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Rev. 0

Enbrel®

Etanercept

25 mg powder and solvent for solution for injection

CDS

AfME markets using the same as LPD: Kenya

1. NAME OF THE MEDICINAL PRODUCT

ENBREL®

Enbrel 25 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients, active moieties

Etanercept (INN)

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, CH2 and CH3 regions, but not the CH1 region of IgG1.

Solubility: Etanercept is soluble in water
Molecular weight: (apparent) 150 kilodaltons

For a full list of excipients, see section 6.1.

Physical characteristics

Powder and solvent for solution for injection

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

3. PHARMACEUTICAL FORM

All Enbrel dosage forms are intended for subcutaneous injection.

Powder and solvent for solution for injection.

Composition and pharmaceutical characteristics

Powder and solvent for solution for injection

Each single-use vial contains 25 mg of etanercept (active ingredient).

Pre-filled solvent syringes contain 1 mL water for injection.

The excipients in Enbrel lyophilized powder are mannitol, sucrose, and trometamol (tromethamine).

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Rheumatoid arthritis

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). Enbrel can be initiated in combination with methotrexate or used alone.

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 antirheumatic 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

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

Axial spondyloarthritis

Ankylosing spondylitis (AS)

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

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, or are intolerant to, conventional therapy.

Plaque psoriasis

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

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***

Use in adults

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

Patients aged 18 years or older: 50 mg 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 Enbrel twice weekly (72 to 96 hours apart) as a subcutaneous injection.

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

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

Plaque psoriasis

The dose of 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). 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 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 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, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with Enbrel in children.

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 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 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 etanercept 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. Reconstituted Enbrel solution is colorless to slightly yellow or pale brown and clear to slightly opalescent liquid.

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

Enbrel has not been studied in children <2 years of age (see section 4.1). For pediatric specific safety information concerning malignancies and vaccinations, see sections 4.4 and 4.8.

4.3. Contraindications

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

Sepsis or risk of sepsis (see sections 4.4 and 4.8).

Treatment with 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 Enbrel (see section 4.8). 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 and 4.8).

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 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 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. 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 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 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 benefit; such use is not recommended (see section 4.5).

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).

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.

Alcoholic hepatitis

In a study of 48 hospitalized 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.

Allergic reactions

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

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.

Immunosuppression

Anti-TNF therapies, including 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 postmarketing 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 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 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 Enbrel. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with Enbrel. Periodic skin examination is recommended for all patients 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.

Hematologic 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 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 Enbrel, they should seek immediate medical advice. Such patients should be evaluated urgently, including full blood count; if blood dyscrasias are confirmed, etanercept should be discontinued.

Autoantibody formation

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

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 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 Enbrel. The clinical significance of this is unknown. Live vaccines should not be given concurrently with Enbrel. If possible, bring pediatric patients up to date with immunizations 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). 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 postmarketing 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.

Hypoglycemia in patients treated for diabetes

There have been reports of hypoglycemia following initiation of 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 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).

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).

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.

Non-interactions

No interactions have been observed when Enbrel was administered with glucocorticoids, salicylates (except sulfasalazine), nonsteroidal 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 postnatal growth deficits or delayed postnatal 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 fetus.

Preclinical data about peri- and postnatal 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 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.

In lactating rats, following subcutaneous administration etanercept was excreted in the milk and detected in the serum of the pups. Limited information from the published literature indicates etanercept has been detected at low levels in human milk. Etanercept could be considered for use during breast-feeding taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

While systemic exposure in a breastfed infant is expected to be low because etanercept is largely degraded in the gastrointenstinal tract, limited data regarding systemic exposure in the breastfed infant are available. Therefore, the administration of live vaccines (e.g., BCG) to a breastfed infant when the mother is receiving etanercept could be considered 16 weeks after stopping breast-feeding (or at an earlier time point if the infant etanercept serum levels are undetectable).

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 Enbrel and placebo treatment groups.

Injection site reactions

Patients in controlled clinical studies treated with 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 postmarketing 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). 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 hospitalisation or intravenous antibiotics) and non-serious infections were similar for 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 Enbrel treatment may increase mortality in these patients.

Malignancies and lymphoproliferative disorders

Reports of malignancies affecting various sites have been received in the postmarketing period. There have been reports of malignancies in a clinical trial of patients being treated for Wegener's granulomatosis (see section 4.4).

