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ETANERCEPT

ENBREL®
25 mg/0.5 mL and 50 mg/mL Solution for Injection (Pre-filled Syringe)

1.0 PHARMACOLOGIC CATEGORY

Immunosuppressive Agent

2.0 DESCRIPTION

Etanercept is a human tumor necrosis factor receptor (TNFR) p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. Etanercept is a dimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human tumor necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. The Fc component of etanercept contains the hinge, CH_2 and CH_3 regions but not the CH_1 region of IgG1.

Solubility: Etanercept is soluble in water.

Molecular weight: (apparent) 150 kilodaltons.

Physical characteristics

The solution for injection in the pre-filled syringe is clear to opalescent, colorless 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.

3.0 FORMULATION/COMPOSITION

Etanercept (Enbrel) dosage forms are intended for subcutaneous injection.

Each pre-filled syringe contains 25 mg or 50 mg of Etanercept (active ingredient).

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Rheumatoid arthritis

Etanercept (Enbrel) is indicated for reducing signs and symptoms and inhibiting the progression of structural damage in patients with moderately to severely active rheumatoid arthritis (RA). Etanercept (Enbrel) can be initiated in combination with methotrexate or used alone.

Etanercept (Enbrel) can be used alone or in combination with methotrexate for the treatment of active RA in adults when the response to one or more disease modifying anti-rheumatic drugs (DMARDs), including methotrexate (unless contraindicated), has proved inadequate.

Juvenile idiopathic arthritis

Treatment of polyarticular-course juvenile idiopathic arthritis (JIA) in children and adolescents from the age of 2 years when the response to one or more DMARDs has proved inadequate.

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.

Psoriatic arthritis

Etanercept (Enbrel) is indicated for reducing signs and symptoms and inhibiting the progression of structural damage of active arthritis in patients with psoriatic arthritis. Etanercept (Enbrel) can be used in combination with methotrexate in adult patients who do not respond adequately to methotrexate alone.

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Etanercept (Enbrel) is indicated for reducing signs and symptoms in patients with ankylosing spondylitis.

Non-radiographic axial spondyloarthritis

Etanercept (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, or are intolerant to, conventional therapy.

Plaque psoriasis

Etanercept (Enbrel) is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Pediatric plaque psoriasis

Etanercept (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 Dosage and Method of Administration

Use in adults

Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis

Patients aged 18 years or older: 50 mg etanercept (Enbrel) per week administered either once weekly (as one subcutaneous injection using a 50 mg syringe or as two 25 mg injections given at approximately the same time) or 25 mg etanercept (Enbrel) twice weekly (72 to 96 hours apart) as a subcutaneous injection.

Methotrexate, glucocorticoids, salicylates, non-steroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with etanercept (Enbrel) in adults.

Twenty-five mg administered once weekly gives a slower response and may be less effective.

Plaque psoriasis

The dose of etanercept (Enbrel) is 50 mg once weekly (as one subcutaneous injection using a 50 mg syringe or as two 25 mg injections given at approximately the same time) or 25 mg twice weekly (72 to 96 hours apart) as a subcutaneous injection. Higher responses may be achieved from initial treatment with a dose of 50 mg twice weekly for up to 12 weeks, followed, if necessary, by a dose of 50 mg once weekly or 25 mg twice weekly.

Adult patients may be treated intermittently or continuously, based on physician judgment and individual patient needs (see section **5.1 Pharmacodynamic Properties**). Treatment should be discontinued in patients who show no response after 12 weeks. With intermittent use, treatment cycles subsequent to the initial cycle should use a dose of 50 mg once weekly or 25 mg twice weekly.

Pediatric population

The dosage of etanercept (Enbrel) is based on body weight for pediatric patients. Patients weighing less than 62.5 kg should be accurately dosed on a mg/kg basis using etanercept (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.

Juvenile idiopathic arthritis (age 2 years and above)

Children (≥2 to <18 years): 0.4 mg/kg (up to a maximum of 25 mg per dose) twice weekly (72 to 96 hours apart), or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly.

Glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with etanercept (Enbrel) in children.

Etanercept (Enbrel) has not been studied in children <2 years of age.

Pediatric plaque psoriasis (age 6 years and above)

Children (≥6 to <18 years): 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 etanercept (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.

Elderly (≥65 years)

No dosage adjustment is required.

Renal impairment

No dosage adjustment is required.

Hepatic impairment

No dosage adjustment is required.

Method of administration

Administer etanercept (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 etanercept (Enbrel) must be instructed in injection techniques. The first injection should be performed under the supervision of a qualified healthcare professional if etanercept (Enbrel) is to be administered by a patient or caregiver.

Before injection, etanercept (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, colorless to yellow or pale brown, and liquid may contain trace levels of translucent to white amorphous particles.

See also enclosed **Instructions for Patients: Preparing and Injecting Etanercept (Enbrel)**.

