1. NAME OF MEDICINAL PRODUCT

ENBREL®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredients, Active Moieties

Etanercept (INN)

ENBREL (etanercept) is a human tumour necrosis factor receptor (TNFR) p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. ENBREL 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, CH_2 and CH_3 regions, but not the CH_1 region of the IgG1. ENBREL contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. The potency is determined by measuring the ability of ENBREL to neutralise the TNFα-mediated growth inhibition of A375 cells. The specific activity of ENBREL is 1.7×10^6 units/mg.

Physical Characteristics

Powder and Solvent for Solution for Injection

Reconstituted ENBREL solution is clear to slightly opalescent and colourless to slightly yellow or pale brown, with a pH of 7.4 ± 0.3.

Solution for Injection in Pre-filled Syringe and Solution of Injection in Pre-filled Pen

The solution for injection in the pre-filled syringe and pen is clear to opalescent, colourless to yellow or pale brown, and liquid may contain trace levels of translucent to white amorphous particles, with a pH of 6.3 ± 0.2.

3. PHARMACEUTICAL FORM

Powder and Solvent for Solution for Injection

ENBREL is supplied in a carton containing four dose trays. Each dose tray contains one 25 mg single-use vial of ENBREL, one syringe (1 mL Sterile Water for Injection), one stainless steel needle, 1 vial adaptor, and two alcohol swabs. Clear glass vial (2 mL or 4 mL, type I glass) with rubber stopper, aluminium seal, and flip-off plastic cap.

The excipients in ENBREL lyophilised powder are mannitol, nitrogen, sucrose, trometamol and water for injections.

Solution for Injection in Pre-filled Syringe

ENBREL is supplied in a carton containing four dose trays. Each dose tray contains one pre-filled syringe 25 mg (single use) or 50 mg (single use) of etanercept and one alcohol swab.

The excipients in the pre-filled syringe are sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate and water for injections.

Solution for Injection in Pre-filled Pen

Each pre-filled pen contains 50 mg of etanercept. Pre-filled pen containing a pre-filled syringe of ENBREL. The syringe inside the pen is made from clear type 1 glass with a stainless steel 27 gauge needle, rubber needle cover and plastic plunger. The needle cap of the pre-filled pen contains dry natural rubber (a derivative of latex). Cartons contain 2 pre-filled pens of ENBREL with 2 alcohol swabs.

The excipients in the pre-filled pen are sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate and water for injections.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults with Rheumatoid Arthritis

Treatment of signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis. ENBREL can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

Paediatric Patients with Juvenile Idiopathic Arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Adults with Psoriatic Arthritis

ENBREL is indicated for reducing signs and symptoms of active arthritis in adult patients with psoriatic arthritis. ENBREL can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

Axial Spondyloarthritis

Adults with Ankylosing Spondylitis (AS)

Treatment of signs and symptoms of active ankylosing spondylitis in adults who have had an inadequate response to conventional therapy.

Adults with Non-radiographic Axial Spondyloarthritis

ENBREL is indicated for the treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence, who have had an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs).

Adults with Plaque Psoriasis

Treatment of adults with moderate to severe chronic plaque psoriasis who failed to respond to, or who have contraindications to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

Paediatric Patients with Plaque Psoriasis

ENBREL is indicated for the 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, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis or paediatric plaque psoriasis.

Use in Adults (18-64 years)

Rheumatoid Arthritis

25 mg ENBREL administered twice weekly (72 to 96 hours apart) is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective. Refer to Section **5. PHARMACOLOGICAL PROPERTIES**.

Psoriatic Arthritis, Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis

The recommended dose is 25 mg ENBREL administered twice weekly (72 to 96 hours apart), or 50 mg administered once weekly.

For all of the above indications, available data suggest that a 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.

Plaque Psoriasis

The recommended dose of ENBREL is 25 mg administered twice weekly (72 to 96 hours apart) 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. 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

Elderly (≥65 years)

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

Renal and Hepatic Impairment

No dose adjustment is required.

Use in Children

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 (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.

Juvenile Idiopathic Arthritis

The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose) given twice weekly (72 to 96 hours apart) as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly. Discontinuation of treatment should be considered in patients who show no response after 4 months.

The 10 mg vial strength may be more appropriate for administration to children with Juvenile Idiopathic Arthritis (JIA) below the weight of 25 kg. No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously.

There is generally no applicable use of ENBREL in children aged below 2 years in the indication juvenile idiopathic arthritis.

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

Administer ENBREL as subcutaneous injections in the thigh, abdomen, or upper arm. Give each new injection at least 3 cm from a previous site. Do NOT inject into areas where the skin is tender, bruised, red, or hard.

Patients or caregivers who are to administer ENBREL must be instructed in injection techniques. The first injection should be performed under the supervision of a qualified healthcare professional if ENBREL is to be administered by a patient or caregiver.

Powder and Solvent for Solution for Injection

Patients or caregivers who are to administer ENBREL must be instructed in mixing the powder with the liquid.

ENBREL should be reconstituted aseptically with 1 mL of the supplied Sterile Water for Injection. During reconstitution of ENBREL, the solvent should be slowly injected into the vial. Some foaming

will occur. To avoid excessive foaming, do not shake or vigorously agitate. The contents should be swirled gently during dissolution. Generally, dissolution of ENBREL takes less than 10 minutes. The reconstituted ENBREL solution is colourless to slightly yellow or pale brown and clear to slightly opalescent liquid.

Visually inspect the solution for particulate matter and discolouration prior to administration. The solution should not be used if discoloured or cloudy, or if particulate matter remains. Withdraw the solution into the syringe, removing as much liquid as possible from the vial. Some foam or bubbles may remain in the vial. The final volume in the syringe will be approximately 1 mL.

No other medications should be added to solutions containing ENBREL, and ENBREL should not be reconstituted with other solvents. Do not filter reconstituted solution during preparation or administration.

Solution for Injection in Pre-filled Syringe

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 to opalescent, colourless to yellow or pale brown, and liquid may contain trace levels of translucent to white amorphous particles.

Solution for Injection in Pre-filled Pen

Before injection, ENBREL single-use pre-filled pens should be allowed to reach room temperature (approximately 15 to 30 minutes). The needle cover should not be removed while allowing the pre-filled pen to reach room temperature. The pen should not be left at room temperature for more than 12 hours. By looking through the inspection window, the solution should be clear to opalescent, colourless to yellow or pale brown, and liquid may contain trace levels of translucent to white amorphous particles.

Missed Doses

If a dose is missed, patients should be advised to administer the dose as soon as they remember, unless the next scheduled dose is the next day, in which case the missed dose should be skipped. Patients should continue to inject the medicine on their usual day(s). If a patient does not remember until the day that the next injection is due, instruct the patient not to take a double dose.

4.3 Contraindications

Hypersensitivity to etanercept or to any component of the product formulation.

Active tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections (see Section **4.4 Special Warnings and Precautions for Use**).

4.4 Special Warnings and Precautions for Use

Infections

Serious infections, including sepsis and tuberculosis (TB), have been reported with the use of ENBREL (see Section **4.8 Undesirable Effects**). Some of these infections have been fatal. These infections were due to bacteria, mycobacteria, fungi, viruses and parasites (including protozoa). Opportunistic infections have also been reported (including listeriosis and legionellosis). Patients who develop a new infection while undergoing treatment with etanercept should be monitored closely. Administration of ENBREL should be discontinued if a patient develops a serious infection. Caution

should be exercised when considering the use of ENBREL in patients with a history of recurring or chronic infections or with underlying conditions which may predispose patients to infections (see Sections **4.3 Contraindications** and **4.8 Undesirable Effects**).

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 80 hours (standard deviation of 28 hours; range from 7 to 300 hours).

