis, anti-adalimumab antibodies were identified in 10.9% (5/46) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 13.6% (3/22), compared to 8.3% (2/24) when adalimumab was used as add-on to methotrexate.

Patients in rheumatoid arthritis studies I, II and III were tested at multiple time points for anti-adalimumab antibodies during the 6 to 12 month period. In the pivotal trials, anti-adalimumab antibodies were identified in 5.5% (58/1053) of patients treated with adalimumab, compared to 0.5% (2/370) on placebo. In patients not given concomitant methotrexate, the incidence was 12.4%, compared to 0.6% when adalimumab was used as add-on to methotrexate.

In patients with paediatric psoriasis, anti-adalimumab antibodies were identified in 5/38 subjects (13%) treated with 0.8 mg/kg adalimumab monotherapy.

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

In adult plaque psoriasis patients on long term adalimumab monotherapy who participated in a withdrawal and retreatment study, the rate of antibodies to adalimumab after retreatment (11 of 482 subjects, 2.3%) was similar to the rate observed prior to withdrawal (11 of 590 subjects, 1.9%).

In patients with moderately to severely active paediatric Crohn's disease, the rate of anti-adalimumab antibody development in patients receiving adalimumab was 3.3%.

In patients with Crohn's disease, anti-adalimumab antibodies were identified in 7/269 subjects (2.6%).

In adult patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab.

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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of the studies with adalimumab in one or more subsets of the paediatric population in ulcerative colitis, see section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption and distribution

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.

In patients with polyarticular JIA who were 2 to < 4 years old or aged 4 and above weighing < 15 kg dosed with adalimumab 24 mg/m², the mean trough steady-state

serum adalimumab concentrations was $6.0 \pm 6.1 \mu\text{g/ml}$ (101% CV) for adalimumab without concomitant methotrexate and $7.9 \pm 5.6 \mu\text{g/ml}$ (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 who were 6 to 17 years, the mean trough steady-state (values measured at week 24) serum adalimumab concentrations were $8.8 \pm 6.6 \mu\text{g/ml}$ for adalimumab without concomitant methotrexate and $11.8 \pm 4.3 \mu\text{g/ml}$ with concomitant methotrexate.

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 \pm SD steady-state adalimumab trough concentration was approximately $7.4 \pm 5.8 \mu\text{g/ml}$ (79% CV).

In paediatric patients with moderate to severe CD, 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 randomised 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 (\pm SD) serum adalimumab trough concentrations achieved at week 4 were $15.7 \pm 6.6 \mu\text{g/ml}$ for patients $\geq 40 \text{ kg}$ (160/80 mg) and $10.6 \pm 6.1 \mu\text{g/ml}$ for patients $< 40 \text{ kg}$ (80/40 mg).

For patients who stayed on their randomised therapy, the mean (\pm SD) adalimumab trough concentrations at week 52 were $9.5 \pm 5.6 \mu\text{g/ml}$ for the Standard Dose group and $3.5 \pm 2.2 \mu\text{g/ml}$ 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 (\pm SD) serum concentrations of adalimumab at week 52 were $15.3 \pm 11.4 \mu\text{g/ml}$ (40/20 mg, weekly) and $6.7 \pm 3.5 \mu\text{g/ml}$ (20/10 mg, weekly).

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

Exposure-response relationship in paediatric population

On the basis of clinical trial data in patients with JIA (pJIA and ERA), an exposure-response relationship was established between plasma concentrations and PedACR 50 response. The apparent adalimumab plasma concentration that produces half the maximum probability of PedACR 50 response (EC₅₀) was $3 \mu\text{g/ml}$ (95% CI: 1-6 $\mu\text{g/ml}$).

Exposure-response relationships between adalimumab concentration and efficacy in paediatric patients with severe chronic plaque psoriasis were established for PASI 75 and PGA clear or minimal, respectively. PASI 75 and PGA clear or minimal increased with increasing adalimumab concentrations, both with a similar apparent EC50 of approximately 4.5 µg/mL (95% CI 0.4-47.6 and 1.9-10.5, respectively).

Adults

After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. After single intravenous doses ranging from 0.25 to 10 mg/kg, concentrations were dose proportional. After doses of 0.5 mg/kg (~40 mg), clearances ranged from 11 to 15 ml/hour, the distribution volume (V_{ss}) ranged from 5 to 6 litres and the mean terminal phase half-life was approximately two weeks. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31-96% of those in serum.

Following subcutaneous administration of 40 mg of adalimumab every other week in adult rheumatoid arthritis (RA) patients the mean steady-state trough concentrations were approximately 5 µg/ml (without concomitant methotrexate) and 8 to 9 µg/ml (with concomitant methotrexate), respectively. The serum adalimumab trough levels at steady-state increased roughly proportionally with dose following 20, 40 and 80 mg subcutaneous dosing every other week and every week.

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

In patients with Crohn's disease, the loading dose of 80 mg adalimumab on week 0 followed by 40 mg adalimumab on week 2 achieves serum adalimumab trough concentrations of approximately 5.5 µg/ml during the induction period. A loading dose of 160 mg adalimumab on week 0 followed by 80 mg adalimumab on week 2 achieves serum adalimumab trough concentrations of approximately 12 µg/ml during the induction period. Mean steady-state trough levels of approximately 7 µg/ml were observed in Crohn's disease patients who received a maintenance dose of 40 mg adalimumab every other week.

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

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, patients with adolescent HS, and paediatric patients \geq 40 kg with CD).

Elimination

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

Hepatic or renal impairment

Adalimumab has not been studied in patients with hepatic or renal impairment.

5.3 Preclinical safety data

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

An embryo-foetal developmental toxicity/perinatal developmental study has been performed in cynomolgous monkeys at 0, 30 and 100 mg/kg (9-17 monkeys/group) and has revealed no evidence of harm to the foetuses due to adalimumab. Neither carcinogenicity studies, nor a standard assessment of fertility and postnatal toxicity, were performed with adalimumab due to the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and to the development of neutralising antibodies in rodents.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monosodium glutamate

Sorbitol (E420)

Methionine

Polysorbate 80

Hydrochloric acid (for pH-adjustment)

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

Hulio 20 mg solution for injection in single-use pre-filled syringe with an automatic needle guard. The syringe is made from cyclo olefin polymer plastic with a stopper (chlorobutyl rubber) and a needle (stainless steel) with a needle cap (butyl /diene blend polymer and polypropylene).

Pack sizes of:

- 1 pre-filled syringe (with 2 alcohol pads)
- 2 pre-filled syringes (with 2 alcohol pads)

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.

7 MARKETING AUTHORISATION HOLDER

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Dublin
D13 R20R
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 58141/0007

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

10/01/2025

10 DATE OF REVISION OF THE TEXT

10/01/2025