Etanercept Solution for Injection

ENBREL®

1. GENERIC NAME

Etanercept Solution for Injection:

25 mg Pre-filled Syringe

50 mg in MYCLIC® Pre-filled Pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 25 mg Pre-filled Syringe contains: Etanercept 25 mg.
Each 50 mg MYCLIC® Pre-filled Pen contains: Etanercept 50 mg.

List of Excipients

The excipients in the pre-filled syringe, pre-filled pen are sucrose, sodium chloride, L-arginine hydrochloride, sodium dihydrogen phosphate (sodium phosphate monobasic monohydrate), disodium hydrogen phosphate (sodium phosphate dibasic dihydrate), and water for injection.

3. DOSAGE FORM AND STRENGTH

Dosage Form: Solution for injection in Pre-filled Syringe and Pre-filled Pen.
Strength: 50 mg/ml

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

- Reduction in signs and symptoms of moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more disease modifying anti-rheumatic drugs.
- Moderately to severely active early rheumatoid arthritis and juvenile rheumatoid arthritis.
- Treatment of ankylosing spondylitis in adults who have had inadequate therapy response to conventional therapy.

® Trademark Proprietor: Wyeth LLC, USA
Licensed User: Pfizer Limited, India

- For reduction in signs and symptoms of active arthritis in patients with psoriatic arthritis.
- Treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
- Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years who are inadequately controlled by, or are intolerant to other systemic therapies or photo therapies.

4.2 Posology and method of administration

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

The Etanercept pre-filled pen is available in 25 mg and 50 mg strengths. Other presentations of Etanercept are available in strengths of 25 mg and 50 mg.

Posology

Rheumatoid arthritis

25 mg Etanercept administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective (see section 5.2).

Psoriatic arthritis, ankylosing spondylitis

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

For all of the above indications, available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Plaque psoriasis

The recommended dose of Etanercept 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 Etanercept 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 5.2). Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Etanercept is indicated, the same guidance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly.

Special populations

Renal and hepatic impairment

No dose adjustment is required.

Elderly

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

Paediatric population

The safety and efficacy of Etanercept in children aged less than 2 years has not been established. No data are available.

Pre-filled syringe or pre-filled pen

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

Juvenile idiopathic arthritis

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

No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously (see section 5.2).

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

Paediatric plaque psoriasis (age 8 years and above)

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

If re-treatment with Etanercept 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.

Method of administration

Etanercept is administered by subcutaneous injection.

- Administration

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

Patients or caregivers who are to administer etanercept 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.

Solution for injection in pre-filled syringe

Before injection, single-use pre-filled syringe should be allowed to reach room temperature (approximately 15 to 30 minutes). The needle cover should not be removed while allowing the pre-filled syringe to reach room temperature. The solution should be clear and colorless or pale yellow and practically free from visible particles (see also section INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION OF ETANERCEPT).

Solution for injection in pre-filled pen

Before injection, etanercept single-use pre-filled pens should be allowed to reach room temperature (approximately 15 to 30 minutes). The needle cover should not be removed while allowing the pre-filled pen to reach room temperature. By looking though the inspection window, the solution should be clear and colorless or pale yellow and practically free from visible particles.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 2.

Sepsis or risk of sepsis.

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

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the Etanercept trademark and batch number of the administered product should be clearly recorded (or stated) in the patient file.

Infections

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

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

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

Tuberculosis

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

Before starting treatment with etanercept, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e., tuberculin skin test and chest X-ray, should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the Patient Card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Etanercept therapy must not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of Etanercept, and in accordance with local recommendations. In this situation, the benefit/risk balance of Etanercept therapy should be very carefully considered.

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

Hepatitis B reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-antagonists, including etanercept, has been reported.

This includes reports of reactivation of hepatitis B in patients who were anti-HBc positive but HBsAg negative. Patients should be tested for HBV infection before initiating treatment with Etanercept. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. 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 throughout therapy and for several weeks following termination of therapy. Adequate data from treating patients infected with HBV with anti-viral therapy in conjunction with TNF-antagonist therapy are not available. In patients who develop HBV infection, Etanercept should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Worsening of hepatitis C

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

Concurrent treatment with anakinra

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

Concurrent treatment with abatacept

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

Allergic reactions

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

Pre-filled syringe or pre-filled pen

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

Immunosuppression

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

levels, or change in enumeration of effector cell populations.

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

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

Malignancies and lymphoproliferative disorders

Solid and haematopoietic malignancies (excluding skin cancers)

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

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

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

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

Skin cancers

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

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

Vaccinations

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

Autoantibody formation

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

Haematologic reactions

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

Neurological disorders

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

Combination therapy

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

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

Renal and hepatic impairment

Based on pharmacokinetic data (see section 5.3), no dose adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited.

Congestive heart failure (Cardiac failure congestive)

Physicians should use caution when using Etanercept in patients who have congestive heart failure (CHF). There have been postmarketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking 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.

Alcoholic hepatitis

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

Wegener's granulomatosis

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

Hypoglycaemia in patients treated for diabetes

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

Special populations

Elderly

In the Phase 3 studies in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, no overall differences in adverse events, serious adverse events, and serious infections in patients age 65 or older who received etanercept were observed compared with younger patients. However, caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections.

Paediatric population

Vaccinations

It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating etanercept therapy (see Vaccinations, above).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium free'.