Opportunistic infections, including invasive fungal infections, have been reported in patients receiving ENBREL. In some cases, fungal and other opportunistic infections are not recognised, and this has resulted in delays in appropriate treatment, sometimes resulting in death. In many of the reports, patients have also received concomitant medicines including immunosuppressants. In evaluating patients for infections, healthcare providers should consider the patient's risk for relevant opportunistic infections (e.g., exposure to endemic mycoses).

Tuberculosis (TB)

Tuberculosis (including disseminated or extrapulmonary presentation) has been observed in patients receiving TNF-blocking agents, including ENBREL. Tuberculosis may be due to reactivation of latent TB infection or to new infection.

Before initiation of therapy with ENBREL, any patient at increased risk for TB should be evaluated for active or latent infection. Prophylaxis of latent TB infection should be initiated prior to therapy with ENBREL. Some patients who tested negative for latent TB prior to receiving ENBREL have developed active TB. Physicians should monitor patients receiving ENBREL for signs and symptoms of active TB, including patients who tested negative for latent TB infection. Applicable local guidelines should be consulted. Patients with RA appear to have an increased rate of TB infection.

Hepatitis B-reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant anti-TNF agents including ENBREL has been reported. A causal relationship has not been established for ENBREL. In some instances, HBV reactivation occurring in conjunction with anti-TNF therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to hepatitis B-reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating anti-TNF therapy. Prescribers should exercise caution in prescribing anti-TNF agents in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with anti-TNF therapy to prevent HBV reactivation. If HBV reactivation should develop in patients who are receiving ENBREL, treatment should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Worsening of Hepatitis C

There have been reports of worsening of hepatitis C in patients receiving ENBREL, although a causal relationship with ENBREL has not been established.

Concurrent Treatment with Anakinra

Concurrent administration of ENBREL and Anakinra has been associated with an increased risk of serious infections and neutropenia. This combination has not demonstrated increased clinical benefits;

such use is not recommended (see Section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Concurrent Treatment with Abatacept

In clinical studies, concurrent administration of Abatacept and ENBREL therapy 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 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Wegener's Granulomatosis

In a placebo-controlled study of 180 patients with Wegener's granulomatosis, the addition of ENBREL to standard treatment (including cyclophosphamide and high-dose steroids) was no more efficacious than standard treatment alone. The group of patients who received ENBREL experienced more non-cutaneous malignancies of various types than the patient group receiving standard treatment alone. The use of ENBREL for treatment of Wegener's granulomatosis is not recommended.

Allergic Reactions

Parenteral administration of any biological product should be attended by appropriate precautions in case an allergic or untoward reaction occurs. Allergic reactions associated with ENBREL administration have been reported. Allergic reactions have included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, discontinue administration of ENBREL immediately (see Section **4.8 Undesirable Effects**).

Powder and Solvent for Solution for Injection

The rubber closure of the solvent syringe contains latex (dry natural rubber). Patients or caregivers should contact their doctor before using ENBREL if the rubber closure of the solvent syringe will be handled by or if ENBREL will be given to someone with a known or possible hypersensitivity (allergy) to latex.

Solution for Injection in Pre-filled Syringe and Solution for Injection in Pre-filled Pen

The needle cover of the pre-filled syringe and the needle cap of the pre-filled pen contain latex (dry natural rubber). Patients or caregivers should contact their doctor before using ENBREL if the needle cover will be handled by or if ENBREL will be given to someone with a known or possible hypersensitivity (allergy) to latex.

Immunosuppression and Malignancy

TNF modulates immune responses and has a protective effect against the development of some tumours. The impact of treatment with ENBREL, on the course of development of malignancies, including those caused by immunosuppressive agents, is not understood and has not been studied. The possibility exists for TNF therapies, including ENBREL, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. The impact of treatment with ENBREL on the development and course of malignancies and active and/or chronic infections is not fully understood (see Section **4.8 Undesirable Effects**). Reports of malignancies affecting various sites have been received in the post-marketing period including breast and lung carcinoma and lymphoma.

In a study of 49 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. Reports of malignancies affecting various sites have been

received in the post-marketing period. Based on current knowledge, a possible risk for the development of lymphomas or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Whether treatment with ENBREL might influence the development and course of active and/or chronic infections is unknown. The safety and efficacy of ENBREL in patients with immunosuppression or chronic infections have not been evaluated.

Two juvenile chronic 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.

Solid and Haematopoietic Malignancies (excluding skin cancers)

Reports of malignancies affecting various sites have been received in the post-marketing period. 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 for placebo patients was shorter than for patients receiving TNF-antagonist therapy. 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 the risk estimation. *Post hoc* analyses of rheumatoid arthritis clinical trials with ENBREL have neither confirmed nor excluded an increased risk for malignancies. During the controlled portions of ENBREL trials, 3 lymphomas were observed among 4,509 ENBREL-treated patients vs. 0 among 2,040 control patients (duration of controlled treatment ranged from 3 to 24 months). In the controlled and open-label portions of clinical trials of ENBREL, 9 lymphomas were observed in 5,723 patients over approximately 11,201 patient-years of therapy. This is 3-fold higher than that expected in the general population.

Based on current knowledge, a possible risk for the development of lymphomas or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded.

Malignancies (particularly Hodgkin's and non-Hodgkin's lymphomas), some fatal, have been reported among children and adolescents who received treatment with TNF-antagonists, including ENBREL. Most of the patients were receiving concomitant immunosuppressants.

Skin Cancers

Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including ENBREL. Post-marketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with ENBREL. Periodic skin examination is recommended for all patients who are at increased risk for skin cancer.

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

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.

Autoantibody Formation

Treatment with ENBREL may be associated with the formation of autoimmune antibodies (see Section **4.8 Undesirable Effects**).

Vaccinations

In a double-blind, placebo-controlled, randomised clinical study in 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 fewer patients had two-fold rises in titres compared to patients not receiving ENBREL. The clinical significance of this is unknown. 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. If possible, bring paediatric patients up to date with immunisations according to current local guidelines before beginning ENBREL therapy.

Neurological Disorders

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. There have been rare reports of central nervous system (CNS) demyelinating disorders in patients treated with ENBREL (see Section **4.8 Undesirable Effects**). Additionally, there have been rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome). A careful risk/benefit evaluation, including a neurological assessment, is recommended when prescribing ENBREL therapy 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.

Congestive Heart Failure (Cardiac failure congestive)

There have been post-marketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking ENBREL. There have also been rare (<0.1%) reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. 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. In addition, a clinical trial evaluating the use of infliximab (a monoclonal antibody that binds to TNF-alpha) in the treatment of CHF was terminated early due to an increase in mortality among infliximab treated patients. Physicians should use caution when using ENBREL in patients who also have CHF.

Hypoglycaemia in Patients Treated with 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.

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. PHARMACOLOGICAL PROPERTIES: 5.2 Pharmacokinetic Properties**), no dosage adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited.

Alcoholic Hepatitis

In a study of 48 hospitalised patients treated with ENBREL or placebo for moderate to severe alcoholic hepatitis [mean Model of End-stage Liver Disease (MELD) score = 25], ENBREL was not efficacious and the mortality rate in patients treated with ENBREL was significantly higher after 6 months. Infections were also higher in the group treated with ENBREL. The use of ENBREL in patients for the treatment of alcoholic hepatitis is not recommended. Physicians should use caution when using ENBREL in patients who also have moderate to severe alcoholic hepatitis.

Use in Psoriasis

The safety and efficacy of ENBREL in combination with other immunosuppressive agents used in psoriasis or with phototherapy have not been studied. ENBREL should not be used in combination with such agents because of the possibility of excessive immunosuppression.

Monitoring

Based on the results of clinical studies in rheumatoid arthritis, normally no special laboratory evaluations are necessary in addition to careful medical management and supervision of patients.