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.

Pediatric use

Etanercept (Enbrel) has not been studied in children <2 years of age (see section **4.1 Therapeutic Indications**). For pediatric specific safety information concerning malignancies and vaccinations, see sections **4.4 Special Warnings and Precautions for Use** and **4.8 Undesirable Effects**.

4.3 Contraindications

Hypersensitivity to any component of the product formulation, such as etanercept, sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate, and water for injection.

Sepsis or risk of sepsis (see sections **4.4 Special Warnings and Precautions for Use** and **4.8 Undesirable Effects**).

Treatment with Etanercept (Enbrel) should not be initiated in patients with serious active infections, including chronic or localized infections.

4.4 Special Warnings and Precautions for Use

Infections

Serious infections, including sepsis and tuberculosis (TB), have been reported with the use of etanercept (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 (Enbrel) should be monitored closely. Administration of etanercept (Enbrel) should be discontinued if a patient develops a serious infection. Caution should be exercised when considering the use of etanercept (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 etanercept (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 etanercept (Enbrel). In some cases, fungal and other opportunistic infections are not recognized, 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 etanercept (Enbrel). Tuberculosis may be due to reactivation of latent TB infection or to new infection.

Before initiation of therapy with etanercept (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 etanercept (Enbrel). Some patients who tested negative for latent TB prior to receiving etanercept (Enbrel) have developed active TB. Physicians should monitor patients receiving etanercept (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 etanercept (Enbrel) has been reported. 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.

Caution should be exercised when administering etanercept (Enbrel) in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection.

Worsening of hepatitis C

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

Concurrent treatment with anakinra

Concurrent administration of etanercept (Enbrel) and anakinra has been associated with an increased risk of serious infections and neutropenia. 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**).

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and etanercept (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

etanercept (Enbrel) to standard treatment (including cyclophosphamide and high-dose steroids) was no more efficacious than standard treatment alone. The group of patients who received etanercept (Enbrel) experienced more non-cutaneous malignancies of various types than the patient group receiving standard treatment alone. The use of etanercept (Enbrel) for treatment of Wegener's granulomatosis is not recommended.

Alcoholic hepatitis

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

Allergic reactions

Allergic reactions associated with etanercept (Enbrel) administration have been reported. If any serious allergic or anaphylactic reaction occurs, discontinue administration of etanercept (Enbrel) immediately (see section **4.8 Undesirable Effects**).

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

Immunosuppression

Anti-TNF therapies, including etanercept (Enbrel), may affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses.

Malignancies and lymphoproliferative disorders

Solid and hematopoietic 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 leukemia have been reported in patients treated with TNF-antagonists. There is an increased background risk for lymphoma and leukemia 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 etanercept (Enbrel) have neither confirmed nor excluded an increased risk for malignancies.

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 etanercept (Enbrel). Most of the patients were receiving concomitant immunosuppressants.

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

Skin cancers

Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists including etanercept (Enbrel). Post-marketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with etanercept (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 etanercept (Enbrel), more cases of NMSC were observed in patients receiving etanercept (Enbrel) compared with control patients, particularly in patients with psoriasis.

Hematologic reactions

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

Autoantibody formation

Treatment with etanercept (Enbrel) may be associated with the formation of autoimmune antibodies (see section **4.8 Undesirable Effects**).

Vaccinations

In a double-blind, placebo-controlled, randomized 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 etanercept (Enbrel) were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had two-fold rises in titers compared to patients not receiving etanercept (Enbrel). The clinical significance of this is unknown. Live vaccines should not be given concurrently with etanercept (Enbrel). If possible, bring pediatric patients up to date with immunizations according to current local guidelines before beginning etanercept (Enbrel) therapy.

Neurological disorders

Although no clinical trials have been performed evaluating etanercept (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 etanercept (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 etanercept (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 etanercept (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 etanercept (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 etanercept (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 etanercept (Enbrel) in patients who also have CHF.

Hypoglycemia in patients treated for diabetes

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

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Concurrent treatment with anakinra

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

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and etanercept (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 sulfasalazine

In a clinical study of patients who were receiving established doses of sulfasalazine, to which etanercept (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 etanercept (Enbrel) or sulfasalazine alone. The clinical significance of this interaction is unknown.

Non-interactions

No interactions have been observed when etanercept (Enbrel) was administered with glucocorticoids, salicylates (except sulfasalazine), non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate in clinical trials with adult rheumatoid arthritis patients.

Methotrexate has no effect on the pharmacokinetics of etanercept.

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

4.6 Fertility, Pregnancy and Lactation

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. Etanercept (Enbrel) should only be used during pregnancy if the potential benefits to the mother outweigh the potential risks to the fetus.

Preclinical data about peri- and post-natal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available. 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 fetus in rats or rabbits or neonatal rats due to etanercept was observed. Animal reproduction 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 etanercept (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 etanercept (Enbrel) is generally not recommended.