4.5 Drugs interactions

Concurrent treatment with anakinra

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

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

Concurrent treatment with abatacept

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

Concurrent treatment with sulfasalazine

In a clinical study of adult patients who were receiving established doses of sulfasalazine, to which 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. Physicians should use caution when considering combination therapy with sulfasalazine.

Non-interactions

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

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

4.6 Use in special populations

Fertility, Pregnancy and Lactation

Women of childbearing potential

Women of childbearing potential should consider the use of appropriate contraception to avoid becoming pregnant during Etanercept therapy and for three weeks after discontinuation of therapy.

Pregnancy

Developmental toxicity studies performed in rats and rabbits have revealed no evidence of harm to the foetus or neonatal rat due to etanercept. The effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. A higher rate of major birth defects was observed in one observational study comparing pregnancies exposed to etanercept (n=370) during the first trimester with pregnancies not exposed to etanercept or other TNF-antagonists (n=164) (adjusted odds ratio 2.4, 95% CI: 1.0-5.5). The types of major birth defects were consistent with those most commonly reported in the general population and no particular pattern of abnormalities was identified. No change in the rate of spontaneous abortion, stillbirth, or minor malformations was observed. In another observational multi-country registry study comparing the risk of adverse pregnancy outcomes in women exposed to etanercept during the first 90 days of pregnancy (n=425) to those exposed to non-biologic drugs (n=3497), there was no observed increased risk of major birth defects (crude odds ratio [OR]= 1.22, 95% CI: 0.79-1.90; adjusted OR = 0.96, 95% CI: 0.58-1.60 after adjusting for country, maternal disease, parity, maternal age and smoking in early pregnancy). This study also showed no increased risks of minor birth defects, preterm birth, stillbirth, or infections in the first year of life for infants born to women exposed to etanercept during pregnancy. Etanercept should only be used during pregnancy if clearly needed.

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.

Breast-feeding

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 pups. Because immunoglobulins, in common with many medicinal products, can be excreted in human milk, a decision must be made whether to discontinue breast-feeding or to discontinue etanercept therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Preclinical data about peri- and postnatal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available.

4.7 Effects on ability to drive and use machines

Etanercept has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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

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

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

Tabulated list of adverse reactions

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

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

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	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, protozoal, bacterial, atypical mycobacterial, viral infections, and Legionella)*		Hepatitis B reactivation, listeria
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancers* (see section 4.4)	Malignant melanoma (see section 4.4), lymphoma, leukaemia		Merkel cell carcinoma (see section 4.4), Kaposi's sarcoma
Blood and lymphatic system disorders			Thrombocytopenia, anaemia, leukopenia, neutropenia	Pancytopenia*	Aplastic anaemia*	Histiocytosis haematophagic (macrophage activation syndrome)*
Immune system disorders		Allergic reactions (see Skin and subcutaneous tissue disorders), autoantibody formation*	Vasculitis (including anti-neutrophilic cytoplasmic antibody positive vasculitis)	Serious allergic/anaphylactic reactions (including angioedema, bronchospasm), sarcoidosis		Worsening of symptoms of dermatomyositis
Nervous system disorders	Headache			CNS demyelinating events suggestive of multiple sclerosis or localised 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		
Eye disorders			Uveitis, scleritis			
Cardiac disorders			Worsening of cardiac failure congestive (see section 4.4)	New onset cardiac failure congestive (see section 4.4)		

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	Not Known (Cannot be Estimated from Available Data)
Respiratory, thoracic, and mediastinal disorders				Interstitial lung disease (including pneumonitis and pulmonary fibrosis)*		
Gastrointestinal disorders			Inflammatory bowel disease			
Hepatobiliary disorders			Elevated liver enzymes*	Autoimmune hepatitis*		
Skin and subcutaneous tissue disorders		Pruritus, rash	Angioedema, psoriasis (including new onset or worsening and pustular, primarily palms and soles), urticaria, psoriasiform rash	Stevens-Johnson syndrome, cutaneous vasculitis (including hypersensitivity vasculitis), erythema multiforme, lichenoid reactions	Toxic epidermal necrolysis	
Musculoskeletal and connective tissue disorders				Cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus, lupus-like syndrome		
General disorders and administration site conditions	Injection site reactions (including bleeding, bruising, erythema, itching, pain, swelling)*	Pyrexia				

* see Description of selected adverse reactions, below.

Description of selected adverse reactions

Malignancies and lymphoproliferative disorders

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

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

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

Injection site reactions

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

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

Serious infections

In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life-threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with Etanercept for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active-controlled study where patients were treated with either etanercept alone, methotrexate alone or etanercept in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of etanercept with methotrexate could be associated with an increase in the rate of infections.

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

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

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

Autoantibodies

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

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

Pancytopenia and aplastic anaemia

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

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.

Concurrent treatment with anakinra

In studies when adult patients received concurrent treatment with etanercept plus anakinra, a

higher rate of serious infections compared to etanercept alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count <1000/mm^3). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see sections 4.4 and 4.5)

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).

Paediatric population

Undesirable effects in paediatric patients with juvenile idiopathic arthritis

In general, the adverse events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients. Differences from adults and other special considerations are discussed in the following paragraphs.

The types of infections seen in clinical trials in juvenile idiopathic arthritis patients aged 2 to 18 years were generally mild to moderate and consistent with those commonly seen in outpatient paediatric populations. Severe adverse events reported included varicella with signs and symptoms of aseptic meningitis, which resolved without sequelae (see also section 4.4), appendicitis, gastroenteritis, depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.