Genotoxicity and Effects on Fertility

Genotoxicity studies showed no evidence of gene mutations or chromosomal damage. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of ENBREL or its effects on fertility.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Concurrent Treatment with Abatacept

In clinical studies, concurrent administration of abatacept and ENBREL therapy 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 Special Warnings and Precautions for Use**).

Concurrent Treatment with Methotrexate

ENBREL may be administered in combination with methotrexate for the treatment of rheumatoid arthritis. In a safety and efficacy clinical trial, methotrexate had no effect on the pharmacokinetics of ENBREL. The effect of ENBREL on the human pharmacokinetics of methotrexate has not been investigated. The safety and efficacy of ENBREL in combination with methotrexate for the treatment of psoriasis have not been studied. ENBREL should not be administered in combination with methotrexate for the treatment of psoriasis (see Section **4.4 Special Warnings and Precautions for Use**).

Concurrent Treatment with Anakinra

Patients treated with ENBREL and anakinra were observed to have a higher rate of serious infection when compared with patients who were treated with ENBREL alone (historical data). In addition, in a double-blind placebo-controlled trial in patients receiving background methotrexate, patients treated with ENBREL and anakinra were observed to have a higher rate of serious infections and neutropenia than patients treated with ENBREL alone (see Section **4.4 Special Warnings and Precautions for Use**).

Concurrent Treatment with Sulfasalazine

In a clinical study of 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.

Live Vaccines

No safety data are available on the effects of live vaccine when used in combination with ENBREL. Live vaccines should therefore not be given concurrently with ENBREL.

Other

Product Information for methotrexate should be referenced when ENBREL is administered with methotrexate. Interactions between ENBREL and other drugs have not been evaluated in formal studies. No interactions have been observed when ENBREL was administered with glucocorticoids, salicylates (except sulfasalazine), NSAIDs, analgesics, or methotrexate in clinical trials with adult rheumatoid arthritis patients.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with methotrexate, digoxin and warfarin.

Effects on Laboratory Tests

No effects on laboratory tests have been reported in adults. An analysis of 54 JCA patients in an open-label study demonstrated low haemoglobin, low albumin and low lymphocyte counts in 63%, 39% and 30% of juvenile patients, respectively. These observations, however, appear to be attributed to the underlying disease, rather than treatment with ENBREL.

4.6 Fertility, Pregnancy and Lactation

Fertility

Preclinical data about peri- and post-natal toxicity of ENBREL and of effects of ENBREL on fertility and general reproductive performance are not available.

Pregnancy

The effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. One pregnancy registry compared rates of major birth defects in liveborn infants of mothers with rheumatic diseases or psoriasis exposed to ENBREL in the first trimester (n = 319) versus those unexposed to ENBREL during pregnancy (n = 144). The all-inclusive adjusted odds ratio for major birth defects was 2.77 (95% CI 1.04-7.35) and when chromosomal and known genetic disorders were removed was 2.49 (95% CI 0.92-6.68). The findings showed no increased rate of minor

malformations, and no pattern of major or minor malformations. In addition, there was no increase in rates of intrauterine or post-natal growth deficits or delayed post-natal development. In a second observational multi-country registry study comparing the risk of adverse pregnancy outcomes in women exposed to etanercept (n = 522) to those exposed to non-biologic drugs (n = 3508), there was no observed increased risk of major birth defects (adjusted odds ratio 0.96, 95% CI 0.58-1.60). This study also showed no increased risks of minor birth defects, preterm birth, stillbirth or infections in the first year of life for infants born to women exposed to etanercept during pregnancy. ENBREL should only be used during pregnancy if the potential benefits to the mother outweigh the potential risks to the foetus.

The use of ENBREL in pregnant women is not recommended and the women of child-bearing potential should be advised not to get pregnant during ENBREL therapy.

Developmental toxicity studies have been performed in rats and rabbits. The AUC-based systemic exposures of etanercept in rats and rabbits are 21- to 25-times higher than in humans at the usual human therapeutic dose of 50 mg weekly, and are approximately 10- to 13-times higher than in humans at the maximum recommended human dose of etanercept of 50 mg twice weekly (for psoriasis). No evidence of harm to the foetus in rats or rabbits or neonatal rats due to etanercept was observed. There are, however, no studies in pregnant women. Animal studies are not always predictive of human response.

Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with ENBREL during pregnancy. The clinical impact of this is unknown; however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after the mother's last dose of ENBREL is generally not recommended.

Lactation

In lactating rats, following subcutaneous administration etanercept was excreted in the milk and detected in the serum of the pups. Etanercept has been reported to be excreted in human milk in insignificant amounts following subcutaneous administration. The safe use of ENBREL during lactation has not been fully established, therefore ENBREL should only be used during breastfeeding if the benefits outweigh the potential risks.

While systemic exposure in a breastfed infant is expected to be low because etanercept is poorly excreted in the breast milk, the possibility to administer live vaccines to a breastfed infant when the mother is receiving etanercept should be carefully considered by the doctor.

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

ENBREL has been studied in 2,680 patients with rheumatoid arthritis in double-blind and open-label trials. This experience includes 2 placebo-controlled studies (349 ENBREL patients and 152 placebo patients) and 2 active-controlled trials, one active-controlled trial comparing ENBREL to methotrexate (415 ENBREL patients and 217 methotrexate patients) and another active-controlled trial comparing ENBREL (223 patients), methotrexate (228 patients) and ENBREL in combination with methotrexate (231 patients). The proportion of patients who discontinued treatment due to adverse reactions was the same in both the ENBREL and placebo treatment groups; in the first active-controlled trial, the dropout rate was significantly higher for methotrexate (10%) than for ENBREL (5%). In the second active-controlled trial, the rate of discontinuation for adverse events after 2 years of treatment was similar among all three treatment groups, ENBREL (16%), methotrexate (21%) and

ENBREL in combination with methotrexate (17%). Additionally, ENBREL has been studied in 131 psoriatic arthritis patients who participated in 2 double-blind placebo-controlled studies and an open-label extension study. Five hundred and eight (508) ankylosing spondylitis patients were treated with ENBREL in 4 double-blind placebo-controlled studies. ENBREL has also been studied in 1,084 patients with plaque psoriasis for up to 6 months in 3 double-blind placebo-controlled studies.

In double-blind clinical trials comparing ENBREL to placebo, injection site reactions were the most frequent adverse events among ENBREL-treated patients. Among patients with rheumatoid arthritis treated in placebo-controlled trials, serious adverse events occurred at a frequency of 4% in 349 patients treated with ENBREL compared with 5% of 152 placebo-treated patients. In the first active-controlled trial, serious adverse events occurred at a frequency of 6% in 415 patients treated with ENBREL compared with 8% of 217 methotrexate-treated patients. In the second active-controlled trial the rate of serious adverse events after 2 years treatment was similar among the three treatment groups (ENBREL 16%, methotrexate 15% and ENBREL in combination with methotrexate 17%). Among patients with plaque psoriasis treated in placebo-controlled trials, the frequency of serious adverse events was about 1% of 933 patients treated with ENBREL compared with 1% of 414 placebo-treated patients.

The following list of adverse reactions is based on experience from clinical trials in adults and on post-marketing 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, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000); frequency not known (frequency could not be accurately estimated from clinical studies).