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 postmarketing 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 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 postmarketing 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)
	Listeria*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Malignant melanoma (see section 4.4)
	Merkel cell carcinoma* (see section 4.4)
	Lymphoma*
	Leukaemia*
	Non-melanoma skin cancers (see section 4.4)

Adverse Drug Reaction Table

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Aplastic anaemia* (see section 4.4)
	Pancytopenia (see section 4.4)
	Thrombocytopenia
	Anaemia
	Leukopenia
	Neutropenia
	Histiocytosis haematophagic (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)
	Peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy* (see section 4.4)
	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*)

Adverse Drug Reaction Table

System Organ Class	Adverse Drug Reactions
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
Renal and urinary disorders	Glomerulonephritis*
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 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 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

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

TNF-alpha Inhibitor
ATC code: L04AB01

Geriatric use

No specific dosage adjustments of 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 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 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 Enbrel at 3 and 6 months than in patients treated with placebo (ACR 20: Enbrel 62% and 59%, placebo 23% and 11% at 3 and 6 months, respectively; ACR 50: Enbrel 41% and 40%, placebo 8% and 5% at months 3 and 6, respectively; $p<0.01$ Enbrel vs. placebo at all timepoints for both ACR 20 and ACR 50 responses).

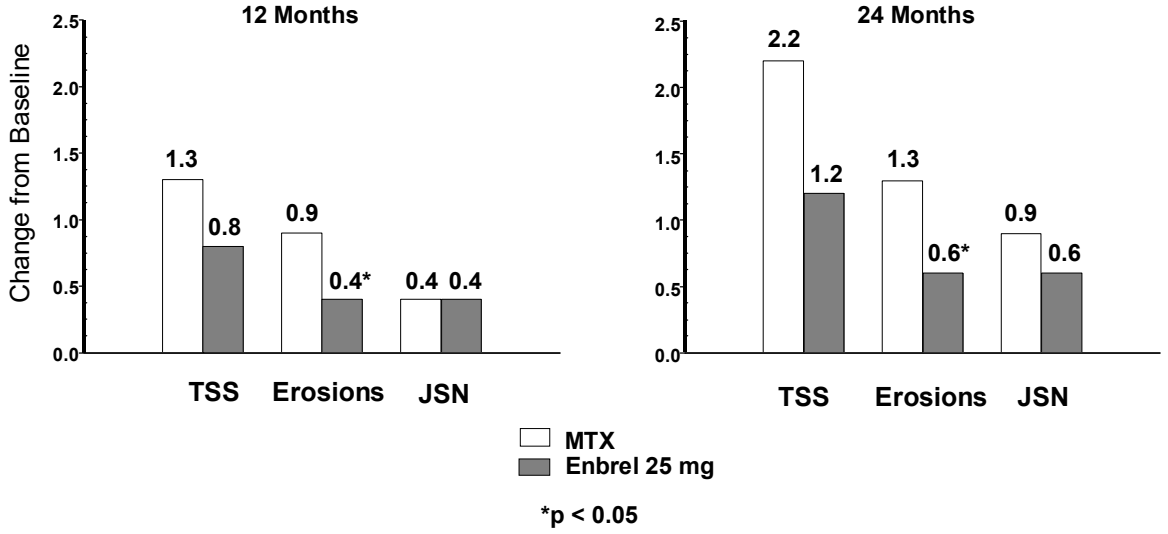
Approximately 15% of subjects who received Enbrel achieved an ACR 70 response at month 3 and month 6 compared to fewer than 5% of subjects in the placebo arm. Among patients receiving Enbrel, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred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

After discontinuation of Enbrel, symptoms of arthritis generally returned within a month. Re-introduction of treatment with Enbrel after 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.

The efficacy of 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 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 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



In another active-controlled, double-blind, randomized 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.

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

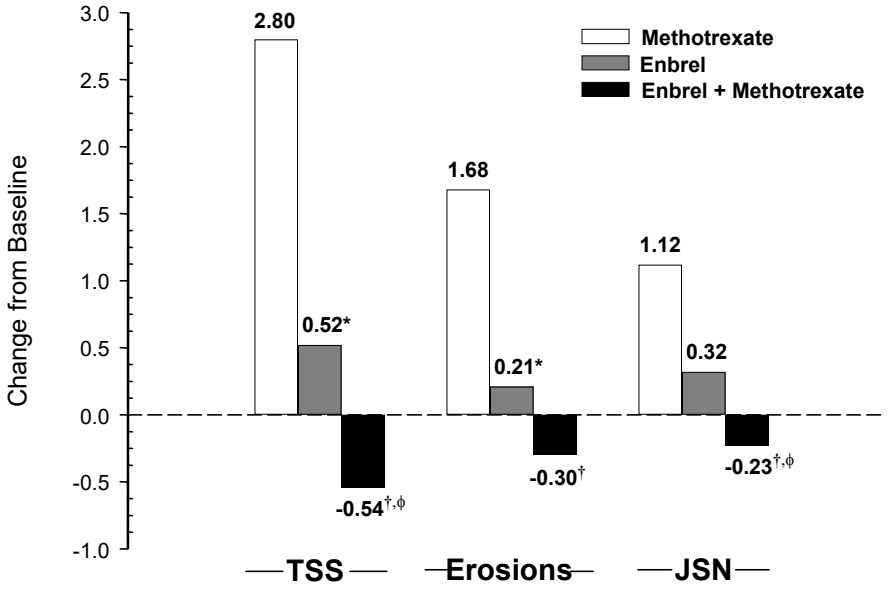
CLINICAL EFFICACY RESULTS AT 12 MONTHS: COMPARISON OF ENBREL vs. METHOTREXATE vs. ENBREL IN COMBINATION WITH METHOTREXATE IN PATIENTS WITH RA OF 6 MONTHS TO 20 YEARS DURATION