In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children experienced an infection while receiving Etanercept during 3 months of the study (part 1, open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types and proportion of adverse events in juvenile idiopathic arthritis patients were similar to those seen in trials of Etanercept in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 69 juvenile idiopathic arthritis patients receiving 3 months of Etanercept compared to the 349 adult rheumatoid arthritis patients. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

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

Undesirable effects in paediatric patients with plaque psoriasis

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

No dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been an intravenous loading dose of 32 mg/m^2 followed by subcutaneous doses of 16 mg/m^2 administered twice weekly. One rheumatoid arthritis patient mistakenly self-administered 62 mg Etanercept subcutaneously twice weekly for 3 weeks without experiencing undesirable effects. There is no known antidote to Etanercept.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

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

5.2. Pharmacodynamic properties

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

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

receptors (TNFRs). Both TNFRs exist naturally in membrane bound and soluble forms. Soluble TNFRs are thought to regulate TNF biological activity.

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

Clinical efficacy and safety

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

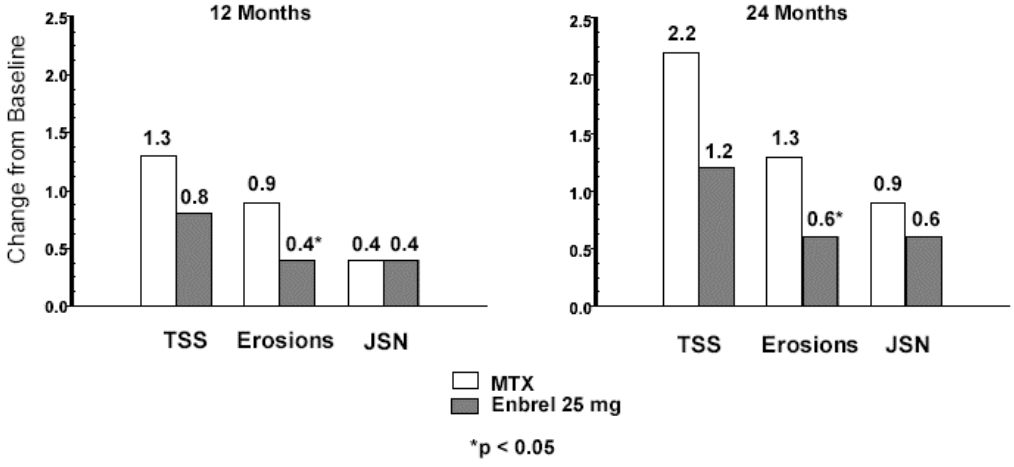
After discontinuation of Etanercept, symptoms of arthritis generally returned within a month. Re-introduction of treatment with Etanercept after discontinuation of up to 24 months resulted in the same magnitudes of responses as patients who received Etanercept without interruption of

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 subcutaneously (SC) twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement including onset of action within 2 weeks with 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 (JSN) score. 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 ENBREL vs. METHOTREXATE IN PATIENTS WITH RA OF <3 YEARS DURATION



In another active-controlled, double-blind, randomised study, clinical efficacy, safety, and radiographic progression in RA patients treated with 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.

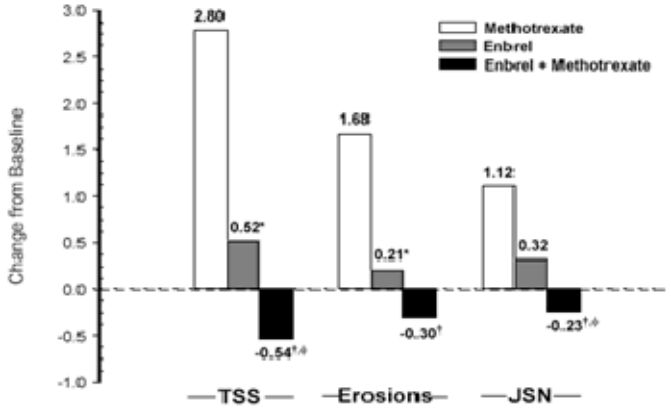
Clinical Efficacy Results at 12 Months: Comparison of Etanercept vs. Methotrexate vs. Etanercept in Combination with Methotrexate in Patients with RA of 6 Months to 20 Years Duration

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 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 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.

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		
	Percent of Patients	
	Placebo	**Etanercept[a]**
Psoriatic Arthritis Response	**n = 104**	**n = 101**
ACR 20		
Month 3	15	59[b]
Month 6	13	50[b]
ACR 50		
Month 3	4	38[b]
Month 6	4	37[b]
ACR 70		
Month 3	0	11[b]
Month 6	1	9[c]
PsARC		
Month 3	31	72[b]
Month 6	23	70[b]
[a]: 25 mg Etanercept 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, $p\leq0.001$). 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 in the ASAS 20, ASAS 50 and ASAS 70 as early as 2 weeks after the initiation of therapy.

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

	Percent of Patients	
Ankylosing Spondylitis Response	**Placebo N = 139**	**Etanercept 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 plaque psoriasis

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

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

Study 1 was a Phase 2 study in patients with active, but clinically stable plaque psoriasis involving ≥10% of the body surface area who were ≥18 years old. One hundred and twelve (112) patients were randomised to receive a dose of 25 mg of 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.

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

Responses of Patients with Psoriasis in Studies 2, 3 and 4

	Study 2					**Study 3**			**Study 4**		
		----------Etanercept---------					------Etanercept---			----Etanercept-----	
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	Placebo n = 46 wk 12	50 mg QW n = 96 wk 12	50 mg QW n = 90 wk 24[a]
PASI 50	14	58*	70	74*	77	9	64*	77*	9	69*	83
PASI 75	4	34*	44	49*	59	3	34*	49*	2	38*	71
DSGA[b], clear or almost clear	5	34*	39	49*	55	4	39*	57*	4	39*	64

*p ≤0.0001 compared with placebo.