Adverse Reactions Table

System Organ Class	**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**	**Frequency Not Known (cannot be estimated from available data)**
Infections and infestations	Infection (including upper respiratory tract infection, bronchitis, cystitis, skin infection)		Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis, and parasitic infection)	Tuberculosis, opportunistic infection (including invasive fungal, bacterial, atypical mycobacterial, viral infections, and Legionella) (see section **4.4 Special Warnings and Precautions for Use**)		Hepatitis B reactivation*, Listeria*
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancers (see section **4.4 Special Warnings and Precautions for Use**)	Malignant melanoma (see section **4.4 Special Warnings and Precautions for Use**), lymphoma,* leukaemia*		Merkel cell carcinoma* (see section **4.4 Special Warnings and Precautions for Use**)
Blood and lymphatic system disorders			Thrombocytopenia, anaemia, leukopenia, neutropenia	Pancytopenia (see section **4.4 Special Warnings and**	Aplastic anaemia* (see section **4.4 Special**	Histiocytosis haematophagic (macrophage activation

Adverse Reactions Table

System Organ Class	**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**	**Frequency Not Known (cannot be estimated from available data)**
				Precautions for Use)	**Warnings and Precautions for Use**)	syndrome)*
Immune system disorders		Allergic reactions (*see Skin and subcutaneous tissue disorders, below*), autoantibody formation	Vasculitis (including ANCA positive vasculitis)	Serious allergic/ anaphylactic reactions (including bronchospasm), sarcoidosis		
Nervous system disorders	Headache*			CNS demyelinating events, including multiple sclerosis and localised demyelinating conditions such as optic neuritis and transverse myelitis (see section **4.4 Special Warnings and Precautions for Use**), peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy* (see section **4.4 Special Warnings and Precautions for Use**), seizure		
Eye disorders			Uveitis, scleritis			
Cardiac disorders			Worsening of cardiac failure congestive	New onset cardiac failure congestive		
Respiratory, thoracic, and mediastinal disorders				Interstitial lung disease (including pulmonary fibrosis and pneumonitis)		

Adverse Reactions Table

System Organ Class	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	Frequency Not Known (cannot be estimated from available data)
Gastrointestinal disorder			Inflammatory bowel disease*			
Hepatobiliary disorders			Elevated liver enzymes (*see Elevated liver enzymes below*)	Autoimmune hepatitis		
Skin and subcutaneous tissue disorders		Pruritus, rash	Angioedema, psoriasis (new onset or exacerbation, including all sub-types), urticaria, psoriasiform rash*	Stevens-Johnson syndrome,* cutaneous vasculitis (including hypersensitivity vasculitis), erythema multiforme*	Toxic epidermal necrolysis*	
Musculoskeletal and connective tissue disorders				Cutaneous lupus erythematosus,* subacute cutaneous lupus erythematosus,* lupus-like syndrome		
General disorders and administration site conditions	Injection site reactions (including bleeding, bruising, erythema, itching, pain, and swelling)	Pyrexia				

*ADR identified post-marketing.

ADDITIONAL INFORMATION

Serious Adverse Events Reported in Clinical Trials

Among rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis patients in placebo-controlled, active-controlled, and open-label trials of ENBREL, serious adverse events reported included malignancies (see below), asthma, infections (see below), heart failure, myocardial infarction, myocardial ischaemia, chest pain, syncope, cerebral ischaemia, hypertension, hypotension, cholecystitis, pancreatitis, gastrointestinal haemorrhage, bursitis, confusion, depression, dyspnoea, abnormal healing, renal insufficiency, kidney calculus, deep vein thrombosis, pulmonary embolism, membranous glomerulonephropathy, polymyositis, thrombophlebitis, liver damage, leucopenia, paresis, paraesthesia, vertigo, allergic alveolitis, angioedema, scleritis, bone fracture, lymphadenopathy, ulcerative colitis, intestinal obstruction, eosinophilia, haematuria, and sarcoidosis.

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 and subsequently decreased in frequency. In clinical trials, these reactions were generally transient with a mean duration of 4 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 14% of patients treated with ENBREL developed injection site reactions compared with 6% of placebo-treated patients during the first 12 weeks of treatment.

In post-marketing experience, injection site bleeding and bruising have also been observed in conjunction with ENBREL therapy.

Infections

Serious and fatal infections have been reported; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses, and fungi. Opportunistic infections have also been reported including invasive fungal, parasitic (including protozoal), viral (including herpes zoster), bacterial (including *Listeria* and *Legionella*), and atypical mycobacterial infections (see Section **4.4 Special Warnings and Precautions for Use**). The most commonly reported invasive fungal infections included *Candida, Pneumocystis, Aspergillus,* and *Histoplasma*. 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 Special Warnings and Precautions for Use**). Data from a sepsis clinical trial not specifically in patients with rheumatoid arthritis suggest that ENBREL treatment may increase mortality in patients with established sepsis.

In clinical trials in rheumatic disorders, upper respiratory infections ("colds") and sinusitis were the most frequently reported non-serious infections in patients receiving ENBREL or placebo. In placebo-controlled trials, the incidence of upper respiratory tract infections was 17% in the placebo treatment group and 22% in the group treated with ENBREL. In controlled trials in patients with rheumatoid arthritis, the rates of reported serious (fatal, life threatening, or required hospitalisation or intravenous antibiotics) and non-serious infection were similar for ENBREL and placebo when adjusted for duration of exposure. In rheumatoid arthritis patients participating in placebo-controlled trials, there were 0.68 events per patient year in the placebo group and 0.82 events per patient year in the group treated with ENBREL when the longer observation of patients on ENBREL was accounted for. In placebo-controlled trials evaluating ENBREL, no increase in the incidence of serious infections (fatal, life threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Among the 2,680 rheumatoid arthritis patients treated with ENBREL for up to 48 months, including 231 patients treated with ENBREL in combination with methotrexate in the 2-year active-controlled study, 186 serious infections were observed. These serious infections 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.

In placebo-controlled psoriatic arthritis trials and plaque psoriasis trials, there were no differences in rates of infection among patients treated with ENBREL and those treated with placebo. In the psoriatic arthritis trials, no serious infections occurred in patients treated with ENBREL. In the double-blind and open-label plaque psoriasis trials up to 15 months, serious infections experienced by

ENBREL-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis and abscess.

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 non-melanoma 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 post-marketing period. There have been reports of malignancies in a clinical trial of patients being treated for Wegener's granulomatosis (see Section **4.4 Special Warnings and Precautions for Use**).

Interstitial Lung Disease

In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without concomitant methotrexate was 0.06% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of interstitial lung disease was 0.47% (frequency uncommon). There have been post-marketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Elevated Liver Enzymes

In the double-blind periods of controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving etanercept without concomitant methotrexate was 0.54% (frequency uncommon). In the double-blind periods of controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of adverse events of elevated liver enzymes was 4.18% (frequency common).

Autoimmune Hepatitis

In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of autoimmune hepatitis in patients receiving etanercept without concomitant methotrexate was 0.02% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of autoimmune hepatitis was 0.24% (frequency uncommon).

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 *Crithidia luciliae* 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 post-marketing reports of pancytopenia and aplastic anaemia, some of which had fatal outcomes (see Section 4.4 **Special Warnings and Precautions for Use**).

Laboratory Evaluations

Based on the results of clinical studies, normally no special laboratory evaluations are necessary in addition to careful medical management and supervision of patients.

Concurrent ENBREL and Anakinra Treatment

In studies when 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/mm^3). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see Sections **4.4 Special Warnings and Precautions for Use** and **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Paediatric Patients

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

Undesirable Effects in Paediatric Patients with Juvenile Idiopathic Arthritis

Infection was the most common adverse event reported in paediatric patients taking ENBREL and occurred at an incidence similar to placebo. The types of infections reported in juvenile idiopathic arthritis patients were generally mild and consistent with those commonly seen in outpatient paediatric populations.

In clinical trials, two cases of varicella infection with signs and symptoms suggestive of aseptic meningitis have been reported among juvenile idiopathic arthritis patients treated with ENBREL.

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

Undesirable Effects in Paediatric Patients with Plaque Psoriasis

In a 48-week study of 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.

4.9 Overdose

The maximum tolerated dose of etanercept has not been established in humans. Single intravenous

doses up to 60 mg/m^2 have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities. The highest dose level evaluated in rheumatoid arthritis patients has been an intravenous loading dose of 32 mg/m^2 followed by subcutaneous doses of 16 mg/m^2 (~25 mg) administered twice weekly.

Etanercept 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.

