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Before you contact this company: often several companies will market medicines with the same active ingredient. Please check that this is the correct company before contacting them. Why?

Summary of Product Characteristics last updated on the eMC: 25/10/2011

Enbrel 50mg solution for injection in pre-filled syringe

This medicine is monitored intensively by the CHM and MHRA

1. NAME OF THE MEDICINAL PRODUCT

Enbrel® 50 mg solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 50 mg of etanercept.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. Etanercept is a dimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. This Fc component contains the hinge, CH₂ and CH₃ regions, but not the CH₁ region of IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. The specific activity of etanercept is 1.7 x 10⁶ units/mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear, and colourless or pale yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Enbrel in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

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

Enbrel is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Enbrel, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Enbrel has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Ankylosing spondylitis

Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Plaque psoriasis

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1).

Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

4.2 Posology and method of administration

Enbrel treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis or paediatric plaque psoriasis. Patients treated with Enbrel should be given the Patient Alert Card.

Enbrel is available in strengths of 10, 25 and 50 mg.

Posology

Rheumatoid arthritis

25 mg Enbrel administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective (see section 5.1).

Psoriatic arthritis and ankylosing spondylitis

The recommended dose is 25 mg Enbrel administered twice weekly, or 50 mg administered once weekly.

Plaque psoriasis

The recommended dose of Enbrel is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients (see section 5.1). Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Enbrel is indicated, the same guidance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly.

Special populations

Renal and hepatic impairment

No dose adjustment is required.

Elderly (≥ 65 years)

No dose adjustment is required. Posology and administration are the same as for adults 18-64 years of age.

Paediatric population

The dosage of Enbrel is based on body weight for paediatric patients. Patients weighing less than 62.5 kg should be accurately dosed on a mg/kg basis using Enbrel 25 mg/ml powder and solvent for solution for injection for paediatric use (see below for dosing for specific indications). Patients weighing 62.5 kg or more, may be dosed using a fixed-dose pre-filled syringe or pre-filled pen.

Paediatric plaque psoriasis (age 6 years and above)

The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

If re-treatment with Enbrel is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.

There is generally no applicable use of Enbrel in children aged below 6 years in the indication plaque psoriasis.

Method of administration
Enbrel is administered by subcutaneous injection.

Comprehensive instructions for administration are given in the package leaflet, section 7, "Instructions for preparation and giving an injection of Enbrel”.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Sepsis or risk of sepsis.

Treatment with Enbrel should not be initiated in patients with active infections, including chronic or localised infections.

4.4 Special warnings and precautions for use

Infections

Patients should be evaluated for infections before, during, and after treatment with Enbrel, taking into consideration that the mean elimination half-life of etanercept is approximately 70 hours (range 7 to 300 hours).

Serious infections, sepsis, tuberculosis, and opportunistic infections, including invasive fungal infections, have been reported with the use of Enbrel (see section 4.8). These infections were due to bacteria, mycobacteria, fungi and viruses. In some cases, particular fungal and other opportunistic infections have not been recognised, resulting in delay of appropriate treatment and sometimes death. In evaluating patients for infections, the patient’s risk for relevant opportunistic infections (e.g., exposure to endemic mycoses) should be considered.

Patients who develop a new infection while undergoing treatment with Enbrel should be monitored closely. Administration of Enbrel should be discontinued if a patient develops a serious infection. The safety and efficacy of Enbrel in patients with chronic infections have not been evaluated. Physicians should exercise caution when considering the use of Enbrel in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections, such as advanced or poorly controlled diabetes.

Tuberculosis

Cases of active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary location, have been reported in patients treated with Enbrel.

Before starting treatment with Enbrel, all patients must be evaluated for both active and inactive (‘latent’) tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with 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 of these tests should be recorded in the patient’s alert 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, Enbrel therapy must not be initiated. If inactive (‘latent’) tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of Enbrel, and in accordance with local recommendations. In this situation, the benefit/risk balance of Enbrel therapy should be very carefully considered.

All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g., persistent cough, wasting/weight loss, low-grade fever) appear during or after Enbrel treatment.

Hepatitis B virus reactivation

Reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus who are receiving TNF-antagonists, including Enbrel, has been reported. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating Enbrel therapy. Caution should be exercised when administering Enbrel to patients identified as carriers of HBV. If Enbrel is used in carriers of HBV, the patients should be monitored for signs and symptoms of active HBV infection, and, if necessary, appropriate treatment should be initiated.

Worsening of hepatitis C

There have been reports of worsening of hepatitis C in patients receiving Enbrel. Enbrel should be used with caution in patients with a history of hepatitis C.

Concurrent treatment with anakinra

Concurrent administration of Enbrel and anakinra has been associated with an increased risk of serious infections and neutropenia compared to Enbrel alone. This combination has not demonstrated increased clinical benefit. Thus, the combined use of Enbrel and anakinra is not recommended (see sections 4.5 and 4.8).
Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.5).

Allergic reactions

The needle cover of the pre-filled syringe contains latex (dry natural rubber) that may cause hypersensitivity reactions when handled by or when Enbrel is administered to persons with known or possible latex sensitivity.

Allergic reactions associated with Enbrel administration have been reported commonly. Allergic reactions have included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, Enbrel therapy should be discontinued immediately and appropriate therapy initiated.

Immunosuppression

The possibility exists for TNF-antagonists, including Enbrel, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 adult patients with rheumatoid arthritis treated with Enbrel, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations.

Two juvenile idiopathic arthritis patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue Enbrel therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

The safety and efficacy of Enbrel in patients with immunosuppression have not been evaluated.

Malignancies and lymphoproliferative disorders

Solid and haematopoietic malignancies (excluding skin cancers)

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the postmarketing period (see section 4.8).

In the controlled portions of clinical trials of TNF-antagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. In the postmarketing setting, cases of leukaemia have been reported in patients treated with TNF-antagonists. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.

Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

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

Skin cancers

Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including Enbrel. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with Enbrel. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Combining the results of controlled clinical trials, more cases of NMSC were observed in patients receiving Enbrel compared with control patients, particularly in patients with psoriasis.

Vaccinations

Live vaccines should not be given concurrently with Enbrel. No data are available on the secondary transmission of infection by live vaccines in patients receiving Enbrel. In a double-blind, placebo-controlled, randomised clinical study in adult patients with psoriatic arthritis, 184 patients also received a multivalent pneumococcal polysaccharide vaccine at week 4. In this study, most psoriatic arthritis patients receiving Enbrel were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titres in aggregate were moderately lower, and few patients had two-fold rises in titres compared to patients not receiving Enbrel. The clinical significance of this is unknown.
Autoantibody formation

Treatment with Enbrel may result in the formation of autoimmune antibodies (see section 4.8).

Haematologic reactions

Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with Enbrel. Caution should be exercised in patients being treated with Enbrel who have a previous history of blood dyscrasias. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on Enbrel, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, Enbrel should be discontinued.

Neurological disorders

There have been rare reports of CNS demyelinating disorders in patients treated with Enbrel (see section 4.8). Additionally, there have been very rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating Enbrel therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing Enbrel to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

Combination therapy

In a controlled clinical trial of two years duration in rheumatoid arthritis patients, the combination of Enbrel and methotrexate did not result in unexpected safety findings, and the safety profile of Enbrel when given in combination with methotrexate was similar to the profiles reported in studies of Enbrel and methotrexate alone. Long-term studies to assess the safety of the combination are ongoing. The long-term safety of Enbrel in combination with other disease-modifying antirheumatic drugs (DMARD) has not been established.

The use of Enbrel in combination with other systemic therapies or phototherapy for the treatment of psoriasis has not been studied.

Renal and hepatic impairment

Based on pharmacokinetic data (see section 5.2), no dose adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited.

Congestive heart failure

Physicians should use caution when using Enbrel in patients who have congestive heart failure (CHF). There have been postmarketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking Enbrel. Two large clinical trials evaluating the use of Enbrel in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data from one of these trials suggest a possible tendency toward worsening CHF in those patients assigned to Enbrel treatment.

Alcoholic hepatitis

In a phase II randomised placebo-controlled study of 48 hospitalised patients treated with Enbrel or placebo for moderate to severe alcoholic hepatitis, Enbrel was not efficacious, and the mortality rate in patients treated with Enbrel was significantly higher after 6 months. Consequently, Enbrel should not be used in patients for the treatment of alcoholic hepatitis. Physicians should use caution when using Enbrel in patients who also have moderate to severe alcoholic hepatitis.

Wegener's granulomatosis

A placebo-controlled trial, in which 89 adult patients were treated with Enbrel in addition to standard therapy (including cyclophosphamide or methotrexate, and glucocorticoids) for a median duration of 25 months, has not shown Enbrel to be an effective treatment for Wegener’s granulomatosis. The incidence of non-cutaneous malignancies of various types was significantly higher in patients treated with Enbrel than in the control group. Enbrel is not recommended for the treatment of Wegener’s granulomatosis.

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of Enbrel in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

Special populations

Elderly patients (≥ 65 years)
In the Phase 3 studies in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, no overall differences in adverse events, serious adverse events, and serious infections in patients age 65 or older who received Enbrel were observed compared with younger patients.

However, caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections.

**Paediatric population**

**Vaccinations**

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 Enbrel therapy.

**Inflammatory bowel disease (IBD) in patients with juvenile idiopathic arthritis (JIA)**

There have been reports of IBD in JIA patients being treated with Enbrel (see section 4.8).

### 4.5 Interaction with other medicinal products and other forms of interaction

**Concurrent treatment with anakinra**

Adult patients treated with Enbrel and anakinra were observed to have a higher rate of serious infection when compared with patients treated with either Enbrel or anakinra alone (historical data).

In addition, in a double-blind, placebo-controlled trial in adult patients receiving background methotrexate, patients treated with Enbrel and anakinra were observed to have a higher rate of serious infections (7%) and neutropenia than patients treated with Enbrel (see sections 4.4 and 4.8). The combination Enbrel and anakinra has not demonstrated increased clinical benefit, and is therefore not recommended.

**Concurrent treatment with abatacept**

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.4).

**Concurrent treatment with sulfasalazine**

In a clinical study of adult patients who were receiving established doses of sulfasalazine, to which Enbrel was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with Enbrel or sulfasalazine alone. The clinical significance of this interaction is unknown. Physicians should use caution when considering combination therapy with sulfasalazine.

**Non-interactions**

In clinical trials, no interactions have been observed when Enbrel was administered with glucocorticoids, salicylates (except sulfasalazine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate. See section 4.4 for vaccination advice.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with digoxin or warfarin.

### 4.6 Pregnancy and lactation

**Women of childbearing potential**

Women of childbearing potential should be advised to use appropriate contraception to avoid becoming pregnant during Enbrel therapy and for three weeks after discontinuation of therapy.

**Pregnancy**

Developmental toxicity studies performed in rats and rabbits have revealed no evidence of harm to the foetus or neonatal rat due to etanercept. There are no studies of Enbrel in pregnant women. Thus, Enbrel is not recommended during pregnancy.

**Breast-feeding**

It is not known whether etanercept is excreted in human milk. Following subcutaneous administration to lactating rats, etanercept was excreted in the milk and detected in the serum of pups. Because immunoglobulins, in common with many medicinal products, can be excreted in human milk, a decision must be made whether to discontinue breast-feeding or to discontinue Enbrel therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

### 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), infections (such as upper respiratory infections, bronchitis, bladder infections and skin infections), allergic reactions, development of autoantibodies, itching, and fever.