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

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

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

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

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

Antibodies to Etanercept

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

In subjects treated with approved doses of etanercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were approximately 6% of subjects with rheumatoid arthritis, 7.5% of subjects with psoriatic arthritis, 2% of subjects with ankylosing spondylitis, 7% of subjects with psoriasis, 9.7% of subjects with paediatric psoriasis, and 4.8% of subjects with juvenile idiopathic arthritis.

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

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

Paediatric population

Paediatric patients 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 aged 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) etanercept subcutaneously twice weekly. In part 2, patients with a clinical response at Day 90 were randomised to remain on etanercept or receive placebo for four months and assessed for disease flare. Responses were measured using the ACR Pedi 30, defined as ≥30% improvement in at least three of six and ≥30% worsening in no more than one of six JRA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and erythrocyte sedimentation rate (ESR). Disease flare was defined as a ≥30% worsening in three of six JRA core set criteria and ≥30% improvement in not more than one of the six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on etanercept experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo (p = 0.007). From the start of part 2, the median time to flare was ≥116 days for patients who received etanercept and 28 days for patients who received placebo. 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 paediatric patients from the above study (from the age of 4 years at time of enrollment) continued to receive Etanercept for up to 10 years. Rates of serious adverse events and serious infections did not increase with long-term exposure.

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

In another open-label single-arm study (n=127), 60 patients with extended oligoarthritis (EO) (15 patients aged 2 to 4, 23 patients aged 5 to 11 and 22 patients aged 12 to 17 years old), 38 patients with enthesitis-related arthritis (12 to 17 years old), and 29 patients with psoriatic arthritis (12 to 17 years old) were treated with Etanercept 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 8 years. At the end of the extension study, 84/109 (77%) patients had completed the study; 27 (25%) while actively taking Etanercept, 7 (6%) had withdrawn from treatment due to low/inactive disease; 5 (5%) had re-started Etanercept following an earlier withdrawal from treatment; and 45 (41%) had stopped Etanercept (but remained under observation); 25/109 (23%) patients permanently discontinued from the study. Improvements in clinical status achieved in the parent study were generally maintained for all efficacy endpoints during the entire follow-up period. Patients actively taking Etanercept could enter an optional withdrawal-retreatment period once during the extension study based on investigator's judgement of clinical response. 30 patients entered the withdrawal period. 17 patients were reported to have a flare (defined as ≥ 30% worsening in at least 3 of the 6 ACR Pedi components with ≥ 30% improvement in not more than 1 of the remaining 6 components and a minimum of 2 active joints); median time to flare after Etanercept withdrawal was 190 days. 13 patients were re-treated and the median time to re-treatment from withdrawal was estimated as 274 days. Due to the small number of data points, these results should be interpreted with caution.

The safety profile was consistent with that observed in the parent study.

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 reducing the recommended dose of Etanercept following its long-term use in patients with JIA.

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.

Pediatric 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 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 paediatric 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.

5.3 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%. With twice-weekly doses, it is anticipated that steady-state concentrations are approximately twice as high as those observed after single doses. After a single subcutaneous dose of 25 mg 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.

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

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

Distribution

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

Elimination

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

There is no apparent pharmacokinetic difference between males and females.

Linearity

Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

Special populations

Renal 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 failure. The presence of renal impairment should not require a change in dosage.

Hepatic impairment

Increased etanercept concentrations were not observed in patients with acute hepatic failure. The presence of hepatic impairment should not require a change in dosage.

Elderly

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

Paediatric population

Paediatric patients with juvenile idiopathic arthritis

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

Paediatric patients with plaque psoriasis

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

were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice weekly.

6. NONCLINICAL PROPERTIES

6.1. Animal Toxicology or Pharmacology

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

Etanercept did not induce lethality or notable signs of toxicity in mice or rats following a single subcutaneous dose of 2,000 mg/kg or a single intravenous dose of 1,000 mg/kg. Etanercept did not elicit dose-limiting or target organ toxicity in cynomolgus monkeys following twice weekly subcutaneous administration for 4 or 26 consecutive weeks at a dose (15 mg/kg) that resulted in AUC-based serum drug concentrations that were over 27-fold higher than that obtained in humans at the recommended dose of 25 mg.

7. DESCRIPTION

ENBREL (Etanercept) is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of etanercept contains the CH_2 domain, the CH_3 domain and hinge region, but not the CH_1 domain of IgG1. Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. Etanercept is soluble in water.

8. PHARMACEUTICAL PARTICULARS

8.1. Incompatibilities

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

8.2. Shelf-life

30 months

8.3. Packaging information

Pre-filled syringe

Clear glass syringe (type I glass) with stainless steel needle, rubber needle cover and plastic plunger. The needle cover contains dry natural rubber (latex) (see section 4.4).

Enbrel is single use pre-filled syringes of etanercept (25 mg).

Enbrel 25 mg pre-filled syringes are available in a carton in 2's pack with alcohol swabs.

Pre-filled pen

Pre-filled pen containing clear type 1 glass pre-filled syringe with a stainless steel 27-gauge needle, rubber needle cover, and plastic plunger. The needle cap of the pre-filled pen contains dry natural rubber [latex].

Enbrel is single-use pre-filled syringe in MYCLIC® pen contains etanercept (50 mg).

