Package Insert

1. NAME OF THE MEDICINAL PRODUCT

Eucept 25 mg / 0.5 mL Solution for Injection in Pre-filled Syringe
Eucept 50 mg / mL Solution for Injection in Pre-filled Syringe
Eucept 50 mg / mL Autoinjector in Pre-filled Syringe
Eucept is a biosimilar of Enbrel®.

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.

Physical characteristics

Solution for injection in pre-filled syringe or Autoinjector

The solution for injection in the pre-filled syringe or autoinjector syringe is colourless to light yellow, clear to opalescent solution for injection, with a pH of 6.0~6.6. It is sterile and does not contain preservatives.

3. PHARMACEUTICAL FORM

All Eucept dosage forms are intended for subcutaneous injection.

Solution for injection in pre-filled syringe or autoinjector

Composition and pharmaceutical characteristics

Eucept 25 mg / 0.5 mL Solution for Injection in Pre-filled Syringe

Each pre-filled syringe contains 25 mg of etanercept (active ingredient).

Eucept 50 mg / mL Solution for Injection in Pre-filled Syringe

Each pre-filled syringe contains 50 mg of etanercept (active ingredient).

Eucept 50 mg / mL Autoinjector in Pre-filled Syringe

Each autoinjector syringe contains 50 mg of etanercept (active ingredient).

For full list of ingredients see section 6.1 List of Excipients

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

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

Polyarticular juvenile idiopathic arthritis

Treatment of active polyarticular juvenile idiopathic arthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Eucept has not been studied in children aged less than 2 years.

Psoriatic arthritis

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

Axial spondyloarthritis

Ankylosing spondylitis

Treatment of active ankylosing spondylitis in adults.

Non-radiographic axial spondyloarthritis

Treatment of adults with active* non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

*Active disease is defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4.

Plaque psoriasis

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

Pediatric plaque psoriasis

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

4.2 Posology and method of administration

Eucept treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, polyarticularjuvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis.

Adults (18-64 years)

Rheumatoid Arthritis

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

Psoriatic Arthritis, Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis

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

Plaque Psoriasis

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

Special populations

Elderly

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

Renal and Hepatic Impairment

No dose adjustment is required.

Pediatric population

Treatment with Eucept should be considered in patients above the weight of 62.5 kg.

Polyarticular Juvenile Idiopathic Arthritis

The recommended dose of Eucept for patients above the weight of 62.5 kg is 25 mg administered

twice weekly or 50 mg administered once weekly. Treatment should be discontinued in patients who show no response after 4 months.

Pediatric plaque psoriasis (age 6 years and above)
The recommended dose of Eucept for patients above the weight of 62.5 kg is 50 mg administered once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.
If re-treatment with Eucept is indicated, the above guidance on treatment duration should be followed.
The dose should be 50 mg per dose once weekly.
There is generally no applicable use of Eucept in children aged below 6 years in the indication of plaque psoriasis.

Method of administration
Administer Eucept 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 Eucept must be instructed in injection techniques. The first injection should be performed under the supervision of a qualified health care professional if Eucept is to be administered by a patient or caregiver.

Solution for injection in pre-filled syringe
Please refer to section 6.6 *Instructions for use* before injection, Eucept single-use pre-filled syringes or autoinjector should be allowed to reach room temperature (approximately 15 to 30 minutes). The needle cover/cap should not be removed while allowing the pre-filled syringe to reach room temperature. The solution should be colourless to light yellow, clear to opalescent.

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

4.3 Contraindications
Hypersensitivity to etanercept or to any component of the product formulation.
Sepsis or risk of sepsis (see sections 4.4 *Special Warnings and Precautions for Use* and 4.8 *Undesirable Effects*).

Treatment with Eucept should not be initiated in patients with serious active infections, including chronic or localized infections.

4.4 Special warnings and precautions for use

Eucept is a biosimilar product of Enbrel® and interchangeability or auto-substitution between Eucept and Enbrel® is not allowed.

Infections

Serious infections, including sepsis and tuberculosis (TB), have been reported with the use of etanercept (see section 4.8 *Undesirable Effects*). Some of these infections have been fatal. These infections were due to bacteria, mycobacteria, fungi, viruses and parasites (including protozoa). Opportunistic infections have also been reported (including listeriosis and legionellosis). Patients who develop a new infection while undergoing treatment with etanercept should be monitored closely. Administration of etanercept should be discontinued if a patient develops a serious infection. Caution should be exercised when considering the use of etanercept 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, taking into consideration that the mean elimination half-life of entanercept 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. 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. Tuberculosis may be due to reactivation of latent TB infection or to new infection.

Before initiation of therapy with etanercept, 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. Some patients who tested negative for latent TB prior to receiving etanercept have developed active TB. Physicians should monitor patients receiving etanercept 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 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 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, although a causal relationship with etanercept has not been established.

Concurrent treatment with anakinra:

Concurrent administration of etanercept 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 *Interactions*).

Concurrent treatment with abatacept:

In clinical studies, concurrent administration of abatacept and etanercept 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 *Interactions*).

Wegener's granulomatosis

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

Alcoholic hepatitis

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

should use caution when using etanercept in patients who also have moderate to severe alcoholic hepatitis.