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 and not detected in infant circulation. Etanercept (Enbrel) can be used during breastfeeding if clearly needed.

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

Adult patients

The proportion of patients who discontinued treatment due to adverse reactions in controlled clinical studies in patients with rheumatoid arthritis was the same in both the etanercept (Enbrel) and placebo treatment groups.

Injection site reactions

Patients in controlled clinical studies treated with etanercept (Enbrel) had a significantly higher incidence of injection site reactions (erythema and/or itching, pain, or swelling) compared with placebo-treated patients. The frequency of injection site reactions was greatest in the first month and subsequently decreased in frequency. In clinical trials, these reactions were generally transient with a mean duration of 4 days. Some patients who experienced injection site reactions also experienced reactions at previous injection sites.

In post-marketing experience, injection site bleeding and bruising have also been observed in conjunction with etanercept (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*.

In controlled trials in patients with rheumatoid arthritis, the rates of reported serious (fatal, life-threatening, or required hospitalization or intravenous antibiotics) and non-serious infections were similar for etanercept (Enbrel) and placebo when adjusted for duration of exposure. Upper respiratory infections were the most commonly reported non-serious infections.

Data from a clinical trial in patients with established sepsis suggest that etanercept (Enbrel) treatment may increase mortality in these patients.

Malignancies and lymphoproliferative disorders

Reports of malignancies affecting various sites have 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

In controlled trials, the percentage of patients who developed new positive antinuclear antibodies [ANA] (≥1:40), new positive anti-double-stranded DNA antibodies, and new anticardiolipin antibodies was increased compared to placebo-treated patients. The impact of long-term treatment with etanercept (Enbrel) on the development of autoimmune diseases is unknown.

Rare reports have been described in patients, including those with rheumatoid factor positive RA, who have developed additional autoantibodies in conjunction with a lupus-like syndrome or rashes compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy (see table below, **Other Adverse Reactions**).

Other Adverse Reactions

The following table of suspected undesirable effects is based on clinical trials and/or spontaneous post-marketing reporting rates:

Adverse Drug Reaction Table

System Organ Class	Adverse Drug Reactions
Infections and infestations	Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis, and parasitic infection)
	Tuberculosis
	Hepatitis B reactivation*
	Infection (including upper respiratory tract infection, bronchitis, cystitis, skin infection)
	Opportunistic infection (including invasive fungal, bacterial, atypical mycobacterial, viral infections, and Legionella) (see section **4.4 Special Warnings and Precautions for Use**)
	Listeria*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Malignant melanoma (see section **4.4 Special Warnings and Precautions for Use**)
	Merkel cell carcinoma* (see section **4.4 Special Warnings and Precautions for Use**)
	Lymphoma*
	Leukemia*
	Non-melanoma skin cancers (see section **4.4 Special Warnings and Precautions for Use**)
Blood and lymphatic system disorders	Aplastic anemia* (see section **4.4 Special Warnings and Precautions for Use**)
	Pancytopenia (see section **4.4 Special Warnings and Precautions for Use**)
	Thrombocytopenia
	Anemia
	Leukopenia
	Neutropenia
	Histiocytosis hematophagic (macrophage activation syndrome)*
Immune system disorders	Serious allergic/anaphylactic reactions (including bronchospasm)
	Vasculitis (including ANCA positive vasculitis)
	Sarcoidosis
	Allergic reactions (*see Skin and subcutaneous tissue disorders, below*)
	Autoantibody formation
Nervous system disorders	CNS demyelinating events, including multiple sclerosis and localized 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
	Headache*
Eye disorders	Uveitis
	Scleritis
Cardiac disorders	New onset cardiac failure congestive
	Worsening of cardiac failure congestive
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease (including pulmonary fibrosis and pneumonitis)

Gastrointestinal disorders	Inflammatory bowel disease*
Hepatobiliary disorders	Autoimmune hepatitis
	Elevated liver enzymes (*see Elevated liver enzymes above*)
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome*
	Toxic epidermal necrolysis*
	Angioedema
	Cutaneous vasculitis (including hypersensitivity vasculitis)
	Erythema multiforme*
	Psoriasis (new onset or exacerbation, including all sub-types)
	Urticaria
	Pruritus
	Psoriasiform rash*
	Rash
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.

Pediatric Population

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

Undesirable effects in pediatric patients with juvenile idiopathic arthritis

Infection was the most common adverse event reported in pediatric patients taking etanercept (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 pediatric 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 etanercept (Enbrel).

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

Undesirable effects in pediatric patients with plaque psoriasis

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

4.9 Overdose and Treatment

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 2,000 mg/kg or a single intravenous dose of 1,000 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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group

TNF-alpha Inhibitor.
ATC code: L04AB01.