Serious adverse reactions have also been reported for Enbrel. TNF-antagonists, such as Enbrel, affect the immune system and their use may affect the body's defenses against infection and cancer. Serious infections affect fewer than 1 in 100 patients treated with Enbrel. Reports have included fatal and life-threatening infections and sepsis. Various malignancies have also been reported with use of Enbrel, including cancers of the breast, lung, skin and lymph glands (lymphoma).

Serious haematological, neurological and autoimmunological reactions have also been reported. These include rare reports of pancytopenia and very rare reports of aplastic anaemia. Central and peripheral demyelinating events have been seen rarely and very rarely, respectively, with Enbrel use. There have been rare reports of lupus, lupus-related conditions, and vasculitis.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials in adults and on postmarketing experience.

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1000 to <1/100); rare (≥ 1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from the available data).

**Infections and infestations:**
- Very common: Infections (including upper respiratory tract infections, bronchitis, cystitis, skin infections)*
- Uncommon: Serious infections (including pneumonia, cellulitis, septic arthritis, sepsis)*
- Rare: Tuberculosis, opportunistic infections (including invasive fungal, protozoal, bacterial and atypical mycobacterial infections)*

**Neoplasms benign, malignant and unspecified (including cysts and polyps):**
- Uncommon: Non-melanoma skin cancers* (see section 4.4)
- Rare: Lymphoma, melanoma (see section 4.4)
- Not known: Leukaemia, Merkel cell carcinoma (see section 4.4)

**Blood and lymphatic system disorders:**
- Uncommon: Thrombocytopenia
- Rare: Anaemia, leukopenia, neutropenia, pancytopenia*
- Very rare: Aplastic anaemia*

**Immune system disorders:**
- Common: Allergic reactions (see Skin and subcutaneous tissue disorders), autoantibody formation*
- Uncommon: Systemic vasculitis (including anti-neutrophilic cytoplasmic antibody positive vasculitis)
- Rare: Serious allergic/anaphylactic reactions (including angioedema, bronchospasm)
- Not known: Macrophage activation syndrome*

**Nervous system disorders:**
- Rare: Seizures
- Very rare: CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis (see section 4.4), sarcoidosis

**Eye disorders:**
- Uncommon: Uveitis

**Cardiac disorders:**
- Rare: Worsening of congestive heart failure (see section 4.4)

**Respiratory, thoracic and mediastinal disorders:**
- Uncommon: Interstitial lung disease (including pneumonitis and pulmonary fibrosis)*
Side effects:

**Hepatobiliary disorders:**
- Rare: Elevated liver enzymes, autoimmune hepatitis

**Skin and subcutaneous tissue disorders:**
- Common: Pruritus
- Uncommon: Angioedema, urticaria, rash, psoriasiform rash, psoriasis (including new onset or worsening and pustular, primarily palms and soles)
- Rare: Cutaneous vasculitis (including leukocytoclastic vasculitis), Stevens-Johnson syndrome, erythema multiforme
- Very rare: Toxic epidermal necrolysis

**Musculoskeletal and connective tissue disorders:**
- Rare: Subacute cutaneous lupus erythematosus, discoid lupus erythematosus, lupus-like syndrome

**General disorders and administration site conditions:**
- Very common: Injection site reactions (including bleeding, bruising, erythema, itching, pain, swelling)*
- Common: Fever

*see Description of selected adverse reactions, below.

### Description of selected adverse reactions

#### Malignancies and lymphoproliferative disorders

One hundred and twenty-nine (129) new malignancies of various types were observed in 4,114 rheumatoid arthritis patients treated in clinical trials with Enbrel for up to approximately 6 years, including 231 patients treated with Enbrel in combination with methotrexate in the 2-year active-controlled study. The observed rates and incidences in these clinical trials were similar to those expected for the population studied. A total of 2 malignancies were reported in clinical studies of approximately 2 years duration involving 240 Enbrel-treated psoriatic arthritis patients. In clinical studies conducted for more than 2 years with 351 ankylosing spondylitis patients, 6 malignancies were reported in Enbrel-treated patients. In a group of 2,711 plaque psoriasis patients treated with Enbrel in double-blind and open-label studies of up to 2.5 years, 30 malignancies and 43 nonmelanoma skin cancers were reported.

In a group of 7,416 patients treated with Enbrel in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis clinical trials, 18 lymphomas were reported.

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the postmarketing period (see section 4.4).

#### Injection site reactions

Compared to placebo, patients with rheumatic diseases treated with Enbrel had a significantly higher incidence of injection site reactions (36% vs. 9%). Injection site reactions usually occurred in the first month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the Enbrel treatment groups, and the majority of patients who were given treatment received topical preparations, such as corticosteroids, or oral antihistamines. Additionally, some patients developed recall injection site reactions characterised by a skin reaction at the most recent site of injection, along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment.

In controlled trials in patients with plaque psoriasis, approximately 13.6% of patients treated with Enbrel developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.

#### Serious infections

In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life-threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with Enbrel for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and wound infection.

In the 2-year active-controlled study where patients were treated with either Enbrel alone, methotrexate alone or Enbrel in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of Enbrel with methotrexate could be associated with an increase in the rate of infections.

There were no differences in rates of infection among patients treated with Enbrel and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by Enbrel-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis, gastritis,
appendicitis, *Streptococcal* fasciitis, myositis, septic shock, diverticulitis and abscess. In the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (pneumonia).

Serious and fatal infections have been reported during use of Enbrel; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Some have occurred within a few weeks after initiating treatment with Enbrel in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see section 4.4). Enbrel treatment may increase mortality in patients with established sepsis.