Etanercept 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 human dose of 25 mg.

No dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients.

There is no known antidote to etanercept.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic Group

Selective immunosuppressive agent, Tumour Necrosis Factor alpha (TNF-α) inhibitors, ATC code: L04AB01.

Tumour necrosis factor (TNF) is a dominant cytokine in the inflammatory process of rheumatoid arthritis. Elevated levels of TNF are found in the synovial fluid of patients with rheumatoid arthritis and juvenile idiopathic arthritis. Elevated levels of TNF are also found in the synovium and psoriatic plaques of patient with psoriatic arthritis and in serum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells including T-cells leads to increased TNF levels in psoriatic lesions compared with levels in uninvolved skin. ENBREL is a competitive inhibitor of TNF-binding to its cell surface receptors and thereby inhibits the biological activity of TNF. TNF and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-kilodalton (p55) and 75-kilodalton (p75) tumour necrosis factor receptors (TNFRs). Both TNFRs exist naturally in membrane-bound and soluble forms. Soluble TNFRs are thought to regulate TNF biological activity.

TNF and lymphotoxin exist predominantly as homotrimers, with their biological activity dependent on cross-linking of cell surface TNFRs. Dimeric soluble receptors such as ENBREL 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. Etanercept is a dimeric soluble form of the p75 TNF (tumour necrosis factor) receptor that can bind to two TNF molecules. The mechanism of action of ENBREL is thought to be its competitive inhibition of both TNF (TNF_α) and lymphotoxin alpha [LT_α] (TNF_β) to cell surface TNFR, thus rendering TNF biologically inactive and preventing TNF-mediated cellular responses. TNF and LT_α are expressed in patients with juvenile idiopathic arthritis. The biological activity of TNF is dependent upon binding to either cell surface receptor. ENBREL may also modulate biologic responses

controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF. ENBREL inhibits the activity of TNF *in vitro* and has been shown to affect several animal models of inflammation, including collagen-induced arthritis in mice.

Clinical Efficacy and Safety

This section presents data from four trials in adults with rheumatoid arthritis, 3 studies in juvenile idiopathic arthritis, 1 study in adults with psoriatic arthritis, 4 studies in adults with ankylosing spondylitis, 2 studies in adults with non-radiographic axial spondyloarthritis, 3 studies in adults with plaque psoriasis and 2 studies in paediatric patients with plaque psoriasis.

Adult Patients with Rheumatoid Arthritis

Placebo-controlled Studies

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, 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.

The primary endpoint was achievement of an ACR 20 response at month 3. Subjects who failed to respond based on pre-specified criteria for lack of efficacy before month 3 were allowed to drop out early and were considered treatment failures. By definition, an ACR 20 response is achieved if a patient experiences a ≥20% improvement in their tender joint count and swollen joint count plus ≥20% improvement in at least three of the following five criteria: (1) patient pain assessment, (2) patient global assessment, (3) physician global assessment, (4) patient self-assessed disability, and (5) acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein). ACR 50 and 70 responses are defined using the same criteria with a 50% improvement or a 70% improvement, respectively.

ACR 20 and 50 responses were higher in patients treated with ENBREL at 3 and 6 months than in patients treated with placebo, at all time points as seen in the table below:

ACR Responses (% of patients)		
Response	**Placebo (n=80)**	**ENBREL[a] (n=78)**
ACR 20		
Month 3	23	62[b]
Month 6	11	59[b]
ACR 50		
Month 3	8	41[b]
Month 6	5	40[b]

[a]: 25 mg ENBREL SC twice weekly.
[b]: p <0.01, ENBREL vs. placebo.

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 discontinuations 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 10 years in open-label extension treatment trials when patients received ENBREL without interruption.

An additional randomised, controlled, double-blind trial evaluated 180 patients with similar criteria to the first study. Doses of 0.25 mg/m^2, 2 mg/m^2, and 16 mg/m^2 ENBREL were administered subcutaneously twice a week for 3 consecutive months. A dose dependent increase in the proportion of subjects achieving an ACR20 response was seen, with 75% of subjects responding in the highest dose group (16 mg/m^2 ENBREL).

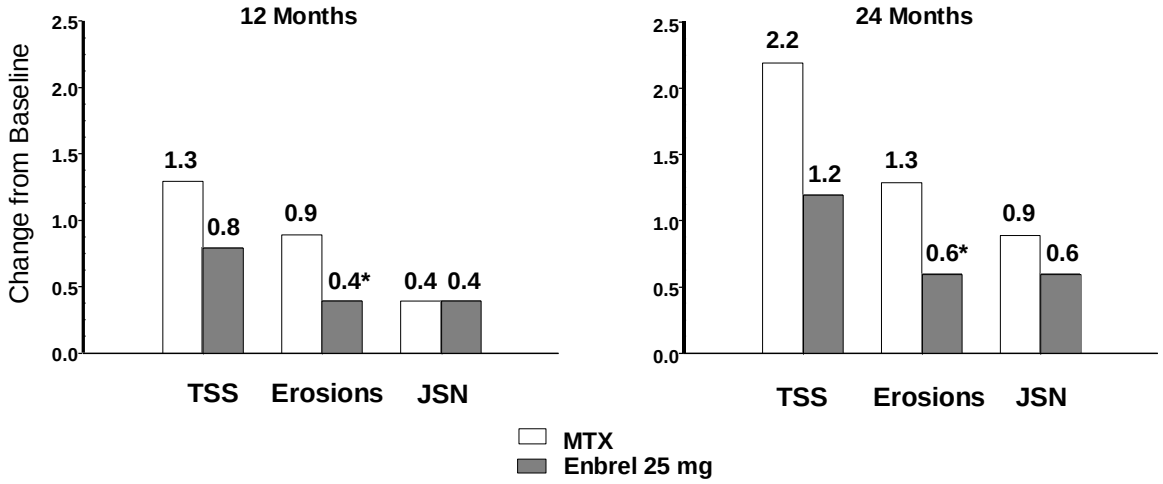
A second randomised, double-blind, placebo-controlled study also compared the safety and efficacy ENBREL (25 mg) against placebo (SC, twice a week over 6 months) in 89 RA patients in addition to a stable dose of methotrexate. The ACR response criteria were used to assess efficacy. The primary endpoint was achievement of an ACR 20 response at 6 months. Responses were higher in patients treated with ENBREL at 3 and 6 months. Clinical responses in ENBREL-treated patients generally appeared after 1-2 weeks of therapy. In addition, approximately 15% of ENBREL-treated patients achieved an ACR 70 response at month 3 and month 6, compared to less than 5% of subjects in the placebo arm. ENBREL-treated patients experienced significantly greater improvements in all components of the ACR criteria, compared to patients in the placebo arm.

Active-controlled Studies

A randomised, active-controlled study with blinded radiographic evaluation as a primary endpoint compared the efficacy of ENBREL to oral methotrexate in 632 adult patients with active rheumatoid arthritis (<3 years duration) who had never received treatment with methotrexate. The patients had to have >12 tender joints, >10 swollen joints, and either ESR > 28 mm/hr, CRP >2.0 mg/dL, or morning stiffness for >45 minutes. Patients were at high risk of erosive disease defined as being rheumatoid factor positive or having at least three erosions at baseline. Doses of 10 mg or 25 mg ENBREL were administered 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 2 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 score (JSN). 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



*p < 0.05

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 of 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 DMARD other than methotrexate.

Forty-three percent of patients had previously received MTX a mean of 2 years prior to the trial at a mean dose of 12.9 mg/week. Patients were excluded from this study if MTX had been discontinued for lack of efficacy or for safety considerations.

Patients in the ENBREL in combination with methotrexate therapy group had significantly higher ACR 20, ACR 50, ACR 70 responses and improvement for disease activity scores (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.