Enbrel 50 mg MYCLIC® pre-filled pens are available in a carton in 2's pack with alcohol swabs.

8.4. Storage and handling instructions

Enbrel pre-filled syringe and pre-filled pen must be stored refrigerated at 2°C to 8°C.

Do not freeze.

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

Keep out of reach of children.

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

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.

INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION OF ENBREL

SOLUTION IN PRE-FILLED SYRINGE PRESENTATION
This section is divided into the following sub-sections:

Introduction
Step 1: Setting Up for an Injection
Step 2: Choosing an Injection Site
Step 3: Injecting the Enbrel Solution
Step 4: Disposing of Supplies

Introduction

The following instructions explain how to prepare and inject Enbrel. Please read the instructions

carefully and follow them step by step. You will be instructed by your doctor or his/her assistant on the techniques of self-injection or on giving an injection to a child. Do not attempt to administer an injection until you are sure that you understand how to prepare and give the injection.

This injection should not be mixed with any other medicine before use.

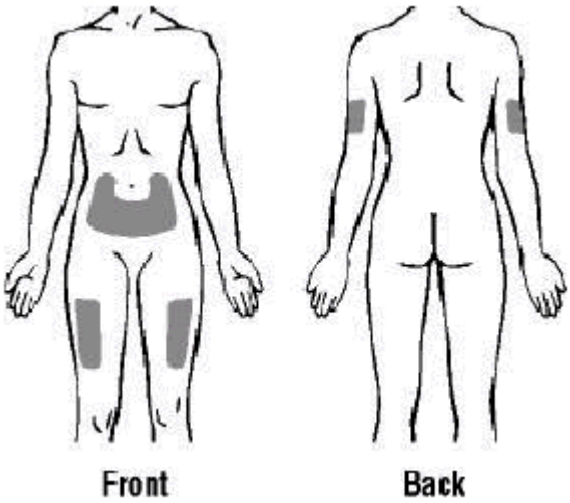
Step 1: Setting Up for an Injection

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

Step 2: Choosing an Injection Site

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

Diagram 1



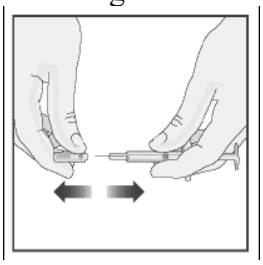
2. A different site should be used for each new injection. Each new injection should be given at least 3 cm from an old site. Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.
3. If you or the child have psoriasis, you should try not to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

Step 3: Injecting the Enbrel Solution

1. Wipe the site where Enbrel is to be injected with an alcohol swab, using a circular motion. DO NOT touch this area again before giving the injection.
2. Pick up the pre-filled syringe from your flat work surface. Remove the needle cover by firmly pulling it straight off the syringe (see Diagram 2). Be careful not to bend or twist the cover during removal to avoid damage to the needle.

When you remove the needle cover, there may be a drop of liquid at the end of the needle; this is normal. Do not touch the needle or allow it to touch any surface. Do not touch or bump the plunger. Doing so could cause the liquid to leak out.

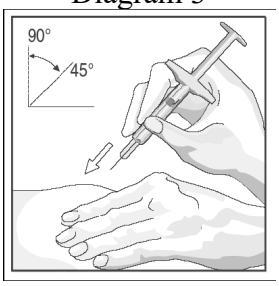
Diagram 2



3. When the cleaned area of skin has dried, pinch and hold it firmly with one hand. With the other hand, hold the syringe like a pencil.
4. With a quick, short motion, push the needle all the way into the skin at an angle between 45° and 90°. With experience, you will find the angle that is most comfortable for you

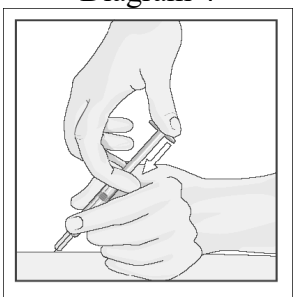
(see Diagram 3). Be careful not to push the needle into the skin too slowly, or with great force.

Diagram 3



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

Diagram 4



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

Step 4: Disposing of Supplies

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

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

SOLUTION IN PRE-FILLED PEN PRESENTATION

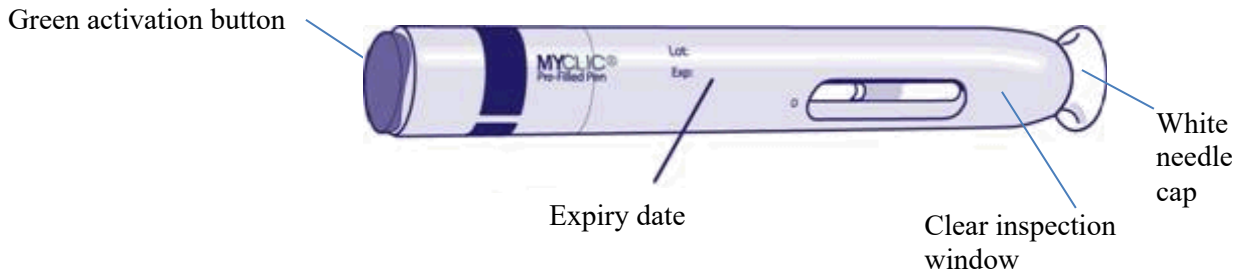
This section is divided into the following sub-sections:

Introduction
Step 1: Preparing for an Enbrel Injection
Step 2: Choosing an Injection Site
Step 3: Injecting the Enbrel Solution
Step 4: Disposing of the Used MYCLIC® PEN