Opportunistic infections have been reported in association with Enbrel, including invasive fungal, protozoal, bacterial (including *Listeria and Legionella*), and atypical mycobacterial infections. In a pooled data set of clinical trials, the overall incidence of opportunistic infections was 0.09% for the 15,402 subjects who received Enbrel. The exposure-adjusted rate was 0.06 events per 100 patient-years. In postmarketing experience, approximately half of all of the case reports of opportunistic infections worldwide were invasive fungal infections. The most commonly reported invasive fungal infections were *Pneumocystis* and *Aspergillus*. Invasive fungal infections accounted for more than half of the fatalities amongst patients who developed opportunistic infections. The majority of the reports with a fatal outcome were in patients with *Pneumocystis* pneumonia, unspecific systemic fungal infections, and aspergillosis (see section 4.4).

**Autoantibodies**

Adult patients had serum samples tested for autoantibodies at multiple timepoints. Of the rheumatoid arthritis patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥ 1:40) was higher in patients treated with Enbrel (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with Enbrel compared to 4% of placebo-treated patients) and by *Citrhida luicaiae* assay (3% of patients treated with Enbrel compared to none of placebo-treated patients). The proportion of patients treated with Enbrel who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. The impact of long-term treatment with Enbrel on the development of autoimmune diseases is unknown.

There have been rare reports of patients, including rheumatoid factor positive patients, who have developed other autoantibodies in conjunction with a lupus-like syndrome or rashes that are compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy.

**Pancytopenia and aplastic anaemia**

There have been postmarketing reports of pancytopenia and aplastic anaemia, some of which had fatal outcomes (see section 4.4).

**Interstitial lung disease**

There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

**Concurrent treatment with anakinra**

In studies when adult patients received concurrent treatment with Enbrel plus anakinra, a higher rate of serious infections compared to Enbrel alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count < 1000/mm³). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see sections 4.4 and 4.5).

**Paediatric population**

Undesirable effects in paediatric patients with plaque psoriasis

In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

There were 4 reports of macrophage activation syndrome in juvenile idiopathic arthritis clinical trials.

There have been reports of inflammatory bowel disease in JIA patients being treated with Enbrel from postmarketing sources, including a very small number of cases indicating a positive rechallenge (see section 4.4).

**4.9 Overdose**

No dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been an intravenous loading dose of 32 mg/m² followed by subcutaneous doses of 16 mg/m² administered twice weekly. One rheumatoid arthritis patient mistakenly self-administered 62 mg Enbrel subcutaneously twice weekly for 3 weeks without experiencing undesirable effects. There is no known antidote to Enbrel.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors, ATC code: L04AB01

TNF and lymphotoxin exist predominantly as homotrimers, with their biological activity dependent on cross-linking of cell surface TNFRs. Dimeric soluble receptors, such as etanercept, possess a higher affinity for TNF than monomeric receptors and are considerably more potent competitive inhibitors of TNF binding to its cellular receptors. In addition, use of an immunoglobulin Fc region as a fusion element in the construction of a dimeric receptor imparts a longer serum half-life.

Mechanism of action

Much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecules that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

Clinical efficacy and safety

This section presents data from four randomised controlled trials in adults with rheumatoid arthritis, one study in adults with psoriatic arthritis, one study in adults with ankylosing spondylitis, four studies in adults with plaque psoriasis and one study in paediatric patients with plaque psoriasis.

Adult patients with rheumatoid arthritis

The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid arthritis who had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs). Doses of 10 mg or 25 mg Enbrel or placebo were administered subcutaneously twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria.

ACR 20 and 50 responses were higher in patients treated with Enbrel at 3 and 6 months than in patients treated with placebo (ACR 20: Enbrel 62% and 59%, placebo 23% and 11% at 3 and 6 months, respectively; ACR 50: Enbrel 41% and 40%, placebo 8% and 5% at months 3 and 6, respectively; p<0.01 Enbrel vs. placebo at all timepoints for both ACR 20 and ACR 50 responses).

Approximately 15% of subjects who received Enbrel achieved an ACR 70 response at month 3 and month 6 compared to fewer than 5% of subjects in the placebo arm. Among patients receiving Enbrel, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen; results with 10 mg were intermediate between placebo and 25 mg. Enbrel was significantly better than placebo in all components of the ACR criteria, as well as other measures of rheumatoid arthritis disease activity not included in the ACR response criteria, such as morning stiffness. A Health Assessment Questionnaire (HAQ), which included disability, vitality, mental health, general health status, and arthritis-associated health status subdomains, was administered every 3 months during the trial. All subdomains of the HAQ were improved in patients treated with Enbrel compared to controls at 3 and 6 months.

After discontinuation of Enbrel, symptoms of arthritis generally returned within a month. Re-introduction of treatment with Enbrel after discontinuation of up to 24 months resulted in the same magnitudes of responses as patients who received Enbrel without interruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 48 months in open-label extension treatment trials when patients received Enbrel without interruption; longer-term experience is not available.

The efficacy of Enbrel was compared to methotrexate in a randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint in 632 adult patients with active rheumatoid arthritis (<3 years duration) who had never received treatment with methotrexate. Doses of 10 mg or 25 mg Enbrel were administered subcutaneously (SC) twice a week for up to 24 months. Methotrexate doses were escalated from...
7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement, including onset of action within 2 weeks with Enbrel 25 mg, was similar to that seen in the previous trials and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with Enbrel 25 mg resulted in substantial improvement at 12 months, with about 44% of patients achieving a normal HAQ score (less than 0.5). This benefit was maintained in Year 2 of this study.

In this study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score. Radiographs of hands/wrists and feet were read at baseline and 6, 12, and 24 months. The 10 mg Enbrel dose had consistently less effect on structural damage than the 25 mg dose. Enbrel 25 mg was significantly superior to methotrexate for erosion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between methotrexate and Enbrel 25 mg. The results are shown in the figure below.

**Radiographic Progression: Comparison of Enbrel vs. Methotrexate in Patients with RA of <3 Years Duration**

In another active-controlled, double-blind, randomised study, clinical efficacy, safety, and radiographic progression in RA patients treated with Enbrel alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg), and the combination of Enbrel and methotrexate initiated concurrently were compared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least 1 disease-modifying antirheumatic drug (DMARD) other than methotrexate.