Geriatric use

No specific dosage adjustments of etanercept (Enbrel) are recommended based on patient age.

Mechanism of action

Etanercept is a dimeric soluble form of the p75 TNF (tumor necrosis factor) receptor that can bind to two TNF molecules. Etanercept inhibits binding of both TNF (TNF_α) and lymphotoxin alpha [LT_α] (TNF_β) to cell surface TNF receptors, thus rendering TNF biologically inactive and preventing TNF-mediated cellular responses. TNF is a dominant cytokine in the inflammatory process of adult rheumatoid arthritis patients. TNF and LT_α are expressed in patients with juvenile idiopathic arthritis. Elevated levels of TNF are found in the synovial fluid of patients with rheumatoid arthritis and juvenile idiopathic arthritis. In plaque psoriasis, infiltration by inflammatory cells including T-cells leads to increased TNF levels in psoriatic lesions compared with levels in uninvolved skin. Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75) exist naturally as monomeric molecules on cell surfaces and in soluble forms. The biological activity of TNF is dependent upon binding to either cell surface receptor. Etanercept may also modulate biologic responses controlled by additional molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by tumor necrosis factor. Etanercept 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

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 pediatric subjects with plaque psoriasis.

Adult patients with rheumatoid arthritis

The efficacy of etanercept (Enbrel) was assessed in a randomized, 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 Etanercept (Enbrel) or placebo were administered subcutaneously (SC) twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria.

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

Approximately 15% of subjects who received etanercept (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 etanercept (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. Etanercept (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 etanercept (Enbrel) compared to controls at 3 and 6 months.

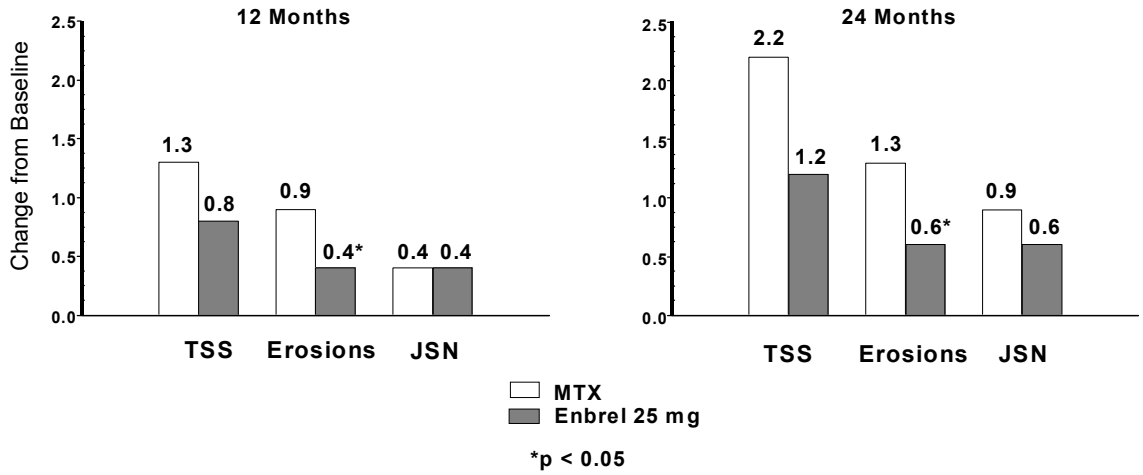
After discontinuation of etanercept (Enbrel), symptoms of arthritis generally returned within a month. Re-introduction of treatment with etanercept (Enbrel) after discontinuations of up to 24 months resulted in the same magnitude of responses as patients who received etanercept (Enbrel) without interruption 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 etanercept (Enbrel) without interruption.

The efficacy of etanercept (Enbrel) was compared to methotrexate in a second randomized, active-controlled study with blinded radiographic evaluations as a primary endpoint in 632 adult patients with active rheumatoid arthritis (<3 years duration) who had never received treatment with methotrexate. Doses of 10 mg or 25 mg etanercept (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 etanercept (Enbrel) 25 mg was similar to that seen in the previous trials, and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with etanercept (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 etanercept (Enbrel) dose had consistently less effect on structural damage than the 25 mg dose. Etanercept (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 etanercept (Enbrel) 25 mg. The results are shown in the figure below.

RADIOGRAPHIC PROGRESSION: COMPARISON OF ETANERCEPT (ENBREL) vs. METHOTREXATE IN PATIENTS WITH RA OF <3 YEARS DURATION



In another active-controlled, double-blind, randomized study, clinical efficacy, safety, and radiographic progression in RA patients treated with etanercept (Enbrel) alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg), and of the combination of etanercept (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.