Introduction

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

Diagram 1
The MYCLIC® pre-filled pen



Step 1: Preparing for an Enbrel Injection

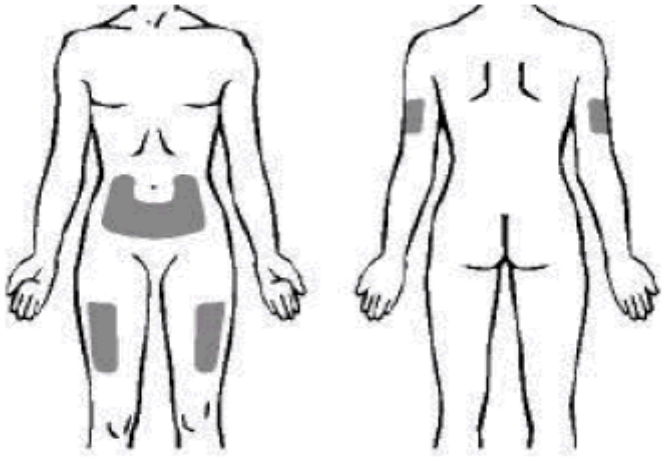
1. Select a clean, well-lit, flat surface.
2. Gather the items that you will need for your injection, and place them on the chosen surface:
   a. One MYCLIC® pre-filled pen and one alcohol swab (take these from the carton of pens you keep in your refrigerator). Do not shake the pen.
   b. One cotton ball or gauze.
3. **Check the expiry date (month/year) on the pen.** If the date has passed, do not use the pen and contact your pharmacist for assistance.
4. Inspect the solution in the pen by looking through the clear inspection window. The solution should be clear or slightly opalescent, colorless or pale yellow, and may contain small white or almost transparent particles of protein. This appearance is normal for Enbrel. Do not use the solution if it is discolored, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.
5. **Leave the white needle cap in place and wait approximately 15-30 minutes** to allow the Enbrel solution in the pen 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 pen out of sight and reach of children.**

While waiting for the solution in the pen 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 5 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

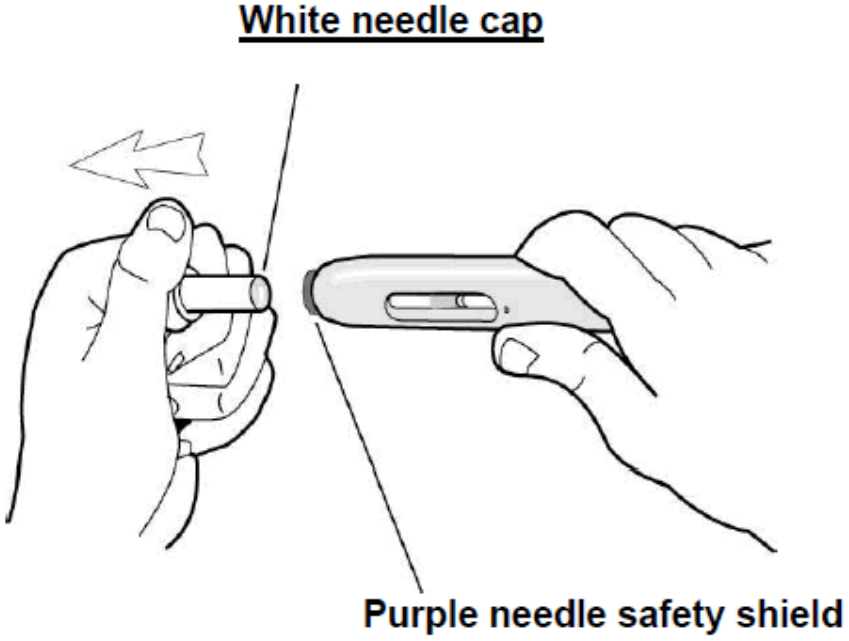


2. Each injection should be given at least 3 cm from where you last injected. Do not inject into tender, bruised or hard skin. Avoid scars or stretch marks. (It may be helpful to keep notes on the location of the previous injections.)
3. If you have psoriasis, you should try not to inject directly into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

Step 3: Injecting the Enbrel Solution

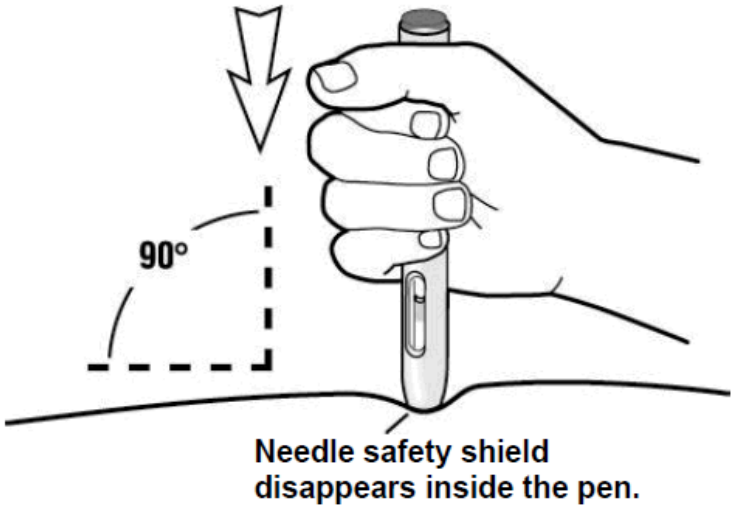
1. After waiting approximately 15-30 minutes for the solution in the pen to warm to room temperature, wash your hands with soap and water.
2. Clean the injection site with the alcohol swab using a circular motion, and allow it to dry. Do not touch this area again before injecting.
3. Pick up the pen and remove the white needle cap by pulling it straight off (see Diagram 3). To avoid damaging the needle inside the pen, do not bend the white needle cap while you are removing it, and do not re-attach it once it has been removed. After removal of the needle cap, you will see a purple needle safety shield extending slightly from the end of the pen. The needle will remain protected inside the pen until the pen is activated. Do not use the pen 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 pen at a right angle (90°) to the injection site. **Push the open end of the pen firmly against the skin,** so that the needle safety shield is pushed completely inside of the pen. A slight depression in the skin will be seen (see Diagram 4). The pen can only be activated when the needle shield is completely pushed inside the pen.