Patients in the Enbrel in combination with methotrexate therapy group had significantly higher ACR 20, ACR 50, ACR 70 responses and improvement for DAS and HAQ scores at both 24 and 52 weeks than patients in either of the single therapy groups (results shown in table below). Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months.

| Clinical Efficacy Results at 12 Months: Comparison of Enbrel vs. Methotrexate vs. Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration |
|---------------------------------|-----------------|-----------------|-----------------|
| **Endpoint**                   | Methotrexate    | Enbrel          | Enbrel + Methotrexate |
| ***ACR Responses***            | (n = 228)       | (n = 223)       | (n = 231)         |
| ACR 20                         | 58.8%           | 65.5%           | 74.5%            |
| ACR 50                         | 36.4%           | 43.0%           | 63.2%            |
| ACR 70                         | 16.7%           | 22.0%           | 39.8%            |
| **DAS**                        |                 |                 |                  |
| Baseline score                 | 5.5             | 5.7             | 5.5              |

*†p < 0.05*
Radiographic progression at 12 months was significantly less in the Enbrel group than in the methotrexate group, while the combination was significantly better than either monotherapy at slowing radiographic progression (see figure below).

**Radiographic Progression: Comparison of Enbrel vs. Methotrexate vs. Enbrel in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration (12 Month Results)**

![Graph showing radiographic progression](image)

Pairwise comparison p-values: * = p < 0.05 for comparisons of Enbrel vs. methotrexate, † = p < 0.05 for comparisons of Enbrel + methotrexate vs. methotrexate and Φ = p < 0.05 for comparisons of Enbrel + methotrexate vs. Enbrel.

Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the significant advantages for Enbrel monotherapy compared with methotrexate monotherapy were also observed after 24 months.

In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 24 months was higher in the Enbrel in combination with methotrexate group compared with the Enbrel alone and methotrexate alone groups (62%, 50%, and 36%, respectively; p<0.05). The difference between Enbrel alone and methotrexate alone was also significant (p<0.05). Among patients who completed a full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively.

The safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg Enbrel once weekly and 153 patients received 25 mg Enbrel twice weekly. The safety and efficacy profiles of the two Enbrel treatment regimens were comparable at week 8 in their effect on signs and symptoms of RA; data at week 16 did not show comparability (non-inferiority) between the two regimens. A single 50 mg/ml injection of Enbrel was found to be bioequivalent to two simultaneous injections of
25 mg/ml.

Adult patients with psoriatic arthritis

The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study in 205 patients with psoriatic arthritis. Patients were between 18 and 70 years of age and had active psoriatic arthritis (≥ 3 swollen joints and ≥ 3 tender joints) in at least one of the following forms: (1) distal interphalangeal (DIP) involvement; (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis); (3) arthritis mutilans; (4) asymmetric psoriatic arthritis; or (5) spondylitis-like ankylosis. Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Patients had previously been treated with NSAIDs (86%), DMARDs (80%), and corticosteroids (24%). Patients currently on methotrexate therapy (stable for ≥ 2 months) could continue at a stable dose of ≤ 25 mg/week methotrexate. Doses of 25 mg of Enbrel (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered SC twice a week for 6 months. At the end of the double-blind study, patients could enter a long-term open-label extension study for a total duration of up to 2 years.

Clinical responses were expressed as percentages of patients achieving the ACR 20, 50, and 70 response and percentages with improvement in Psoriatic Arthritis Response Criteria (PsARC). Results are summarised in the table below.

Responses of Patients with Psoriatic Arthritis in a Placebo-Controlled Trial

<table>
<thead>
<tr>
<th>Psoriatic Arthritis Response</th>
<th>Placebo</th>
<th>Enbrela</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 104</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACR 20

<table>
<thead>
<tr>
<th>Month 3</th>
<th>15</th>
<th>59b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 6</td>
<td>13</td>
<td>50b</td>
</tr>
</tbody>
</table>

ACR 50

<table>
<thead>
<tr>
<th>Month 3</th>
<th>4</th>
<th>38b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 6</td>
<td>4</td>
<td>37b</td>
</tr>
</tbody>
</table>

ACR 70

<table>
<thead>
<tr>
<th>Month 3</th>
<th>0</th>
<th>11b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 6</td>
<td>1</td>
<td>9c</td>
</tr>
</tbody>
</table>

PsARC

<table>
<thead>
<tr>
<th>Month 3</th>
<th>31</th>
<th>72b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 6</td>
<td>23</td>
<td>70b</td>
</tr>
</tbody>
</table>

a: 25 mg Enbrel SC twice weekly
b: p < 0.001, Enbrel vs. placebo
c: p < 0.01, Enbrel vs. placebo

Among patients with psoriatic arthritis who received Enbrel, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. Enbrel was significantly better than placebo in all measures of disease activity (p < 0.001), and responses were similar with and without concomitant methotrexate therapy. Quality of life in psoriatic arthritis patients was assessed at every timepoint using the disability index of the HAQ. The disability index score was significantly improved at all timepoints in psoriatic arthritis patients treated with Enbrel, relative to placebo (p < 0.001).

Radiographic changes were assessed in the psoriatic arthritis study. Radiographs of hands and wrists were obtained at baseline and months 6, 12, and 24. The modified TSS at 12 months is presented in the table below. In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 12 months was higher in the Enbrel group compared with the placebo group (73% vs. 47%, respectively, p ≤ 0.001). The effect of Enbrel on radiographic progression was maintained in patients who continued on treatment during the second year. The
slowing of peripheral joint damage was observed in patients with polyarticular symmetrical joint involvement.