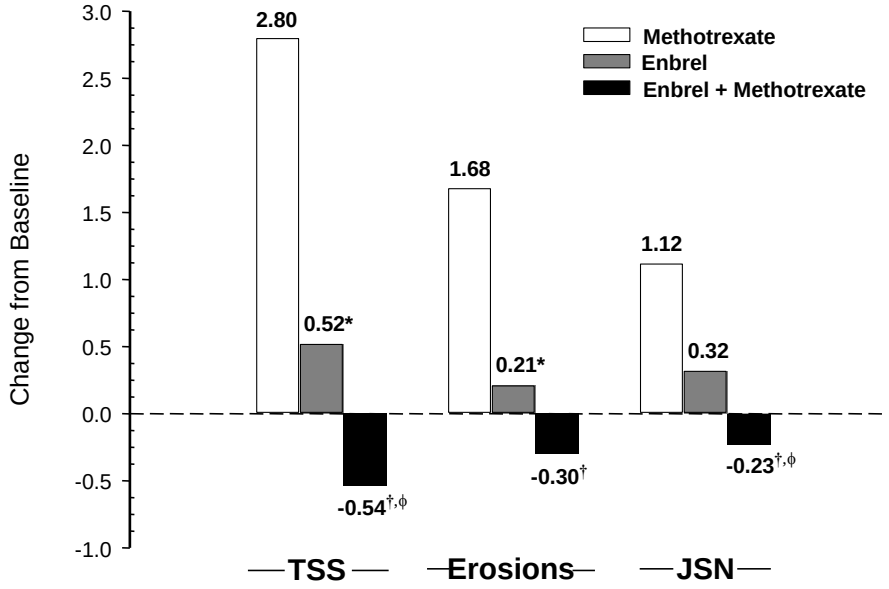
CLINICAL EFFICACY RESULTS AT 12 MONTHS: COMPARISON OF ENBREL vs. METHOTREXATE vs. ENBREL IN COMBINATION WITH METHOTREXATE IN PATIENTS WITH RA OF 6 MONTHS TO 20 YEARS DURATION

Endpoint	Methotrexate (n = 228)	ENBREL (n = 223)	ENBREL +Methotrexate (n = 231)
ACR Responses[a]			
ACR 20	58.8%	65.5%	74.5% †,ϕ
ACR 50	36.4%	43.0%	63.2% †,ϕ
ACR 70	16.7%	22.0%	39.8% †,ϕ
DAS			
Baseline score[b]	5.5	5.7	5.5
Week 52 score[b]	3.0	3.0	2.3 †,ϕ
Remission[c]	14%	18%	37% †,ϕ
HAQ			
Baseline	1.7	1.7	1.8
Week 52	1.1	1.0	0.8 †,ϕ

[a]: Patients who did not complete 12 months in the study were considered to be non-responders.
[b]: Values for Disease Activity Score (DAS) are means.
[c]: Remission is defined as DAS <1.6.
Pairwise comparison p-values: † = p < 0.05 for comparisons of ENBREL + methotrexate vs. methotrexate and ϕ = p <0.05 for comparisons of ENBREL + methotrexate vs. ENBREL.

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 the 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)



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.

Once Weekly Dosing

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.

Paediatric Patients with Juvenile Idiopathic Arthritis

The safety and efficacy of ENBREL were assessed in a two-part study in 69 children with polyarticular-course juvenile chronic arthritis who had a variety of juvenile chronic arthritis onset types (polyarthritis, pauciarthritis, systemic-onset). Patients ages 4 to 17 years with moderately to severely active polyarticular-course juvenile chronic arthritis refractory to or intolerant of methotrexate were enrolled; patients remained on a stable dose of a single non-steroidal anti-inflammatory drug and/or prednisone (≤0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) ENBREL subcutaneously twice weekly. In part 2, patients with a clinical response at day 90 were randomised to remain on ENBREL or receive placebo for four months and assessed for disease flare. Responses were measured using the ACR Pedi 30, defined as ≥30% improvement in at least three of six and ≥30% worsening in no more than one of six JRA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and erythrocyte sedimentation rate (ESR). Disease flare was defined as a ≥30% worsening in three of six JRA core set criteria and ≥30% improvement in not more than one of the six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on ENBREL experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo ($p=0.007$). From the start of part 2, the median time to flare was ≥116 days for patients who received ENBREL and 28 days for patients who received placebo. Each component of the JRA core set criteria worsened in the arm that received placebo and remained stable or improved in the arm that continued on ENBREL. The data suggested the possibility of a higher flare rate among those patients with a higher baseline ESR. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on ENBREL continued to improve from month 3 through month 7, while those who received placebo did not improve.

In an open-label, safety extension study, 58 paediatric patients from the above study (from the age of 4 years at time of enrolment) continued to receive ENBREL for up to 10 years. Rates of serious adverse events and serious infections did not increase with long-term exposure.

In another open-label single-arm study (n=127), 60 patients with extended oligoarthritis (EO) (15 patients aged 2 to 4, 23 patients aged 5 to 11 and 22 patients aged 12 to 17 years old), 38 patients with enthesitis-related arthritis (12 to 17 years old), and 29 patients with psoriatic arthritis (12 to 17 years old) were treated with ENBREL at a dose of 0.8 mg/kg (up to a maximum of 50 mg per dose) administered weekly for 12 weeks. In each of the JIA subtypes, the majority of patients met ACR Pedi 30 criteria and demonstrated clinical improvement in secondary endpoints such as number of tender joints and physician global assessment. The safety profile was consistent with that observed in other JIA studies.

Of the 127 patients in the parent study, 109 participated in the open-label extension study and were followed for an additional 8 years for a total of up to 10 years. At the end of the extension study, 84/109 (77%) patients had completed the study; 27 (25%) while actively taking ENBREL; 7 (6%) had withdrawn from treatment due to low/inactive disease; 5 (5%) had re-started ENBREL following an earlier withdrawal from treatment; and 45 (41%) had stopped ENBREL (but remained under observation); 25/109 (23%) patients permanently discontinued from the study. Improvements in clinical status achieved in the parent study were generally maintained for all efficacy endpoints during the entire follow-up period. Patients actively taking ENBREL could enter an optional withdrawal re-treatment period once during the extension study based on investigator's judgement of clinical response. 30 patients entered the withdrawal period. 17 patients were reported to have a flare (defined as ≥30% worsening in at least 3 of the 6 ACR Pedi components with ≥30% improvement in not more than 1 of the remaining 6 components and a minimum of 2 active joints); median time to flare after ENBREL withdrawal was 190 days. 13 patients were re-treated and the median time to re-treatment from withdrawal was estimated as 274 days. Due to the exploratory nature of these study endpoints and small number of data points, these results should be interpreted with caution.

One malignancy, Hodgkin's disease was reported in the first year of the extension study in an 18 year old EO JIA patient. The number (exposure-adjusted rate per 100 patient years) of serious adverse events, malignancies, and serious infections was 40 (5.85 EP100PY), 1 (0.15 EP100PY), and 14 (2.05 EP100PY), respectively. The safety profile was consistent with that observed in other JIA studies.

Studies have not been done in patients with juvenile idiopathic arthritis to assess the effects of continued ENBREL therapy in patients who do not respond within 3 months of initiating ENBREL therapy. Additionally, studies have not been conducted to assess the effects of reducing the recommended dose of ENBREL following its long-term use in patients with JIA.

Long-term safety of ENBREL monotherapy (n=103), ENBREL plus methotrexate (n=294), or methotrexate monotherapy (n=197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years of age. Overall, infections were more commonly reported in patients treated with ENBREL compared to methotrexate alone (3.8% vs. 2%), and the infections associated with ENBREL use were of a more severe nature.