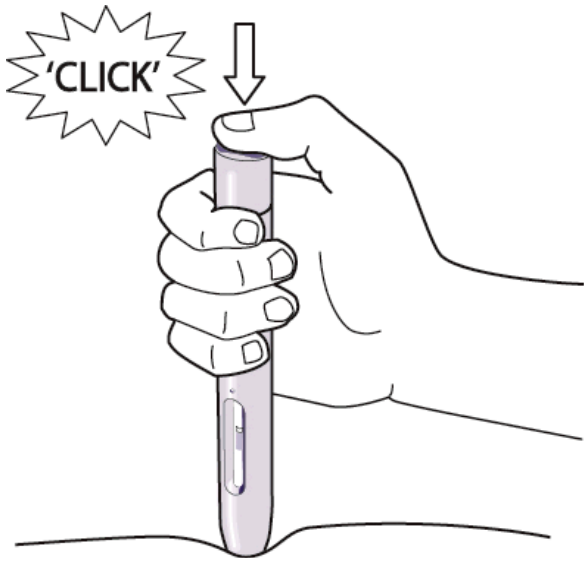
Diagram 4



6. While pushing the pen **firmly** against the skin to ensure that the needle safety shield is fully depressed inside the pen, **press the centre of the green button** on top of the pen with your thumb to start the injection (see Diagram 5). On pressing the centre of the button, you will hear a click. **Continue to hold the pen firmly against your skin until you hear a second click**, or until 10 seconds after the first click (whichever happens first).

Note – <u>If you are unable to start the injection as described, press the pen more firmly against your skin, then press the green button again.</u>

Diagram 5



7. On hearing the second 'click' (or, if you do not hear a second 'click', after 10 seconds have passed), your injection will be complete (see Diagram 6). You may now lift the pen from your skin (see Diagram 7). As you lift the pen, the purple needle safety shield will automatically extend to cover the needle.

Diagram 6

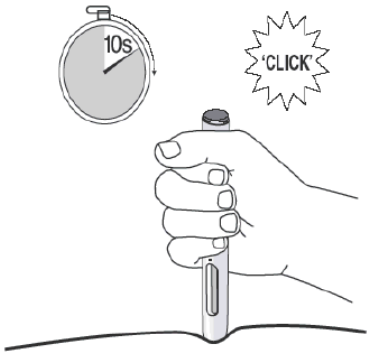
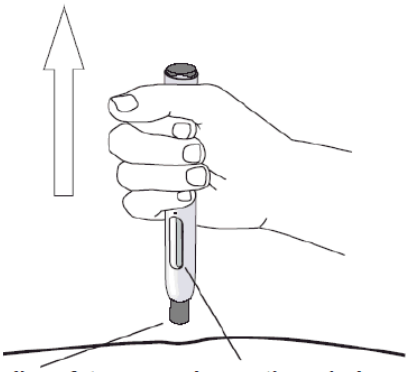


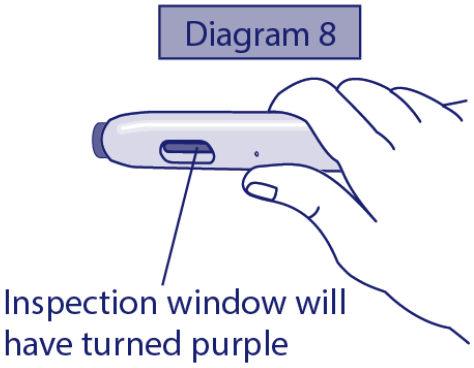
Diagram 7



Purple needle safety shield extends to cover needle.

Inspection window will have turned purple.

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



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 MYCLIC® Pen

- The pen should be used once only - it should never be re-used. Dispose of the used pen as instructed by your doctor, nurse or pharmacist.

9. PATIENT COUNSELLING INFORMATION

1. What you need to know before you use Etanercept

Do not use Etanercept

- if you, or the child you are caring for, are allergic to etanercept or any of the other ingredients of Enbrel (listed in section 6). If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Enbrel, and contact your doctor immediately.
- if you or the child have or are at risk of developing a serious blood infection called sepsis. If you are not sure, please contact your doctor.
- if you or the child have an infection of any kind. If you are not sure, please talk to your doctor.

Warnings and precautions

Talk to your doctor before taking Etanercept.

- **Allergic reactions**: If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Etanercept, and contact your doctor immediately.
- **Infections/surgery**: If you or the child develop a new infection, or are about to have any major surgery, your doctor may wish to monitor the treatment with Etanercept.
- **Infections/diabetes:** Tell your doctor if you or the child have a history of recurrent infections or suffer from diabetes or other conditions that increase the risk of infection.