### Mean (SE) Annualized Change from Baseline in Total Sharp Score

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time</strong></td>
<td>(n = 104)</td>
<td>(n = 101)</td>
</tr>
<tr>
<td><strong>Month 12</strong></td>
<td>1.00 (0.29)</td>
<td>-0.03 (0.09)*</td>
</tr>
</tbody>
</table>

SE = standard error.

a. p = 0.0001.

Enbrel treatment resulted in improvement in physical function during the double-blind period, and this benefit was maintained during the longer-term exposure of up to 2 years.

There is insufficient evidence of the efficacy of Enbrel in patients with ankylosing spondylitis-like and arthritis mutilans psoriatic arthropathies due to the small number of patients studied.

No study has been performed in patients with psoriatic arthritis using the 50 mg once-weekly dosing regimen. Evidence of efficacy for the once-weekly dosing regimen in this patient population has been based on data from the study in patients with ankylosing spondylitis.

**Adult patients with ankylosing spondylitis**

The efficacy of Enbrel in ankylosing spondylitis was assessed in 3 randomised, double-blind studies comparing twice-weekly administration of 25 mg Enbrel with placebo. A total of 401 patients were enrolled, from which 203 were treated with Enbrel. The largest of these trials (n= 277) enrolled patients who were between 18 and 70 years of age and had active ankylosing spondylitis defined as visual analog scale (VAS) scores of ≥ 30 for average of duration and intensity of morning stiffness plus VAS scores of ≥ 30 for at least 2 of the following 3 parameters: patient global assessment; average of VAS values for nocturnal back pain and total back pain; average of 10 questions on the Bath Ankylosing Spondylitis Functional Index (BASFI). Patients receiving DMARDs, NSAIDS, or corticosteroids could continue them on stable doses. Patients with complete ankylosis of the spine were not included in the study. Doses of 25 mg of Enbrel (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered subcutaneously twice a week for 6 months in 138 patients.

The primary measure of efficacy (ASAS 20) was a ≥ 20% improvement in at least 3 of the 4 Assessment in Ankylosing Spondylitis (ASAS) domains (patient global assessments, back pain, BASFI, and inflammation) and absence of deterioration in the remaining domain. ASAS 50 and 70 responses used the same criteria with a 50% improvement or a 70% improvement, respectively.

Compared to placebo, treatment with Enbrel resulted in significant improvements in the ASAS 20, ASAS 50 and ASAS 70 as early as 2 weeks after the initiation of therapy.

### Responses of Patients with Ankylosing Spondylitis in a Placebo-controlled Trial

<table>
<thead>
<tr>
<th>Ankylosing Spondylitis Response</th>
<th>Placebo N = 139</th>
<th>Enbrel N = 138</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASAS 20</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 weeks</td>
<td>22</td>
<td>46a</td>
</tr>
<tr>
<td>3 months</td>
<td>27</td>
<td>60a</td>
</tr>
<tr>
<td>6 months</td>
<td>23</td>
<td>58a</td>
</tr>
<tr>
<td><strong>ASAS 50</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 weeks</td>
<td>7</td>
<td>24a</td>
</tr>
<tr>
<td>3 months</td>
<td>13</td>
<td>45a</td>
</tr>
<tr>
<td>6 months</td>
<td>10</td>
<td>42a</td>
</tr>
<tr>
<td><strong>ASAS 70</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 weeks</td>
<td>2</td>
<td>12b</td>
</tr>
<tr>
<td>3 months</td>
<td>7</td>
<td>29b</td>
</tr>
<tr>
<td>6 months</td>
<td>5</td>
<td>28b</td>
</tr>
</tbody>
</table>

a: p<0.001. Enbrel vs. placebo
b: p = 0.002, Enbrel vs. placebo

Among patients with ankylosing spondylitis who received Enbrel, the clinical responses were apparent at the time of the first visit (2 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant therapies at baseline.

Similar results were obtained in the 2 smaller ankylosing spondylitis trials.

In a fourth study, the safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly vs. 25 mg Enbrel administered twice weekly were evaluated in a double-blind, placebo-controlled study of 356 patients with active ankylosing spondylitis. The safety and efficacy profiles of the 50 mg once-weekly and 25 mg twice-weekly regimens were similar.

Adult patients with plaque psoriasis

Enbrel is recommended for use in patients as defined in section 4.1. Patients who "failed to respond to" in the target population is defined by insufficient response (PASI<50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least each of the three major systemic therapies as available.

The efficacy of Enbrel versus other systemic therapies has not been evaluated in studies directly comparing Enbrel with other systemic therapies. Instead, the safety and efficacy of Enbrel were assessed in four randomised, double-blind, placebo-controlled studies. The primary efficacy endpoint in all four studies was the proportion of patients in each treatment group who achieved the PASI 75 (i.e., at least a 75% improvement in the Psoriasis Area and Severity Index score from baseline) at 12 weeks.

Study 1 was a Phase 2 study in patients with active, but clinically stable, plaque psoriasis involving ≥ 10% of the body surface area who were ≥ 18 years old. One hundred and twelve (112) patients were randomised to receive a dose of 25 mg of Enbrel (n=57) or placebo (n=55) twice a week for 24 weeks.

Study 2 evaluated 652 patients with chronic plaque psoriasis using the same inclusion criteria as study 1 with the addition of a minimum psoriasis area and severity index (PASI) of 10 at screening. Enbrel was administered at doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week for 6 consecutive months. During the first 12 weeks of the double-blind treatment period, patients received placebo or one of the above three Enbrel doses. After 12 weeks of treatment, patients in the placebo group began treatment with blinded Enbrel (25 mg twice a week); patients in the active treatment groups continued to week 24 on the dose to which they were originally randomised.

Study 3 evaluated 583 patients and had the same inclusion criteria as study 2. Patients in this study received a dose of 25 mg or 50 mg Enbrel, or placebo twice a week for 12 weeks and then all patients received open-label 25 mg Enbrel twice weekly for an additional 24 weeks.