Allergic reactions

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

Immunosuppression

Anti-TNF therapies, including etanercept, 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 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. 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. Post-marketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with etanercept. 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, more cases of NMSC were observed in patients receiving etanercept 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 etanercept. Caution should be exercised in patients being treated with etanercept 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, 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 etanercept 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 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. The clinical significance of this is unknown. Live vaccines should not be given concurrently with etanercept. If possible, bring pediatric patients up to date with immunizations according to current local guidelines before beginning etanercept therapy.

Neurological disorders

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

Hypoglycemia in patients treated for diabetes

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

Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and etanercept 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 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 or sulfasalazine alone. The clinical significance of this interaction is unknown.

Non-interactions

No interactions have been observed when etanercept 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. Women of childbearing potential should be advised to use appropriate contraception to avoid becoming pregnant during etanercept therapy and for three weeks after discontinuation of therapy. One pregnancy registry compared rates of major birth defects in live-born infants of mothers with rheumatic diseases or psoriasis exposed to etanercept in the first trimester (n=319) versus those unexposed to etanercept 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. The use of etanercept should be avoided during pregnancy. If etanercept is used during pregnancy, or if the patient becomes pregnant while taking it, the woman should be advised of the possible risk 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 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 is generally not recommended.

The safe use of etanercept during lactation has not been established. Etanercept has been reported to be excreted in human milk following subcutaneous administration. In lactating rats, following subcutaneous administration etanercept was excreted in the milk and detected in the serum of the

pups. Because immunoglobulins and many medicinal products can be excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue etanercept while nursing.

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 and placebo treatment groups.

Injection site reactions

Patients in controlled clinical studies treated with etanercept 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 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 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 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 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:

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to < 1/100	Rare ≥1/10,000 to< 1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from available data)
Infections and infestations	Infection (including upper respiratory tract infection bronchitis, cystitis, skin infection)		Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis, and parasitic infection)	Tuberculosis, opportunistic infection (including invasive fungal, bacterial, atypical mycobacterial, viral infections, and *Legionella*) (see section 4.4 *Special Warnings and Precautions for Use*)		Hepatitis B reactivation* listeria*,
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancers (see section 4.4 *Special Warnings and Precautions for Use*)	Malignant melanoma (see section 4.4 *Special Warnings and Precautions for Use*), lymphoma,* leukaemia*		Merkel cell Carcinoma* (see section 4.4 *Special Warnings and Precautions for Use*)
Blood and lymphatic system disorders			Thrombocytopenia, anaemia, leukopenia, neutropenia,	Pancytopenia (see section 4.4 *Special Warnings and Precautions for Use*)	Aplastic anaemia* (see section 4.4 *Special Warnings and Precautions for Use*)	Histiocytosis haematophagic (macrophage activation syndrome)*,
Immune system disorders		Allergic reactions (see *Skin and subcutaneous tissue disorders, below*), autoantibody formation	Vasculitis (including ANCA positive vasculitis)	Serious allergic/ anaphylactic reactions (including bronchospasm), sarcoidosis		

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to < 1/100	Rare ≥1/10,000 to< 1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from available data)
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*), seizures		
Eye disorders			Uveitis, scleritis			
Cardiac disorders			Worsening of cardiac failure congestive	New onset cardiac failure congestive		
Respiratory, thoracic and mediastinal disorders				Interstitial lung disease (including pulmonary fibrosis and pneumonitis)		
Hepatobiliary disorders			Elevated liver Enzymes (see *Elevated liver enzymes above*)	Autoimmune hepatitis		

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to < 1/100	Rare ≥1/10,000 to< 1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from available data)
Skin and subcutaneous tissue disorders		Pruritus, rash	Angioedema, psoriasis (new onset or exacerbation; including all sub-types) urticaria psoriasiform rash	Stevens Johnson syndrome,* cutaneous vasculitis (including hypersensitivity vasculitis), erythema multiforme*	Toxic epidermal necrolysis*	
Musculo-skeletal 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 populations

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 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. 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: Tumour Necrosis Factor alpha (TNF-α) inhibitor

ATC code: L04AB01

Geriatric use

No specific dosage adjustments of etanercept 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 (TNFα) and lymphotoxin alpha [LTα] (TNFβ) 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 LTα 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 and safety

Studies to compare efficacy of Eucept with Enbrel®

Eucept is a biosimilar of Enbrel®. The biosimilarity in terms of clinical efficacy and safety was determined by two randomised controlled trials that were conducted in adults with rheumatoid arthritis. The first study compared the efficacy profile of Eucept with Enbrel®. The second study was an extension to the first study and was conducted to evaluate the long- term safety and efficacy of Eucept.

Efficacy of Eucept in Rheumatoid arthritis

The similarity in the efficacy and safety of Eucept and Enbrel® was evaluated in a double-blind, randomized, parallel-group study. The study evaluated 374 adult patients with active rheumatoid arthritis who do not respond adequately to methotrexate alone. Doses of 50 mg etanercept injection were administered subcutaneously every week for 52 weeks. The results of this controlled trial were expressed in mean change from baseline in DAS28-ESR score, percentage improvement in rheumatoid arthritis using response rates on American College of Rheumatology (ACR), Remission rate (i.e., DAS28-ESR <2.6), European League Against Rheumatism (EULAR) response on DAS28-ESR.