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

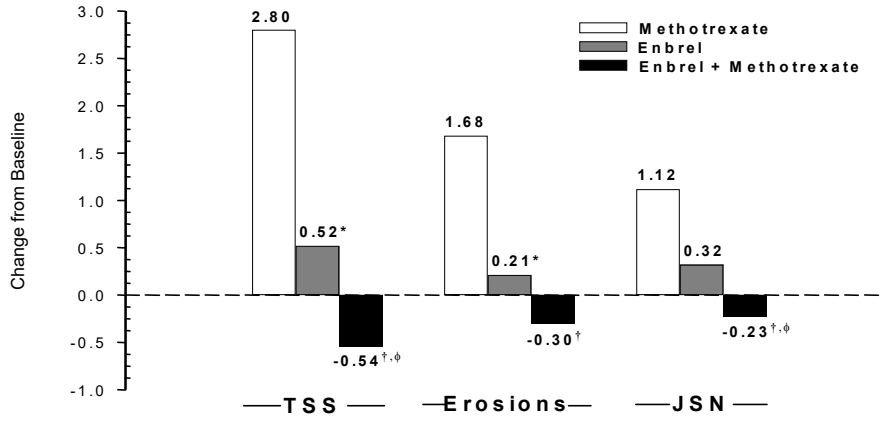
CLINICAL EFFICACY RESULTS AT 12 MONTHS: COMPARISON OF ETANERCEPT (ENBREL) vs. METHOTREXATE vs. ETANERCEPT (ENBREL) IN COMBINATION WITH METHOTREXATE IN PATIENTS WITH RA OF 6 MONTHS TO 20 YEARS DURATION

Endpoint	Methotrexate (n = 228)	Etanercept (Enbrel) (n = 223)	Etanercept (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 Etanercept (Enbrel) + methotrexate vs. methotrexate and ϕ = $p < 0.05$ for comparisons of Etanercept (Enbrel) + methotrexate vs. Etanercept (Enbrel).

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

RADIOGRAPHIC PROGRESSION: COMPARISON OF ETANERCEPT (ENBREL) vs. METHOTREXATE vs. ETANERCEPT (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 etanercept (Enbrel) vs. methotrexate, † = $p < 0.05$ for comparisons of etanercept (Enbrel) + methotrexate vs. methotrexate and ϕ = $p < 0.05$ for comparisons of etanercept (Enbrel) + methotrexate vs. etanercept (Enbrel).

Significant advantages for etanercept (Enbrel) in combination with methotrexate compared with etanercept (Enbrel) monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the significant advantages for etanercept (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 etanercept (Enbrel) in combination with methotrexate group compared with the etanercept (Enbrel) alone and methotrexate alone groups (62%, 50%, and 36%, respectively; $p < 0.05$). The difference between etanercept (Enbrel) alone and methotrexate alone was also significant ($p < 0.05$). Among patients who completed a full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively.

The safety and efficacy of 50 mg etanercept (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 etanercept (Enbrel) once weekly and 153 patients received 25 mg etanercept (Enbrel) twice weekly. The safety and efficacy profiles of the two etanercept (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.

Pediatric population with juvenile idiopathic arthritis

The safety and efficacy of etanercept (Enbrel) were assessed in a two-part study in 69 children with polyarticular-course juvenile idiopathic arthritis who had a variety of juvenile idiopathic arthritis onset types (polyarthritis, pauciarthritis, systemic-onset). Patients ages 4 to 17 years with moderately to severely active polyarticular course juvenile idiopathic 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) etanercept (Enbrel) subcutaneously twice weekly. In part 2, patients with a clinical response at day 90 were randomized to remain on etanercept (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 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 etanercept (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 etanercept (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 etanercept (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 etanercept (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 pediatric patients from the above study (from the age of 4 years at time of enrolment) continued to receive etanercept (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 etanercept (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 etanercept (Enbrel), 7 (6%) had withdrawn from treatment due to low/inactive disease; 5 (5%) had re-started etanercept (Enbrel) following an earlier withdrawal from treatment; and 45 (41%) had stopped etanercept (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 etanercept (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 etanercept (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 small number of data points, these results should be interpreted with caution.

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 etanercept (Enbrel) therapy in patients who do not respond within 3 months of initiating etanercept (Enbrel) therapy. Additionally, studies have not been conducted to assess the effects of reducing the recommended dose of etanercept (Enbrel) following its long-term use in patients with JIA.

Long-term safety of etanercept (Enbrel) monotherapy (n = 103), etanercept (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 etanercept (Enbrel) compared to methotrexate alone (3.8 versus 2%), and the infections associated with etanercept (Enbrel) use were of a more severe nature.

Adult patients with psoriatic arthritis

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

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

RESPONSES OF PATIENTS WITH PSORIATIC ARTHRITIS IN PLACEBO-CONTROLLED TRIAL

	Percent of Patients	
	Placebo	Etanercept (Enbrel)[a]
Psoriatic Arthritis Response	n = 104	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 etanercept (Enbrel) SC twice weekly.
b: p <0.001, etanercept (Enbrel) vs. placebo.
c: p <0.01, etanercept (Enbrel) vs. placebo.