Study 4 evaluated 142 patients and had similar inclusion criteria to studies 2 and 3. Patients in this study received a dose of 50 mg Enbrel or placebo once weekly for 12 weeks and then all patients received open-label 50 mg Enbrel once weekly for an additional 12 weeks.

In study 1, the Enbrel-treated group had a significantly higher proportion of patients with a PASI 75 response at week 12 (30%) compared to the placebo-treated group (2%) (p<0.0001). At 24 weeks, 56% of patients in the Enbrel-treated group had achieved the PASI 75 compared to 5% of placebo-treated patients. Key results of studies 2, 3 and 4 are shown below.

| Responses of Patients with Psoriasis in Studies 2, 3 and 4 |
|------------------|------------------|------------------|------------------|------------------|
| Response (%)     | Study 2          | Study 3          | Study 4          |
|                  | Placebo 25 mg BIW | Placebo 25 mg BIW | Placebo 25 mg BIW |
|                  | Placebo 50 mg BIW | Placebo 50 mg BIW | Placebo 50 mg BIW |
|                  | Enbrel 25 mg BIW | Enbrel 25 mg BIW | Enbrel 25 mg BIW |
|                  | Enbrel 50 mg BIW | Enbrel 50 mg BIW | Enbrel 50 mg BIW |
|                  | n = 166 n = 162  | n = 166 n = 164  | n = 193 n = 196  |
|                  | wk 12 wk 12     | wk 12 wk 12     | wk 12 wk 12     |
| PASI 50          | 58* 70 74* 77   | 9 64* 77* 9     | 9 69* 83       |
| PASI 75          | 4 34* 44 49* 59 | 3 34* 49* 2     | 3 38* 71       |
| DPGA b           | 5 34* 39 49* 55 | 4 39* 57* 4     | 4 39* 64       |

*p \leq 0.0001 compared with placebo

a. No statistical comparisons to placebo were made at week 24 in studies 2 and 4 because the original placebo group began receiving Enbrel 25 mg BIW or 50 mg once weekly from week 13 to week 24.

b. Dermatologist Static Global Assessment. Clear or almost clear defined as 0 or 1 on a 0 to 5 scale.

Among patients with plaque psoriasis who received Enbrel, significant responses relative to placebo were apparent at the time of the first visit (2 weeks) and were maintained through 24 weeks of therapy.

Study 2 also had a drug withdrawal period during which patients who achieved a PASI improvement of at least 50% at week 24 had treatment stopped. Patients were observed off treatment for the occurrence of rebound (PASI \geq 150% of baseline) and for the time to relapse (defined as a loss of at least half of the improvement achieved between baseline and week 24). During the withdrawal period, symptoms of psoriasis gradually returned, with a median time to disease relapse of 3 months. No rebound flare of disease and no psoriasis-related serious adverse events were observed. There was some evidence to support a benefit of re-treatment with Enbrel in patients initially responding to treatment.

In study 3, the majority of patients (77%) who were initially randomised to 50 mg twice weekly and had their Enbrel dose decreased at week 12 to 25 mg twice weekly maintained their PASI 75 response through week 36. For patients who received 25 mg twice weekly throughout the study, the PASI 75 response continued to improve between weeks 12 and 36.

In study 4, the Enbrel-treated group had a higher proportion of patients with PASI 75 at week 12 (38%) compared to the placebo-treated group (2%) (p<0.0001). For patients who received 50 mg once weekly throughout the study, the efficacy responses continued to improve with 71% achieving PASI 75 at week 24.

In long-term (up to 34 months) open-label studies where Enbrel was given without interruption, clinical responses were sustained and safety was comparable to shorter-term studies.

An analysis of clinical trial data did not reveal any baseline disease characteristics that would assist clinicians in selecting the most appropriate dosing option (intermittent or continuous). Consequently, the choice of intermittent or continuous therapy should be based upon physician judgment and individual patient needs.

Antibodies to Enbrel

Antibodies to etanercept have been detected in the sera of some subjects treated with etanercept. These antibodies have all been non-neutralising and are generally transient. There appears to be no correlation between antibody development and clinical response or adverse events.

In subjects treated with approved doses of etanercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were approximately 6% of subjects with rheumatoid arthritis, 7.5% of subjects with psoriatic arthritis, 2% of subjects with ankylosing spondylitis, 7% of subjects with psoriasis, 9.7% of subjects with paediatric psoriasis, and 3% of subjects with juvenile idiopathic arthritis.

The proportion of subjects who developed antibodies to etanercept in longer-term trials (of up to 3.5 years) increases over time, as expected. However, due to their transient nature, the incidence of antibodies detected at each assessment point was typically less than 7% in rheumatoid arthritis subjects and psoriasis subjects.

In a long-term psoriasis study in which patients received 50 mg twice weekly for 96 weeks, the incidence of antibodies observed at each assessment point was up to approximately 9%.

Paediatric patients with plaque psoriasis

The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study in 211 paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasis (as defined by an sPGA score \geq 3, involving \geq 10% of the BSA, and PASI \geq 12). Eligible patients had a history of receiving phototherapy or systemic therapy, or were inadequately controlled on topical therapy.

Patients received Enbrel 0.8 mg/kg (up to 50 mg) or placebo once weekly for 12 weeks. At week 12, more patients randomised to Enbrel had positive efficacy responses (e.g., PASI 75) than those randomised to placebo.

<table>
<thead>
<tr>
<th>Paediatric Plaque Psoriasis Outcomes at 12 Weeks</th>
<th>Enbrel 0.8 mg/kg Once Weekly</th>
<th>Placebo (N = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

After the 12-week double-blind treatment period, all patients received Enbrel 0.8 mg/kg (up to 50 mg) once weekly for additional 24 weeks. Responses observed during the open-label period were similar to those observed in the double-blind period.

During a randomised withdrawal period, significantly more patients re-randomised to placebo experienced disease relapse (loss of PASI 75 response) compared with patients re-randomised to Enbrel. With continued therapy, responses were maintained up to 48 weeks.