The primary efficacy endpoint of this study was the mean change from baseline in DAS28-ESR score at Week 24. The least square mean changes from baseline in DAS28-ESR score at Week 24 were -3.009 and -2.859 in the Eucept group (N = 164) and Enbrel® group (N = 165), respectively. Estimated treatment difference in change from baseline to Week 24 in DAS28-ESR between the two treatment groups was -0.150 and which was completely within the pre-specified equivalence margin of -0.6 to 0.6, indicating equivalence in efficacy between Eucept and Enbrel®. The results of the secondary efficacy endpoints had consistent pattern with the results of primary efficacy endpoint.

The response rates for ACR20 in the Eucept group and the Enbrel® group were 85.4% and 83.0% at Week 12, 93.3% and 86.7% at Week 24, and 92.0% and 88.4% at Week 52, respectively. The response rates for ACR50 in the Eucept group and the Enbrel® group were 74.4% and 63.0% at Week 24 and 74.7% and 65.8% at Week 52, respectively. The response rates for ACR70 in the Eucept group and the Enbrel® group were 50.6% and 39.4% at Week 24 and 58.0% and 50.0% at

Week 52, respectively.

Remission rate (DAS28-ESR score <2.6) after 24 weeks was 33.5% in Eucept and 30.9% in Enbrel®, and 90% of the subjects displayed Moderate or Good EULAR responses. EULAR response rate and EULAR activity variance were similar between the two groups.
Except for the higher rate of injection site reactions reported in the Enbrel® group, Eucept and Enbrel® displayed a similar safety profile in this analysis.
The results of this study concluded that Eucept and Enbrel® were equivalent in terms of clinical efficacy and displayed a similar safety profile.
In another single-arm, open-label, extension clinical study the long-term safety and efficacy of Eucept 50 mg subcutaneous weekly injection was assessed, when co-administered with methotrexate for additional 48 weeks in patients (N = 148) with rheumatoid arthritis who have completed the treatment period of the above study. The study also compared the injection site reaction after switching to needle size 29G in this study from needle size 27G used in pervious study. The first dose was administered on Week 52 of the previous study, followed by administration once a week until Week 100. Subjects who were administered Eucept in previous study and continued to receive Eucept in this study were termed the "Eucept maintenance group" while those who were taking Enbrel® in the previous study and were switched to Eucept in this study were termed the "Eucept switching group". The results of this controlled trial were expressed in mean change in DAS28-ESR score, mean change in DAS28-CRP score, response rates on ACR, EULAR response on DAS28-ESR.

When compared to Week 52, the least square mean changes in DAS28-ESR score at Weeks 76 and 100 in both groups were similar (Week 76 versus Week 52: -0.067 versus -0.079 in the maintenance and switching groups, respectively; Week 100 versus Week 52: -0.052 and -0.149 in the maintenance and switching groups, respectively) and there was no notable difference in the estimated treatment differences between the two groups: estimated treatment difference in change from the baseline in DAS28-ESR score at Week 76 was 0.012 and was 0.097 at Week 100. Similar results were seen with least square mean changes in DAS28-CRP score at Weeks 76 and 100 in both groups.

Clinical responses were expressed as response rates on ACR 20, 50, and 70. Results are summarised in the table below.

Summary of ACR20, ACR50, and ACR70 - Period II (Week 52)					
Variable Week	**Treatment group**	**N**	**Responder n (%)**	**Response rate difference relative to Switching Group**	**95% confidence interval**
ACR20					
Week 52	Maintenance	69	61 (88.4)	-1.34	-1.34
	Switching	78	70 (89.7)		
Week 76	Maintenance	69	58 (84.1)	-1.84	-13.43, 9.75
	Switching	78	67 (85.9)		
Week 100	Maintenance	69	55 (79.7)	-3.62	-16.21, 8.96
	Switching	78	65 (83.3)		
ACR50					
Week 52	Maintenance	69	48 (69.6)	4.18	-10.96, 19.32
	Switching	78	51 (65.4)		
Week 76	Maintenance	69	49 (71.0)	0.50	-14.23, 15.23
	Switching	78	55 (70.5)		
Week 100	Maintenance	69	45 (65.2)	-1.45	-16.80, 13.90
	Switching	78	52 (66.7)		
ACR70					
Week 52	Maintenance	69	38 (55.1)	6.35	-9.79, 22.50
	Switching	78	38 (48.7)		
Week 76	Maintenance	69	37 (53.6)	7.47	-8.68, 23.62
	Switching	78	36 (46.2)		
Week 100	Maintenance	69	31 (44.9)	2.62	-13.44, 18.68
	Switching	78	33 (42.3)		

The decrease in the proportion of subjects in remission (DAS28-ESR score < 2.6) from Week 52 to Week 76 in the Eucept maintenance group was not considered to be clinically meaningful as the average DAS28-ESR score in the group at both Weeks 52 and 76 were the same (3.068).
The rates of EULAR response and the shift rate of EULAR activity between the two groups were similar with no notable differences observed.

Results showed that Eucept as well tolerated in patients from both groups with no new safety concerns observed. The long-term safety of Eucept was confirmed based on the safety observations obtained from the maintenance group. The change in needle size from 27G (used in previous study) to 29G (used in this study) did not result in any new safety issues. No new safety issues had arisen from the needle size change and the switch from Enbrel® to Eucept.