Among patients with psoriatic arthritis who received etanercept (Enbrel), the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. Etanercept (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 etanercept (Enbrel), relative to placebo ($p < 0.001$).

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

MEAN (SE) ANNUALIZED CHANGE FROM BASELINE IN TOTAL SHARP SCORE (TSS)

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

SE = standard error.
a: p = 0.0001.

Etanercept (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 etanercept (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 etanercept (Enbrel) in ankylosing spondylitis was assessed in 3 randomized, double-blind studies comparing twice-weekly administration of 25 mg etanercept (Enbrel) with placebo. A total of 401 patients were enrolled from which 203 were treated with etanercept (Enbrel). The largest of these trials (n = 277) enrolled patients who were between 18 and 70 years of age and had active ankylosing spondylitis defined as visual analog scale (VAS) scores of ≥30 for average of duration and intensity of morning stiffness plus VAS scores of ≥30 for at least 2 of the following 3 parameters: patient global assessment; average of VAS values for nocturnal back pain and total back pain; average of 10 questions on the Bath Ankylosing Spondylitis Functional Index (BASFI). Patients receiving DMARDs, NSAIDs, or corticosteroids could continue them on stable doses. Patients with complete ankylosis of the spine were not included in the study. Doses of 25 mg of etanercept (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 etanercept (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	Etanercept (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, etanercept (Enbrel) vs. placebo.		
b: p = 0.002, etanercept (Enbrel) vs. placebo.		

Among patients with ankylosing spondylitis who received etanercept (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 etanercept (Enbrel) (two 25 mg SC injections) administered once weekly vs. 25 mg etanercept (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 etanercept (Enbrel) in patients with non-radiographic axial spondyloarthritis (nr-AxSpa) was assessed in a randomized, 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 etanercept (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 etanercept (Enbrel) 50 mg weekly for up to an additional 92 weeks.

Compared to placebo, treatment with etanercept (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*	Etanercept (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 etanercept (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 etanercept (Enbrel). Adjusted mean change from baseline was 3.8 for etanercept (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 (Bath Ankylosing Spondylitis Functional Index), EuroQol 5D and the SF 36 questionnaires. Etanercept (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 etanercept (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-center, open-label, phase 4, 3-period study evaluated the withdrawal and re-treatment of etanercept (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 etanercept (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 (Enbrel), 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 etanercept (Enbrel). Patients who flared were retreated with etanercept (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 etanercept (Enbrel).

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

The median time to flare following withdrawal of etanercept (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 etanercept (Enbrel) treatment (Study 2) compared to subjects who received continuous etanercept (Enbrel) treatment (Study 1), $p<0.0001$.

Of the 87 patients who entered Period 3 and were retreated with etanercept (Enbrel) 50 mg weekly for 12 weeks, 62% (54/87) reachieved inactive disease, with 50% of them reachieving it within 5 weeks (95% CI: 4-8 weeks).

Adult patients with plaque psoriasis

The safety and efficacy of etanercept (Enbrel) in patients with plaque psoriasis were assessed in three randomized, 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 randomized to receive a dose of 25 mg of Etanercept (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. Etanercept (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 etanercept (Enbrel) doses. After 12 weeks of treatment, patients in the placebo group began treatment with blinded etanercept (Enbrel) (25 mg twice a week); patients in the active treatment groups continued to week 24 on the dose to which they were originally randomized.

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 etanercept (Enbrel), or placebo twice a week for 12 weeks and then all patients received open-label 25 mg etanercept (Enbrel) twice weekly for an additional 24 weeks.

In study 1, the etanercept (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 etanercept (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 AND 3

	Study 2					Study 3		
		Etanercept (Enbrel)					Etanercept (Enbrel)	
Response	Placebo n = 166 wk 12	25 mg BIW n = 162 wk 12	n =162 wk 24[a]	50 mg BIW n = 164 wk 12	n = 164 wk 24[a]	Placebo n = 193 wk 12	25 mg BIW n = 196 wk 12	50 mg BIW n = 196 wk 12
PASI 50, %	14	58*	70	74*	77	9	64*	77*
PASI 75, %	4	34*	44	49*	59	3	34*	49*
DSGA[b], clear or almost clear, %	5	34*	39	49*	55	4	39*	57*

*p ≤0.0001 compared with placebo.

a. No statistical comparisons to placebo were made at week 24 in Study 2 because the original placebo group began receiving etanercept (Enbrel) 25 mg BIW 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 etanercept (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 etanercept (Enbrel) in patients initially responding to treatment.

In study 3, the majority of patients (77%) who were initially randomized to 50 mg twice weekly and had their etanercept (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 long-term (up to 34 months), open-label studies where etanercept (Enbrel) was given without interruption, clinical responses were sustained and safety was comparable to shorter-term studies.