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 of methotrexate. Doses of 25 mg 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). The PsARC endpoint comprises of four measures: (1) patient global assessment, (2) physician global assessment, (3) joint pain/tenderness score and (4) joint swelling score. Achievement of the PsARC endpoint requires improvement in at least two of the four measures, one of which must be joint pain/tenderness or swelling, and no worsening in any of the four measures. Data have not been evaluated to establish whether ENBREL inhibits progressive joint destruction in psoriatic arthritis. Results are summarised in the table below.

RESPONSES OF PATIENTS WITH PSORIATIC ARTHRITIS IN PLACEBO-CONTROLLED TRIAL

Psoriatic Arthritis Response	**Percent of Patients**	
	Placebo n = 104	**ENBREL[a] n = 101**
ACR 20		
Month 3	15	59[b]
Month 6	13	50[b]
ACR 50		
Month 3	4	38[b]
Month 6	4	37[b]
ACR 70		
Month 3	0	11[b]
Month 6	1	9[c]
PsARC		
Month 3	31	72[b]
Month 6	23	70[b]

[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 ($p < 0.001$). There is insufficient evidence of the efficacy of ENBREL in patients with ankylosing spondylitis-like psoriatic arthropathy due to the small number of patients studied.

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, $p \leq 0.001$). 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) ANNUALISED CHANGE FROM BASELINE IN TOTAL SHARP SCORE

Time	Placebo (n = 104)	ENBREL (n = 101)
Month 12	1.00 (0.29)	-0.03 (0.09)[a]

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 a visual analogue 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

	Percent of Patients	
Ankylosing Spondylitis Response	**Placebo n= 139**	**ENBREL n= 138**
ASAS 20		
2 weeks	22	46[a]
3 months	27	60[a]
6 months	23	58[a]
ASAS 50		
2 weeks	7	24[a]
3 months	13	45[a]
6 months	10	42[a]

ASAS 70		
2 weeks	2	12[b]
3 months	7	29[b]
6 months	5	28[b]

[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 Non-radiographic Axial Spondyloarthritis

Study 1

The efficacy of ENBREL in patients with non-radiographic axial spondyloarthritis (nr-AxSpa) was assessed in a randomised, 12-week double-blind, placebo-controlled study. The study evaluated 215 adult patients (modified intent-to-treat population) with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS. Patients were also required to have an inadequate response to two or more NSAIDs. In the double-blind period, patients received ENBREL 50 mg weekly or placebo for 12 weeks. The primary measure of efficacy (ASAS 40) was a 40% improvement in at least three of the four ASAS domains and absence of deterioration in the remaining domain. MRIs of the sacroiliac joint and spine were obtained to assess inflammation at baseline and at week 12. The double-blind period was followed by an open-label period during which all patients receive ENBREL 50 mg weekly for up to an additional 92 weeks.

Compared to placebo, treatment with ENBREL resulted in statistically significant improvement in the ASAS 40, ASAS 20 and ASAS 5/6. Significant improvement was also observed for the ASAS partial remission and BASDAI 50. Week 12 results are shown in the table below.

EFFICACY RESPONSE IN PLACEBO-CONTROLLED NR-AXSPA STUDY: PERCENT OF PATIENTS ACHIEVING ENDPOINTS

Double-blind Clinical Responses at Week 12	**Placebo N=106 to 109***	**ENBREL N=103 to 105***
ASAS** 40	15.7	32.4[b]
ASAS 20	36.1	52.4[c]
ASAS 5/6	10.4	33.0[a]
ASAS partial remission	11.9	24.8[c]
BASDAI*** 50	23.9	43.8[b]

* Some patients did not provide complete data for each endpoint.
** ASAS=Assessments in Spondyloarthritis International Society.
*** Bath Ankylosing Spondylitis Disease Activity Index.
[a]: p <0.001, [b]: <0.01 and [c]: <0.05, respectively, between ENBREL and placebo.

At week 12, there was a statistically significant improvement in the SPARCC (Spondyloarthritis Research Consortium of Canada) score for the sacroiliac joint as measured by MRI for patients

receiving ENBREL. Adjusted mean change from baseline was 3.8 for ENBREL-treated (n = 95) versus 0.8 for placebo-treated (n = 105) patients (p <0.001).

Health-related quality of life and physical function were assessed using the BASFI, EuroQol 5D and the SF-36 questionnaires. ENBREL showed statistically significantly greater improvement in the BASFI, EQ5D Overall Health State Score and the SF-36 Physical Component Score (PCS) from baseline to week 12 compared to placebo.

Clinical responses among nr-AxSpa patients who received ENBREL were apparent at the time of the first visit (2 weeks) and were maintained through 2 years of therapy. Improvements in health-related quality of life and physical function were also maintained through 2 years of therapy. The 2 year data did not reveal any new safety findings.

Study 2

This multi-centre, open-label, Phase 4, 3-period study evaluated the withdrawal and re-treatment of ENBREL in patients with active nr-AxSpa who achieved an adequate response (inactive disease defined as Ankylosing Spondylitis Disease Activity Score (ASDAS) C-reactive protein (CRP) less than 1.3) following 24 weeks of treatment.

209 adult patients with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the Assessment of SpondyloArthritis International Society (ASAS) classification criteria of axial spondyloarthritis (but not meeting the modified New York criteria for AS), having positive MRI findings (active inflammation on MRI highly suggestive of sacroiliitis associated with SpA) and/or positive hsCRP (defined as high sensitivity C-reactive protein [hsCRP] >3 mg/l), and active symptoms defined by an ASDAS CRP greater than or equal to 2.1 at the screening visit received open-label ENBREL 50 mg weekly plus stable background NSAID at the optimal tolerated anti-inflammatory dosage for 24 weeks in Period 1. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. At week 24, 119 (57%) patients achieved inactive disease and entered into the Period 2 40-week withdrawal phase where subjects discontinued etanercept, yet maintained the background NSAID. The primary measure of efficacy was the occurrence of flare (defined as an ASDAS erythrocyte sedimentation rate (ESR) greater than or equal to 2.1) within 40 weeks following withdrawal of ENBREL. Patients who flared were re-treated with ENBREL 50 mg weekly for 12 weeks (Period 3).

In Period 2, the proportion of patients experiencing ≥1 flare increased from 22% (25/112) at week 4 to 67% (77/115) at week 40. Overall, 75% (86/115) patients experienced a flare at any time point within 40 weeks following withdrawal of ENBREL.

The key secondary objective of Study 2 was to estimate time to flare after withdrawal of ENBREL and additionally compare the time to flare to patients from Study 1 who met the Study 2 withdrawal phase entry requirements and continued ENBREL therapy.

The median time to flare following withdrawal of ENBREL was 16 weeks (95% CI: 13-24 weeks). Less than 25% of patients in Study 1 who did not have treatment withdrawn experienced a flare over the equivalent 40 weeks as in Period 2 Study 2. The time to flare was statistically significantly shorter in subjects who discontinued ENBREL treatment (Study 2) compared to subjects who received continuous etanercept treatment (Study 1), p<0.0001.

Adult Patients with Plaque Psoriasis

ENBREL is recommended for use in patients as defined in the **4.1 Therapeutic Indications** section. 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 in patients with moderate to severe psoriasis (responsive to 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 three 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 and 3 are shown below.

RESPONSES OF PATIENTS WITH PSORIASIS IN STUDIES 2, 3 AND 4

Response (%)	Study 2					Study 3			Study 4		
	Placebo	----------ENBREL---------				Placebo	-----ENBREL-----		Placebo	----ENBREL----	
		25 mg BIW		50 mg BIW			25 mg BIW	50 mg BIW		50 mg QW	50 mg QW
	n = 166 wk 12	n = 162 wk 12	n = 162 wk 24[a]	n = 164 wk 12	n = 164 wk 24[a]	n = 193 wk 12	n = 196 wk 12	n = 196 wk 12	n = 46 wk 12	n = 96 wk 12	n = 90 wk 24[a]
PASI 50	14	58*	70	74*	77	9	64*	77*	9	69*	83
PASI 75	4	34*	44	49*	59	3	34*	49*	2	38*	71
DSGA[b], clear or almost clear	5	34*	39	49*	55	4	39*	57*	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 ≥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.