Thus, this study showed that the long-term efficacy and safety was sustained after additional 48 weeks of treatment with Eucept and no notable change in efficacy and safety risks were observed after switching the subjects to Eucept from Enbrel®.

Efficacy Studies of Etanercept (Enbrel®)

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, 1 study 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 was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid arthritis who had failed therapy with at least one but no more than four disease modifying antirheumatic drugs (DMARDs). Doses of 10 mg or 25 mg Etanercept 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 at 3 and 6 months than in patients treated with placebo (ACR 20: Etanercept 62% and 59%, placebo 23% and 11% at 3 and 6 months, respectively: ACR 50: Etanercept 41% and 40%, placebo 8% and 5% at months 3 and 6, respectively; $p<0.01$ Etanercept vs. placebo at all timepoints for both ACR 20 and ACR 50 responses).

Approximately 15% of subjects who received Etanercept 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, 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 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 compared to controls at 3 and 6 months.

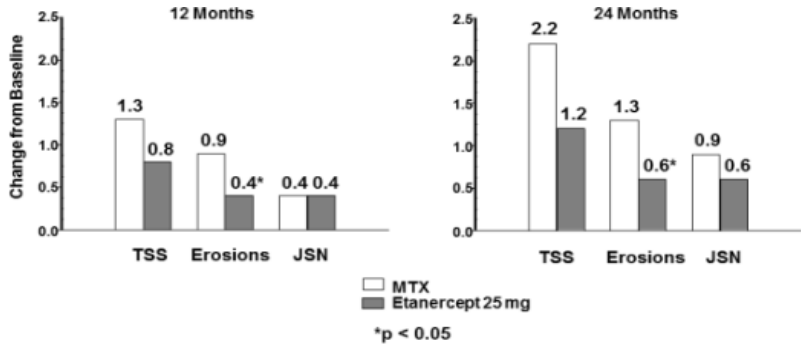
After discontinuation of Etanercept, symptoms of arthritis generally returned within a month. Re-introduction of treatment with Etanercept after discontinuation of up to 24 months resulted in the

same magnitudes of responses as patients who received Etanercept 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 without interruption.

The efficacy of Etanercept was compared to methotrexate in a randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint in 632 adult patients with active rheumatoid arthritis (<3 years duration) who had never received treatment with methotrexate. Doses of 10 mg or 25 mg Etanercept 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 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 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 dose had consistently less effect on structural damage than the 25 mg dose. Etanercept 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 25 mg.
The results are shown in the figure below.

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



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

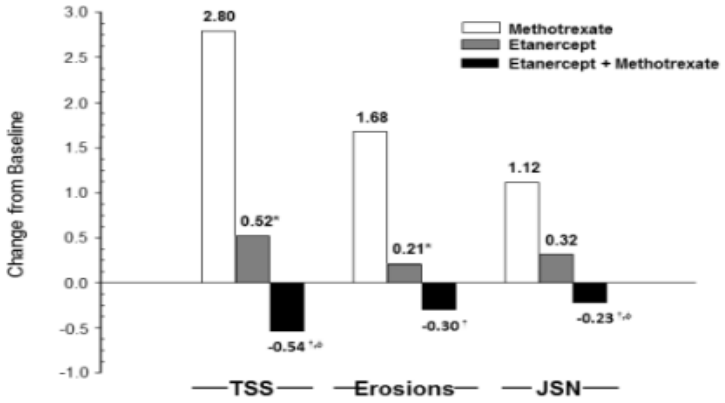
and methotrexate initiated concurrently were compared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least 1 disease-modifying antirheumatic drug (DMARD) other than methotrexate.

Patients in the Etanercept 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 in combination with methotrexate compared with Etanercept monotherapy and methotrexate monotherapy were also observed after 24 months.

Clinical Efficacy Results at 12 Months: Comparison of Etanercept vs. Methotrexate vs. Etanercept in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration			
Endpoint	Methotrexate (n = 228)	Etanercept (n = 223)	Etanercept + 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 + methotrexate vs. methotrexate and ϕ = $p < 0.05$ for comparisons of Etanercept + methotrexate vs. Etanercept.			

Radiographic progression at 12 months was significantly less in the Etanercept 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 vs. Methotrexate vs. Etanercept 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 vs. methotrexate, † = $p < 0.05$ for comparisons of Etanercept + methotrexate vs. methotrexate and ϕ = $p < 0.05$ for comparisons of Etanercept + methotrexate vs. Etanercept.

Significant advantages for Etanercept in combination with methotrexate compared with Etanercept monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the significant advantages for Etanercept 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 in combination with methotrexate group compared with the Etanercept alone and methotrexate alone groups (62%, 50%, and 36%, respectively; $p<0.05$). The difference between Etanercept 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 (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 once weekly and 153 patients received 25 mg Etanercept twice weekly. The safety and efficacy profiles of the two Etanercept treatment regimens were comparable at week 8 in their effect on signs and symptoms of RA; data at week 16 did not show comparability (non-inferiority) between the two regimens.