Pediatric patients with plaque psoriasis

The efficacy of etanercept (Enbrel) was assessed in a randomized, double-blind, placebo-controlled study in 211 pediatric 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 etanercept (Enbrel) 0.8 mg/kg (up to 50 mg) or placebo once weekly for 12 weeks. At week 12, more patients randomized to etanercept (Enbrel) had positive efficacy responses (e.g., PASI 75) than those randomized to placebo.

Pediatric Plaque Psoriasis Outcomes at 12 Weeks

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

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

5.2 Pharmacokinetic Properties

Absorption

Etanercept is slowly absorbed from the site of SC injection, reaching maximum concentration approximately 48 hours after a single dose. The absolute bioavailability is 76%.

Distribution

After a single SC 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•h/mL. Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

The volume of distribution at steady-state after subcutaneous administration is 13.9 ± 9.4 L.

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

Elimination

Etanercept is cleared slowly from the body. The half-life is approximately 80 hours.

The clearance is approximately 175 ± 116 mL/hr in patients with rheumatoid arthritis and 131 ± 81 mL/hr in healthy volunteers.

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

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.

Gender

There is no apparent pharmacokinetic difference between men and women.

Concentration-effect relationship

Steady-state serum concentrations of 1 to 2 mg/L of etanercept are associated with optimal effect, and are obtained with doses of 25 mg twice weekly. In an open-label, single-dose, two-treatment, crossover study in 28 healthy volunteers, etanercept (Enbrel), administered as a single 50 mg/mL injection was found to be bioequivalent to two simultaneous injections of 25 mg/mL.

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.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

Please see outer package for the expiry date of the product.

6.2 Storage Conditions

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

6.3 Availability

1 mL EP Type 1 pre-filled glass syringe with grey bromobutyl rubber plunger, white polystyrene plunger rod and 27G staked-in needle with needle shield.

The needle cover contains dry natural rubber [latex] (see section **4.4 Special Warnings and Precautions for Use**).

Each blister tray contains four single-use pre-filled syringes and four alcohol pads or swabs.

6.4 Incompatibilities

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

6.5 Special Precautions for Disposal and Other Handling

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

Patients or caregivers who are to administer etanercept (Enbrel) must be instructed in proper syringe and needle disposal, and be cautioned against reuse of these items.

Unused etanercept (Enbrel) syringes or waste materials should be disposed of according to local requirements.

See **Instructions For Patients: Preparing And Injecting Etanercept (Enbrel)**.

7.0 FDA REGISTRATION NUMBER

Etanercept (Enbrel) 25 mg/0.5 mL pre-filled syringe: BR-1344
Etanercept (Enbrel) 50 mg/mL pre-filled syringe: BR-1343

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Etanercept (Enbrel) 25 mg/0.5 mL pre-filled syringe: 11 March 2021
Etanercept (Enbrel) 50 mg/mL pre-filled syringe: 11 March 2021

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:
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Revision No.: 7.2
Revision Date: 07 January 2025
Reference: CDS ver. 51.0/Puurs manufacturing site address change/Update primary packaging material
Reference Date: 05 August 2022

INSTRUCTIONS FOR PATIENTS: PREPARING AND INJECTING ETANERCEPT (ENBREL)

This section is divided into the following sub-sections:

Introduction
Step 1: Setting up for an injection
Step 2: Choosing an injection site
Step 3: Injecting the etanercept (Enbrel) solution
Step 4: Disposing of supplies

INTRODUCTION
The following instructions explain how to prepare and inject etanercept (Enbrel). Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or his/her assistant on the techniques of self-injection or on giving an injection to a child. Do not attempt to administer an injection until you are sure that you understand how to prepare and give the injection. The etanercept (Enbrel) solution should not be mixed with any other medicine before use.