Endpoint	Methotrexate (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 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.

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.

Pediatric population with juvenile idiopathic arthritis

The safety and efficacy of 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 nonsteroidal 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 randomized to remain on Enbrel or receive placebo for four months and assessed for disease flair. 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 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 pediatric 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 oligoarthrits (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 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 versus 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 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 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	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 Enbrel SC twice weekly
b: $p < 0.001$, Enbrel vs. placebo
c: $p < 0.01$, Enbrel vs. placebo

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

Radiographic changes were assessed in the psoriatic arthritis study. Radiographs of hands and wrists were obtained at baseline and months 6, 12, and 24. The modified TSS at 12 months is presented in the table below. In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 12 months was higher in the Enbrel group compared with the placebo group (73% vs. 47%, respectively, $p \leq 0.001$). 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) ANNUALIZED CHANGE FROM BASELINE IN TOTAL SHARP SCORE (TSS)

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

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

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

RESPONSES OF PATIENTS WITH ANKYLOSING SPONDYLITIS IN A PLACEBO-CONTROLLED TRIAL		
	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 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 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 (Bath Ankylosing Spondylitis Functional Index), 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-center, 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 retreated 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), $p<0.0001$.

Of the 87 patients who entered Period 3 and were retreated with 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 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 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 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 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.

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 AND 3

	Study 2					Study 3		
		Enbrel					Enbrel	
Response	Placebo n = 166 wk 12	25 mg BIW n = 162 wk 12	25 mg BIW n = 162 wk 24[a]	50 mg BIW n = 164 wk 12	50 mg BIW 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 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 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 randomized 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 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.

Pediatric patients with plaque psoriasis

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

Pediatric 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 randomized withdrawal period, significantly more patients re-randomized to placebo experienced disease relapse (loss of PASI 75 response) compared with patients re-randomized 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 pediatric subjects with plaque psoriasis for up to 2 years beyond the 48 week study discussed above. Long-term experience with Enbrel was generally comparable to the original 48-week study and did not reveal any new safety findings.

5.2. Pharmacokinetic properties

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•hr/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 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, 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. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Enbrel lyophilized powder

Mannitol
Sucrose
Trometamol (Tromethamine)

6.2. Incompatibilities

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

6.3. Shelf life

Keep out of the sight and reach of children.

Do not use Enbrel after the expiry date which is stated on the Carton/Vial label after EXP:. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6.4. Special precautions for storage

Enbrel powder must be stored refrigerated at 2°C to 8°C 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 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.

6.5. Nature and contents of container

Powder and solvent for solution for injection

Clear glass vial (type I glass) with rubber stopper, aluminum seal, and flip-off plastic cap.

Supplied with pre-filled type I glass syringe with stainless steel needle containing 1 mL of solvent.

Cartons contain 25 mg single-use vials of Enbrel with pre-filled solvent syringes, vial adapters, stainless steel needles in plastic containers and alcohol swabs.

4 Dosage Units per Carton.

6.6. Special precautions for disposal and other handling

For vials

Reconstitute the Enbrel powder aseptically by injecting the 1 mL of solvent very slowly into the vial. Gently swirl the contents to avoid excessive foaming. Some foaming will occur; this is normal. Do not shake or vigorously agitate. Dissolution usually takes less than 10 minutes.

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.

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

Unused Enbrel, syringes, or waste materials should be disposed of according to local requirements.

7. FURTHER INFORMATION

MANUFACTURED BY

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8. PRESCRIPTION STATUS

Prescription Only Medicine

9. DATE OF REVISION OF THE TEXT

February 2024

Document Approval Record

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Document Title:	Enbrel 25 mg/vial Powder and Solvent for Solution for Inj LPD Kenya (CDSv53 + Puurs City Name Change) (ADD Pf2 # 2023-0089352 + 2024-0091084)

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