Paediatric population with juvenile idiopathic arthritis

The safety and efficacy of Etanercept 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 intolerantof methotrexate were enrolled; patients remained on a stable dose of a single non-steroidal anti-inflammatorydrug 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 subcutaneously twice weekly. In part 2, patients with a clinical response at day 90 were randomized to remain on Etanercept or receive placebo for four months and assessedfor disease flare. Responses were measured using the ACR Pedi 30, defined as ≥30% improvement in at leastthree 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 erythrocytesedimentation rate (ESR). Disease flare was defined as a ≥30% worsening in three of six JRA core set criteriaand ≥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, 6of 25 (24%) patients remaining on Etanercept experienced a disease flare compared to 20 of 26 (77%) patientsreceiving placebo (p=0.007). From the start of part 2, the median time to flare was ≥116 days for patients whoreceived Etanercept 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 continuedon Etanercept. 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 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 attime of enrolment) continued to receive Etanercept 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, 60 patients with extended oligoarthritis (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 (12to 17 years old), and 29 patients with psoriatic arthritis (12 to 17 years old) were treated with Etanercept at adose of 0.8 mg/kg (up to a maximum of 50 mg per dose) administered weekly for 12 weeks. In each of the JIAsubtypes, 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 wasconsistent 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 therapy in patients who do not respond within 3 months of initiating Etanercept therapy. Additionally, studies have not been conducted to assess the effects of discontinuing or reducing therecommended dose of Etanercept following its long-term use in patients with JIA. Long-term safety of Etanercept monotherapy (n=103), Etanercept plus methotrexate (n=294), or methotrexatemonotherapy (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 compared to methotrexate alone (3.8% versus 2%), and the infections associated with Etanercept use were of a more severe nature.

Adult patients with psoriatic arthritis

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

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

Responses of Patients with Psoriatic Arthritis in a Placebo-Controlled Trial		
Psoriatic Arthritis Response	Percent of Patients	
	Placebo	Etanercept[a]
	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	c 9
PsARC		
Month 3	31	72 [b]
Month 6	23	70 [b]
a: 25 mg Etanercept SC twice weekly b: $p < 0.001$, Etanercept vs. placebo c: $p < 0.01$, Etanercept vs. placebo		

Among patients with psoriatic arthritis who received Etanercept, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. Etanercept 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, 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 group compared with the placebo group (73% vs. 47%, respectively, $p \leq 0.001$). The effect of Etanercept 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		
Time	Placebo (n = 104)	Etanercept (n = 101)
Month 12	1.00 (0.29)	-0.03 (0.09)[a]
SE = standard error a. $p = 0.0001$.		

Etanercept 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 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 in ankylosing spondylitis was assessed in 3 randomised, double- blind studies comparing twice weekly administration of 25 mg Etanercept with placebo. A total of 401 patients were enrolled, from which 203 were treated with Etanercept. 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 (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 resulted in significant improvements inthe 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 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 vs. placebo		
b: p = 0.002, Etanercept vs. placebo		

Among patients with ankylosing spondylitis who received Etanercept, 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 (two 25 mg SC injections) administered once weekly vs. 25 mg Etanercept 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

The efficacy of Etanercept in patients with non-radiographic axial spondyloarthritis (nr- AxSpa) was assessed in a randomised, 12-week double-blind, placebo-controlled study. The study evaluated 215 adult patients (modified intent-to treat population) with active nr-AxSpa

(18 to 49 years of age), defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. In the double-blind period, patients received Etanercept 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 weeks 12. The double-blind period was followed by an open-label period during which all patients receive Etanercept 50 mg weekly for up to an additional 92 weeks..

Compared to placebo, treatment with Etanercept 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 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 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. Adjusted mean change from baseline was 3.8 for Etanercept 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 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 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.

Adult patients with plaque psoriasis

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

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

In study 1, the Etanercept-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-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								
Response	Study 2					Study 3		
	Placebo	Etanercept				Placebo	Etanercept	
		25 mg BIW		50 mg BIW			25mg BIW	50 mg BIW
	n=166 wk 12	n=162 wk 12	n=162 wk24[a]	n=164 wk 12	n=164 wk24[a]	n=193 wk12	n=196 wk 12	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 the original placebo group began receiving Etanercept 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, 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 in patients initially responding to treatment.

In study 3, the majority of patients (77%) who were initially randomised to 50 mg twice weekly and had their Etanercept 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 was given without interruption, clinical responses were sustained and safety was comparable to shorter-term studies.

Paediatric patients with plaque psoriasis

The efficacy of Etanercept was assessed in a randomised, double-blind, placebo-controlled study in 211 paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasis (as defined by an sPGA score ≥ 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 0.8 mg/kg (up to 50 mg) or placebo once weekly for 12 weeks. At week 12, more patients randomised to Etanercept had positive efficacy responses (e.g., PASI 75) than those randomised to placebo.

Paediatric Plaque Psoriasis Outcomes at 12 Weeks		
	Etanercept 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 0.8 mg/kg (up to 50 mg) once weekly for additional 24 weeks. Responses observed during the open- label period were similar to those observed in the double-blind period.

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

The long-term safety and effectiveness of Etanercept 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 was generally comparable to the original 48-week study and did not reveal any new safety findings.