The long-term safety and effectiveness of Enbrel 0.8 mg/kg (up to 50 mg) once weekly was assessed in an open-label extension study of 181 paediatric subjects with plaque psoriasis for up to 2 years beyond the 48 week study discussed above. Long-term experience with Enbrel was generally comparable to the original 48-week study and did not reveal any new safety findings.

### 5.2 Pharmacokinetic properties

Etanercept serum values were determined by an Enzyme-Linked Immunosorbent Assay (ELISA) method, which may detect ELISA-reactive degradation products, as well as the parent compound.

Etanercept is slowly absorbed from the site of subcutaneous injection, reaching maximum concentration approximately 48 hours after a single dose. The absolute bioavailability is 76%. With twice-weekly doses, it is anticipated that steady-state concentrations are approximately twice as high as those observed after single doses. After a single subcutaneous dose of 25 mg Enbrel, the average maximum serum concentration observed in healthy volunteers was $1.65 \pm 0.66 \mu g/ml$, and the area under the curve was $235 \pm 96.6 \mu g\cdot hr/ml$. Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

A biexponential curve is required to describe the concentration time curve of etanercept. The central volume of distribution of etanercept is 7.6 l, while the volume of distribution at steady-state is 10.4 l.

Etanercept is cleared slowly from the body. The half-life is long, approximately 70 hours. Clearance is approximately 0.066 l/hr in patients with rheumatoid arthritis, somewhat lower than the value of 0.11 l/hr observed in healthy volunteers. Additionally, the pharmacokinetics of Enbrel in rheumatoid arthritis patients, ankylosing spondylitis and plaque psoriasis patients are similar.

Mean serum concentration profiles at steady state in treated RA patients were $C_{\text{max}}$ of 2.4 mg/l vs. 2.6 mg/l, $C_{\text{min}}$ of 1.2 mg/l vs. 1.4 mg/l, and partial AUC of 297 mg/h/l vs. 316 mg/h/l for 50 mg Enbrel once weekly (n=21) vs. 25 mg Enbrel twice weekly (n=16), respectively. In an open-label, single-dose, two-treatment, crossover study in healthy volunteers, etanercept administered as a single 50 mg/ml injection was found to be bioequivalent to two simultaneous injections of 25 mg/ml.

In a population pharmacokinetics analysis in ankylosing spondylitis patients, the etanercept steady state AUCs were 466 µg•hr/ml and 474 µg•hr/ml for 50 mg Enbrel once weekly (N= 154) and 25 mg twice weekly (N = 148), respectively.

Although there is elimination of radioactivity in urine after administration of radiolabelled etanercept to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal or hepatic failure. The presence of renal and hepatic impairment should not require a change in dosage. There is no apparent pharmacokinetic difference between males and females.

Methotrexate has no effect on the pharmacokinetics of etanercept. The effect of Enbrel on the human pharmacokinetics of methotrexate has not been investigated.

### Special populations

#### Elderly patients

The impact of advanced age was studied in the population pharmacokinetic analysis of etanercept serum concentrations. Clearance and volume estimates in patients aged 65 to 87 years were similar to estimates in patients less than 65 years of age.

#### Paediatric population
Paediatric patients with plaque psoriasis

Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered 0.8 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks. The mean serum steady-state trough concentrations ranged from 1.6 to 2.1 mcg/ml at weeks 12, 24, and 48. These mean concentrations in patients with paediatric plaque psoriasis were similar to the concentrations observed in patients with juvenile idiopathic arthritis (treated with 0.4 mg/kg etanercept twice weekly, up to maximum dose of 50 mg per week). These mean concentrations were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice-weekly.

5.3 Preclinical safety data

In the toxicological studies with Enbrel, no dose-limiting or target organ toxicity was evident. Enbrel was considered to be non-genotoxic from a battery of in vitro and in vivo studies. Carcinogenicity studies, and standard assessments of fertility and postnatal toxicity, were not performed with Enbrel due to the development of neutralising antibodies in rodents.

Enbrel did not induce lethality or notable signs of toxicity in mice or rats following a single subcutaneous dose of 2000 mg/kg or a single intravenous dose of 1000 mg/kg. Enbrel did not elicit dose-limiting or target organ toxicity in cynomolgus monkeys following twice weekly subcutaneous administration for 4 or 26 consecutive weeks at a dose (15 mg/kg) that resulted in AUC-based serum drug concentrations that were over 27-fold higher than that obtained in humans at the recommended dose of 25 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium chloride
L-Arginine hydrochloride
Sodium phosphate monobasic dihydrate
Sodium phosphate dibasic dihydrate
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

30 months

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.

Enbrel may be stored at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Enbrel should be discarded if not used within four weeks of removal from refrigeration.

Keep the pre-filled syringes in the outer carton in order to protect from light.

6.5 Nature and contents of container

Clear glass syringe (type I glass) with stainless steel needle, rubber needle cover and plastic plunger. Cartons contain 2, 4 or 12 pre-filled syringes of Enbrel with 4, 8 or 24 alcohol swabs. The needle cover contains dry natural rubber (latex) (see section 4.4). Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use and handling

Before injection, Enbrel single-use pre-filled syringe should be allowed to reach room temperature (approximately 15 to 30 minutes). The needle cover should not be removed while allowing the pre-filled syringe to reach room temperature. The solution should be clear and colourless or pale yellow and practically free from visible particles.
Comprehensive instructions for administration are given in the package leaflet, section 7, “INSTRUCTIONS FOR PREPARATION AND GIVING AN INJECTION OF ENBREL”.

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

7. MARKETING AUTHORISATION HOLDER
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   Kent CT13 9NJ
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8. MARKETING AUTHORISATION NUMBER(S)
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    Detailed information on this product is available on the website of the European Medicines Agency
    http://www.ema.europa.eu