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 a sPGA score ≥3, involving ≥10% of the BSA, and PASI ≥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.

PAEDIATRIC PLAQUE PSORIASIS OUTCOMES AT 12 WEEKS

	ENBREL 0.8 mg/kg Once Weekly (N = 106)	**Placebo (N = 105)**
PASI 75, n (%)	60 (57%)[a]	12 (11%)
PASI 50, n (%)	79 (75%)[a]	24 (23%)
sPGA "clear" or "minimal," n (%)	56 (53%)[a]	14 (13%)

Abbreviation: sPGA-static Physician Global Assessment.
[a]: p <0.0001 compared with placebo.

After the 12-week double-blind treatment period, all patients who entered the open-label period 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.

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 4.8% 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%.

5.2 Pharmacokinetic Properties

Etanercept serum values were determined by ELISA method, which may detect ELISA-reactive degradation products as well as the parent compound.

Absorption

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% as calculated in a population pharmacokinetic analysis of several studies. With twice weekly doses, it is anticipated that steady-state concentrations may be 2- to 5-fold greater than those observed after single doses.

Serum concentration profiles at steady state were comparable among patients with RA treated with 50 mg ENBREL powder for injection once weekly and those treated with 25 mg ENBREL powder for injection twice weekly. A single 50 mg/mL injection of ENBREL was also found to be bioequivalent to two simultaneous injections of 25 mg/mL. The mean (±standard deviation) C_{max}, C_{min}, and partial AUC were 2.4 ± 1.5 mg/L, 1.2 ± 0.7 mg/L, and 297 ± 166 mg•h/L, respectively, for patients treated with 50 mg ENBREL once weekly (n = 21); and 2.6 ± 1.2 mg/L, 1.4 ± 0.7 mg/L, and 316 ± 135 mg•h/L for patients treated with 25 mg ENBREL twice weekly (n = 16). Serum concentrations in patients with rheumatoid arthritis have not been measured for periods of dosing that exceed 6 months. In an open-label, single-dose, two treatment crossover study in healthy volunteers, ENBREL administered as a single injection of ENBREL 50 mg solution for injection was found to be bioequivalent to two simultaneous injections of ENBREL 25 mg powder for injection. The mean (±standard deviation) C_{max} and $AUC_{(0-t)}$ are expressed in the table below.

	AUC_{0-t} (mg h/L)	**C_{max} (mg/L)**
1 x 50 mg solution SC (n = 33)	535 ± 192	3.90 ± 1.49
2 x 25 mg solution SC (n = 33)	590 ± 208	4.09 ± 1.65
Point Estimate (%) 90% CI	91.3 (80.9, 103.1)	96.8 (84.1, 111.3)

In a population pharmacokinetics analysis in ankylosing spondylitis patients the ENBREL steady-state AUCs were 466 mg h/L and 474 mg h/L for 50 mg ENBREL once weekly (n = 154) and 25 mg twice weekly (n = 148), respectively.

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

Distribution

After a single subcutaneous dose of 25 mg etanercept, the average maximum serum concentration observed in healthy volunteers was 1.65± 0.66 μg/mL, and the area under the curve was 235 ± 96.6 μg•hr/mL. Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

A bi-exponential curve is required to describe the concentration time curve of ENBREL. The central volume of distribution of ENBREL is 7.6 L, while the volume of distribution at steady-state is 13.9 ± 9.4 L.

After continued dosing of RA patients (n = 25) with ENBREL for 6 months with 25 mg twice weekly, the median observed level was 3.0 mg/L (range 1.7 to 5.6 mg/L). Based on the available data, individual patients may undergo a 2- to 5-fold increase in serum levels with repeated dosing.

Elimination

Etanercept is cleared slowly from the body. The half-life is long, approximately 80 hours. Clearance is approximately 175 ± 116 mL/hr in patients with rheumatoid arthritis, somewhat lower than the value of 131 ± 81 mL/hr observed in healthy volunteers. Additionally, the pharmacokinetics of etanercept in rheumatoid arthritis patients, plague psoriasis and ankylosing spondylitis patients are similar.

Radioactivity is eliminated in urine after administration of radiolabeled etanercept to patients and

volunteers.

Elderly Patients

The impact of advanced age was studied in the population pharmacokinetic analysis of ENBREL 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.

Renal Impairment or Hepatic Impairment

Although there is elimination of radioactivity in urine after administration of radiolabeled etanercept to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal or hepatic failure. The presence of renal or hepatic impairment should not require a change in dosage.

Paediatric Patients with Juvenile Idiopathic Arthritis

In a polyarticular-course juvenile chronic arthritis trial with ENBREL, 69 patients (aged 4 to 17 years) were administered 0.4 mg ENBREL/kg twice weekly for three months. Serum concentration profiles were similar to those seen in adult rheumatoid arthritis patients. The youngest children (4 years of age) had reduced clearance (increased clearance when normalised by weight) compared with older children (12 years of age) and adults. Simulation of dosing suggests that while older children (10-17 years of age) will have serum levels close to those seen in adults, younger children will have appreciably lower levels.

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 μg/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.

Gender

There is no apparent pharmacokinetic difference between men and women.

Paediatric Use

ENBREL has not been studied in children <2 years of age (see Sections **4.1 Therapeutic Indications** and **4.2 Posology and Method of Administration**). For paediatric specific safety information concerning malignancies and vaccinations (see Section **4.4 Special Warnings and Precautions for Use**).

5.3 Preclinical Safety Data

Carcinogenicity

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of etanercept. Long-term animal studies are not feasible because animals can develop antibodies to etanercept, which is a human protein.

Mutagenicity

Mutagenesis studies were conducted *in vitro* and *in vivo*, and no evidence of mutagenic activity was observed.

Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the effect of etanercept on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

ENBREL lyophilised powder:
Mannitol
Sucrose
Trometamol (Tromethamine)

ENBREL pre-filled syringe:
Sucrose
Sodium chloride
L-arginine hydrochloride
Sodium phosphate monobasic dihydrate
Sodium phosphate dibasic dihydrate
Water

6.2 Incompatibilities

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

6.3 Shelf Life

Refer to EXP on carton/label.

6.4 Special Precautions for Storage

Powder and Solvent for Solution for Injection

Store refrigerated at 2°C to 8°C (36°F to 46°F) before reconstitution. **DO NOT FREEZE.** It is recommended that ENBREL solution be administered immediately after reconstitution.

If not used immediately, the reconstituted ENBREL solution may be refrigerated in the vial at 2°C to 8°C (36°F to 46°F) for up to 6 hours. The solution should be discarded if not used within 6 hours. Following refrigeration, the solution should be allowed to reach room temperature prior to injection.

Prior to reconstitution, the powder may be stored at temperatures up to a maximum of 25°C for a single period of up to 4 weeks. ENBREL should be discarded if exposed to high temperatures, or if not used within 4 weeks of initial removal from refrigeration.

Solution for Injection in Pre-filled Syringe

ENBREL pre-filled syringe must be stored refrigerated at 2°C to 8°C (36°F to 46°F).

May be stored at temperatures up to a maximum of 25°C for a single period of up to 4 weeks.

ENBREL should be discarded if exposed to high temperatures, or if not used within 4 weeks of initial removal from refrigeration.

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

Solution for Injection in Pre-filled Pen

ENBREL pre-filled pen must be stored refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze.

May be stored at temperatures up to a maximum of 25°C for a single period of up to 4 weeks.

ENBREL pre-filled pen should be discarded if exposed to high temperatures, or if not used within 4 weeks of initial removal from refrigeration.

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

Keep out of reach of children.

7. PRODUCT OWNER

Pfizer Inc.,
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ENB-SIN-0822/1
Date of last revision: November 2022