5.2 Pharmacokinetic properties

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

Absorption

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

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 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 long, approximately 80 hours. 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 radiolabelled 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, administered as a single 50 mg/mL injection, was found to be bioequivalent to two simultaneous injections of 25 mg/mL

Comparative pharmacokinetic study of Eucept and Enbrel®

Eucept is a biosimilar of Enbrel®. The pharmacokinetic equivalence was determined by a randomized, double-blind, two-treatment, two-period, two-sequence, single-dose, crossover study in 46 healthy male adults receiving either 25mg of Eucept or 25mg Enbrel®. The pharmacokinetic parameters evaluated

for Etanercept in Eucept and Enbrel® group included AUClast, AUCinf, Cmax, Tmax, t1/2, CL/F. The point estimates and 90% CIs of the geometric mean ratios (GMR of Eucept/Enbrel®) of AUClast, AUCinf and Cmax were determined; the GMRs (90% CIs) were 0.96 (0.87 – 1.06), 0.96 (0.87 – 1.05), and 1.02 (0.92 – 1.13), respectively. Results are summarized in the table below.

Comparison of the pharmacokinetic parameters of etanercept by treatment

Parameter	Geometric mean		Geometric Mean Ration (90% CI)
	Enbrel®	Eucept	
Cmax (µg/mL)	1.46	1.49	1.02 (0.92-1.13)
AUClast (h*µg/mL)	314.76	301.67	0.96 (0.87-1.06)
AUCinf (h*µg/mL)	340.16	324.52	0.96 (0.87-1.05)

Both Eucept and Enbrel® were well tolerated when administered to healthy adult patients and Eucept 25 mg was bioequivalent to Enbrel® in terms pharmacokinetic parameters.

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

Sodium Chloride
L-Methionine
Sodium Phosphate Dibasic Anhydrous
Sodium Dihydrogen Phosphate Dihydrate
Water for Injection

6.2 Incompatibilities

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

6.3 Shelf life

36 months

6.4 Special Precautions for Storage

Store in a refrigerator (2 °C to 8 °C).
Do not freeze. DO NOT SHAKE.
Keep product in the outer carton in order to protect from light.
Keep out of reach of children.

6.5 Nature and contents of container

Eucept 25 mg / 0.5 mL and 50 mg / mL Solution for Injection in Pre-filled Syringe:

The primary packaging materials for both strengths of Eucept pre-filled syringe composes a syringe and plunger stopper. The syringe is in the form of a stainless steel needle on a 1 mL glass barrel. The plunger stopper is bromobutyl rubber. Cartons contain 4 prefilled syringes of Eucept.

Eucept 50 mg / mL Autoinjector in Pre-filled Syringe

The Autoinjector contains a 50 mg prefilled syringe of Eucept.
The primary packaging materials for this Eucept 50 mg pre-filled syringe composes a syringe and plunger stopper. The syringe is in the form of stainless steel needle on a 1-mL glass barrel. The plunger stopper is bromobutyl rubber.

This 50 mg prefilled syringe is fixed in an autoinjector, a spring-powered device that facilitates self-injection or injection by a care giver using an automated injection process.
Cartons contain 4 Eucept Autoinjectors.

6.6 Instructions for use

Please see “instructions for use” at the end of the document.

PRODUCT REGISTRATION HOLDER

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MANUFACTURED AND RELEASED BY

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Chungcheongbuk-do,
Korea

DATE OF REVISION

August 2021

INSTRUCTIONS FOR USE

Instructions For Preparation And Giving An Injection Of Eucept Pre-Filled Syringe.

This section is divided into the following subsections:

Introduction

- **Step 1: Setting up for an injection**
- **Step 2: Choosing an injection site**
- **Step 3: Injecting the Eucept solution using a pre-filled syringe**
- **Step 4: Disposing of supplies**

Introduction

The following instructions explain how to prepare and inject Eucept. 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 Eucept solution should not be mixed with any other medicine before use.

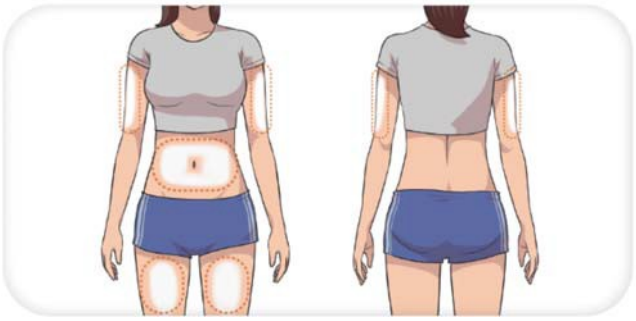
Step 1: Setting up for an injection

1. Select a clean, well-lit, flat working surface.
2. Take the Eucept carton containing the pre-filled syringes out of the refrigerator and place it on the flat work surface. Starting from one of the top corners, pull back the paper cover from the top and sides of the tray. Remove one pre-filled syringe and one alcohol swab and place them on the work surface. Do not shake the pre-filled syringe of Eucept. Fold the paper cover back over the tray and place the carton containing any remaining pre-filled syringes back into the refrigerator. Please see section 6 for instructions on how to store Eucept. If you have any questions about storage, contact your doctor, nurse, or pharmacist for further instructions.
3. You should allow 15 to 30 minutes for the Eucept 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 Eucept in any other way (for example, do not warm it in a microwave or in hot water).
4. Assemble the additional supplies you will need for your injection. These include the alcohol swab and a cotton ball or gauze.
5. Wash your hands with soap and warm water.
6. Inspect the solution in the syringe. It should be colourless to light yellow, clear to opalescent solution. This appearance is normal for Eucept. Do not use the solution if it is discoloured or cloudy. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

Step 2: Choosing an injection site

1. The three recommended injection sites for Eucept 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. (It may be helpful to keep notes on the location of the previous injections.)