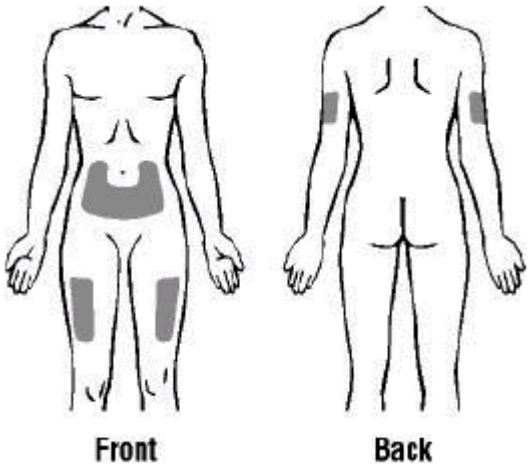
STEP 1: SETTING UP FOR AN INJECTION

1. Select a clean, well-lit, flat working surface.
2. Take the etanercept (Enbrel) carton containing the pre-filled syringes out of the refrigerator and place it on the flat work surface. Remove one pre-filled syringe and one alcohol swab and place them on the work surface. Do not shake the pre-filled syringe of etanercept (Enbrel). Place the carton containing any remaining pre-filled syringes back into the refrigerator (2°C to 8°C). If you have any questions about storage, contact your doctor, nurse, or pharmacist for further instructions.
3. Check the expiration date on the pre-filled syringe. If the expiration date has passed, do not use the pre-filled syringe and contact your pharmacist for assistance.
4. You should allow 15 to 30 minutes for the etanercept (Enbrel) solution in the syringe to reach room temperature. DO NOT remove the needle cover while allowing it to reach room temperature. Waiting until the solution reaches room temperature may make the injection more comfortable for you. Do not warm etanercept (Enbrel) in any other way (for example, do not warm it in a microwave or in hot water).
5. Assemble the additional supplies you will need for your injection. These include an alcohol swab, from the etanercept (Enbrel) carton and a cotton ball or gauze.
6. Wash your hands with soap and warm water.
7. Inspect the solution in the pre-filled syringe. It should be clear to opalescent, colorless to yellow or pale brown, and liquid may contain trace levels of translucent to white amorphous particles. This appearance is normal for etanercept (Enbrel). Do not use the solution if it is discolored, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

STEP 2: CHOOSING AN INJECTION SITE

1. Three recommended injection sites for etanercept (Enbrel) using a pre-filled syringe include: (1) the front of the middle thighs; (2) the abdomen, except for the 5 cm area right around the navel; and (3) the outer area of the upper arms (see Diagram 1). If you are self-injecting, you should not use the outer area of the upper arms.

Diagram 1.

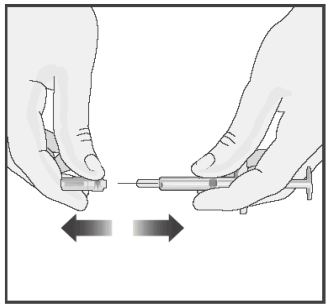


2. A different site should be used for each new injection. Each new injection should be given at least 3 cm from an old site. Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.
3. If you or your child has psoriasis, you should try not to inject directly into any raised, thick, red, or scaly skin patches ("psoriasis skin lesions").

STEP 3: INJECTING THE ETANERCEPT (ENBREL) SOLUTION

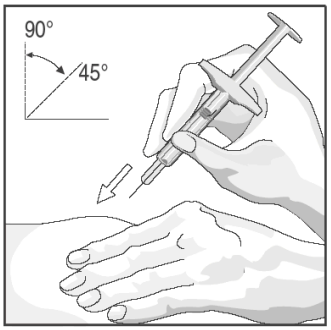
1. Wipe the site where etanercept (Enbrel) is to be injected with an alcohol swab, using a circular motion. DO NOT touch this area again before giving an injection.
2. Pick up the pre-filled syringe from your flat work surface. Remove the needle cover by firmly pulling it straight off the syringe (see Diagram 2). Be careful not to bend or twist the cover during removal to avoid damage to the needle.
   When you remove the needle cover, there may be a drop of liquid at the end of the needle; this is normal. Do not touch the needle or allow it to touch any surface. Do not touch or bump the plunger. Doing so could cause the liquid to leak out.

Diagram 2.



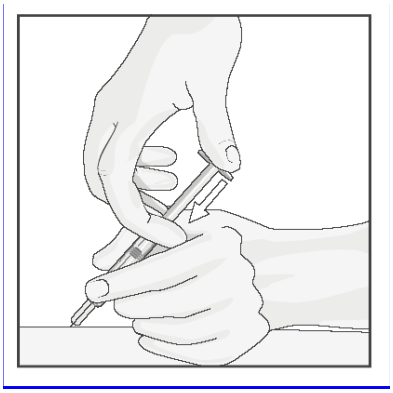
3. When the cleaned area of skin has dried, pinch and hold it firmly with one hand. With the other hand, hold the syringe like a pencil.
4. With a quick, short motion, push the needle all the way into the skin at an angle between 45° and 90°. With experience, you will find the angle that is most comfortable for you (see Diagram 3). Be careful not to push the needle into the skin too slowly, or with great force.

Diagram 3.



5. When the needle is completely inserted into the skin, let go of the skin that you are holding. With your free hand, hold the syringe near its base to stabilize it. Then push the plunger to inject all of the solution at a slow, steady rate (see Diagram 4).

Diagram 4.



6. When the syringe is empty, pull the needle out of the skin, being careful to keep it at the same angle as inserted. There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site for 10 seconds. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

STEP 4: DISPOSING OF SUPPLIES

- The pre-filled syringe is for single-use administration only. The syringe and needle should NEVER be reused. NEVER recap a needle. Dispose of the needle and syringe as instructed by your doctor, nurse or pharmacist.

If you have any questions, please talk to a doctor, nurse or pharmacist who is familiar with etanercept (Enbrel).