3. If you or the child have psoriasis, you should try not to inject directly into any raised, thick, red, or scaly skin patches ("psoriasis skin lesions").

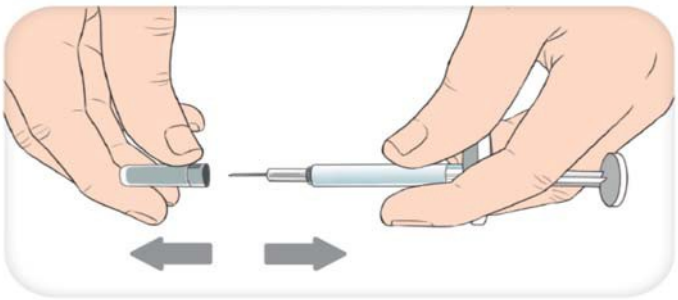
Step 3: Injecting the Eucept solution using a pre-filled syringe

1. Wipe the site where Eucept is to be injected with the alcohol swab, using a circular motion. Do NOT touch this area again before giving the injection.

2. Pick up the pre-filled syringe from the 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.

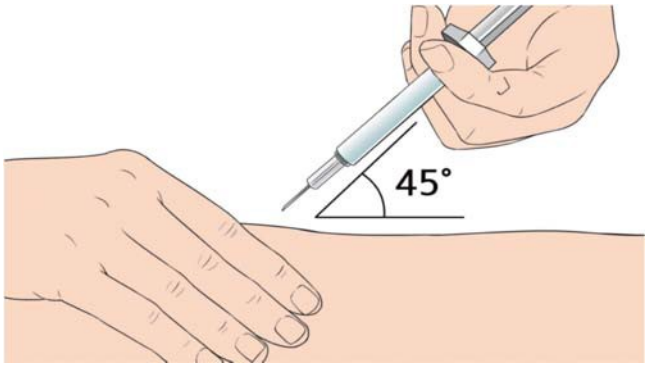
Diagram 2



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° (see Diagram 3). With experience, you will find the angle that is most comfortable for you or the child. Be careful not to push the needle into the skin too slowly, or with great force.

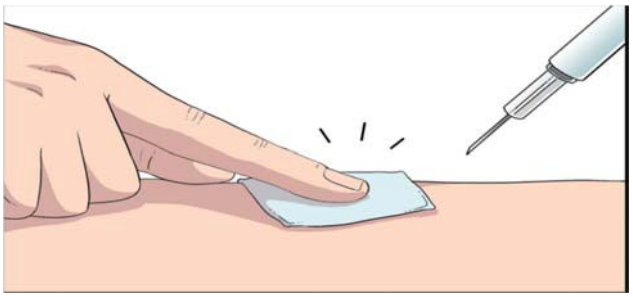
Diagram 3



5. When the needle is completely inserted into the skin, release the skin that you are holding. With your free hand, hold the syringe near its base to stabilise it. Then push the plunger to inject all of the solution at a slow, steady rate.

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.

Diagram 4



Step 4: Disposing of supplies

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

Instructions For Using The Autoinjector To Inject Eucept

This section is divided into the following subsections:

- **Introduction**
- **Step 1: Preparing for an Eucept injection**
- **Step 2: Choosing an injection site**
- **Step 3: Injecting the Eucept solution using the autoinjector**
- **Step 4: Disposing the used autoinjector**

Introduction

The instructions below explain how to use the autoinjector to inject Eucept. Please read the instructions carefully and follow them step by step. Your doctor or nurse will tell you how to inject Eucept. Do not attempt to administer an injection until you are sure that you understand how to use the autoinjector properly. If you have questions about how to inject, please ask your doctor or nurse for help.

Step 1: Preparing for an Eucept injection

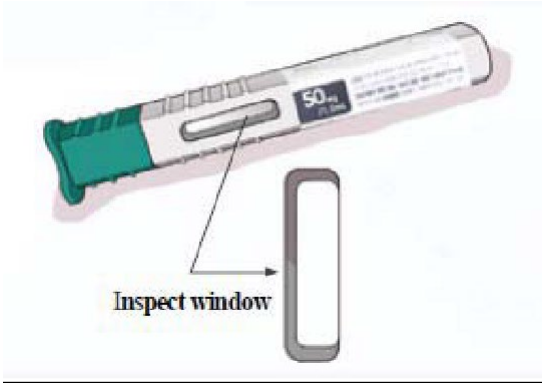
1. Select a clean, well-lit, flat surface.
2. Gather the items that you will need for your injection, and place them on the chosen surface:

a One autoinjector pre-filled (take these from the carton of pens you keep in your refrigerator). Do not shake the autoinjector.

b One alcohol swab and one cotton ball or gauze

3. Check the expiry date (month/year) on the autoinjector. If the date has passed, do not use the autoinjector and contact your pharmacist for assistance.
4. Inspect the solution in the autoinjector by looking through the clear inspection window (see Diagram 1). The solution should be colourless to light yellow, clear to opalescent solution. This appearance is normal for Eucept. Do not use the solution if it is discoloured or cloudy. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

Diagram 1



5. Leave the green cap in place and wait approximately 15-30 minutes to allow the Eucept solution in the autoinjector to reach room temperature. Waiting until the solution reaches room temperature may make the injection more comfortable for you. Do not warm in any other way. Always leave the autoinjector out of sight and reach of children.

Whilst waiting for the solution in the autoinjector syringe to reach room temperature, read Step 2 (below), and choose an injection site.

Step 2: Choosing an injection site (see Diagram 2)

1. The recommended injection site is the middle of the front of the thighs. If you prefer, you may alternatively use the stomach area, but make sure you choose a site at least 3 cm away from the belly button (navel). If someone else is giving you the injection, the outer area of the upper arms may also be used.

Diagram 2

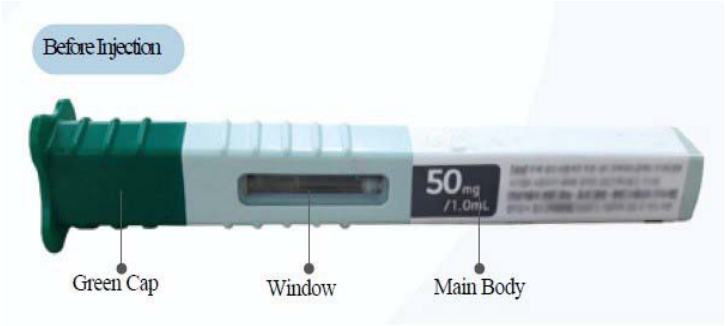
2. Each injection should be given at least 3 cm from where you last injected. Do not inject into tender, bruised or hard skin. Avoid scars or stretch marks. (It may be helpful to keep notes on the location of the previous injections.)
3. If you have psoriasis, you should try not to inject directly into any raised, thick, red, or scaly skin.

Step 3: Injecting the Eucept solution using the autoinjector

1. After waiting approximately 15-30 minutes for the solution in the autoinjector syringe to warm to room temperature, wash your hands with soap and water.
2. Clean the injection site with the alcohol swab using a circular motion and allow it to dry. Do not touch this area again before injecting.
3. Pick up the autoinjector and remove the green cap (see Diagram 3) by pulling it straight off. To avoid damaging the needle inside the autoinjector, do not bend the green cap while you are removing it, and do not re-attach it once it has been removed. After removal of the green cap, you will

see a needle safety shield extending slightly from the end of the autoinjector. Do not use the autoinjector if it is dropped with the needle cap off.

Diagram 3



4. Lightly pinching the skin around the injection site between the thumb and index finger of your free hand may make the injection easier and more comfortable.

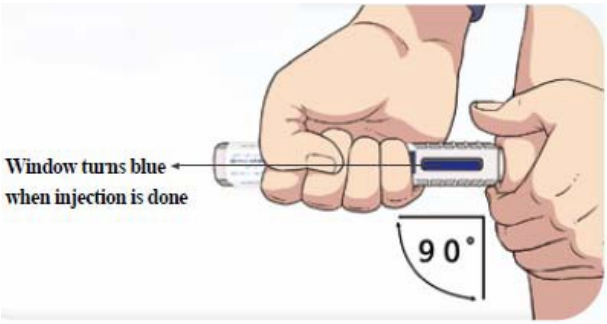
5. Hold the autoinjector at a right angle (90º) to the injection site. Push the open end of the autoinjector firmly against the skin until it stops moving. (see Diagram 4)

Diagram 4

6. Whilst pressing the autoinjector firmly against the skin, Press the autoinjector down to initiate the injection. You will hear first audible “click” sound with initiation. Continue to hold the autoinjector firmly against your skin until you hear a second click.

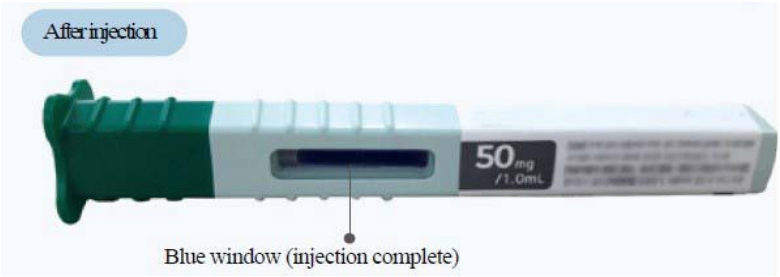
7. On hearing the second ‘click’ (or, if you do not hear a second ‘click’), your injection will be complete. You may now lift the autoinjector from your skin (see Diagram 5).

Diagram 5



8. The autoinjector's inspection window should now be completely blue, confirming that the dose has been injected correctly (see Diagram 6). If the window is not completely blue, contact your nurse or pharmacist for assistance, since the autoinjector may not have injected the Eucept solution completely. Do not try to use the autoinjector again, and do not try to use another autoinjector without agreement from your nurse or pharmacist.

Diagram 6



9. If you notice a spot of blood at the injection site, you should press the cotton ball or gauze over the injection site for 10 seconds. Do not rub the injection site.

Step 4: Disposing of the used autoinjector

• The autoinjector should be used once only - it should never be re-used. Dispose of the used autoinjector along with the green cap 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 Eucept.