- **Infections/monitoring:** Tell your doctor of any recent travel outside the European region. If you or the child develop symptoms of an infection such as fever, chills or cough, notify your doctor immediately. Your doctor may decide to continue to monitor you or the child for the presence of infections after you or the child stop using Etanercept.
- **Tuberculosis:** As cases of tuberculosis have been reported in patients treated with Etanercept, your doctor will check for signs and symptoms of tuberculosis before starting Etanercept. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Card. It is very important that you tell your doctor if you or the child have ever had tuberculosis, or have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- **Hepatitis B:** Tell your doctor if you or the child have or have ever had hepatitis B. Your doctor should test for the presence of hepatitis B infection before you or the child begin treatment with Etanercept. Treatment with Etanercept may result in reactivation of hepatitis B in patients who have previously been infected with the hepatitis B virus. If this occurs, you should stop using Etanercept.
- **Hepatitis C:** Tell your doctor if you or the child have hepatitis C. Your doctor may wish to monitor the treatment with Etanercept in case the infection worsens.
- **Blood disorders:** Seek medical advice immediately if you or the child have any signs or symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of Etanercept.
- **Nervous system and eye disorders:** Tell your doctor if you or the child have multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if Etanercept is an appropriate treatment.
- **Congestive heart failure:** Tell your doctor if you or the child have a history of congestive heart failure, because Etanercept needs to be used with caution under these circumstances.
- **Cancer:** Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) or any other cancer before you are given Etanercept.

Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.

Children and adults taking Etanercept may have an increased risk of developing lymphoma or another cancer.

Some children and teenage patients who have received Etanercept or other medicines that work the same way as Etanercept have developed cancers, including unusual types, which sometimes resulted in death.

Some patients receiving Etanercept have developed skin cancers. Tell your doctor if you or the child develop any change in the appearance of the skin or growths on the skin.

- **Chickenpox:** Tell your doctor if you or the child are exposed to chickenpox when using Etanercept. Your doctor will determine if preventive treatment for chickenpox is appropriate.
- **Latex:** The needle cap of the pre-filled syringe and MYCLIC® pen is made from latex (dry natural rubber). Contact your doctor before using Etanercept if the needle cap will be handled by, or Etanercept will be given to, someone with a known or possible hypersensitivity (allergy) to latex.
- **Alcohol abuse**: Etanercept should not be used for the treatment of hepatitis related to

alcohol abuse. Please tell your doctor if you or the child in your care have a history of alcohol abuse.

- **Wegener's granulomatosis**: Etanercept is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease. If you or the child in your care have Wegener's granulomatosis, talk to your doctor.
- **Anti-diabetic medicines**: Tell your doctor if you or the child have diabetes or are taking medicines to treat diabetes. Your doctor may decide if you or the child need less anti-diabetic medicine while taking Etanercept.

Children and adolescents

- **Vaccinations:** If possible, children should be up to date with all vaccinations before using Etanercept. Some vaccines, such as oral polio vaccine, should not be given while using Etanercept. Please consult your doctor before you or the child receive any vaccines.
- **Inflammatory bowel disease (IBD)**: There have been cases of IBD in patients with juvenile idiopathic arthritis (JIA) treated with Etanercept. Tell the doctor if the child develops any abdominal cramps and pain, diarrhoea, weight loss or blood in the stool.

Etanercept should not normally be used in children with polyarthritis or extended oligoarthritis below the age of 2 years, or in children with enthesitis-related arthritis or psoriatic arthritis below the age of 12 years, or in children with psoriasis below the age of 8 years.

Other medicines and Etanercept

Tell the doctor or pharmacist if you or the child are taking, have recently taken or might take any other medicines (including anakinra, abatacept or sulfasalazine), even those not prescribed by the doctor. You or the child should not use Etanercept with medicines that contain the active substance anakinra or abatacept.

Pregnancy and breast-feeding

Etanercept should only be used during pregnancy if clearly needed. You should consult your doctor if you become pregnant, think you may be pregnant, or are planning to have a baby.

If you received Etanercept during pregnancy, your baby may have a higher risk of getting an infection. In addition, one study found more birth defects when the mother had received Etanercept in pregnancy, compared with mothers who had not received Etanercept or other similar medicines (TNF-antagonists), but there was no particular kind of birth defect reported. Another study found no increased risk of birth defects when the mother had received Etanercept in pregnancy. Your doctor will help you to decide whether the benefits of treatment outweigh the potential risk to your baby. It is important that you tell the baby's doctors and other healthcare professionals about the use of Etanercept during pregnancy before the baby receives any vaccine (for more information see section 2, "Vaccinations").

Women using Etanercept should not breast-feed, since Etanercept passes into human breast milk.

Driving and using machines

The use of Etanercept is not expected to affect the ability to drive or use machines.

2. How to use Etanercept

Always use this medicine exactly as your doctor has told you. Check with your doctor if or pharmacist you are not sure.

If you feel that the effect of Etanercept is too strong or too weak, talk to your doctor or pharmacist.

You have been prescribed a 50 mg strength of Etanercept. A 25 mg strength of Etanercept is available for doses of 25 mg.

Dosing for adult patients (aged 18 years or over)

Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis including ankylosing spondylitis:
The usual dose is 25 mg given twice a week or 50 mg once a week as an injection under the skin. However, your doctor may determine an alternative frequency at which to inject Etanercept.
Plaque psoriasis:
The usual dose is 25 mg twice a week or 50 mg once a week.
Alternatively, 50 mg may be given twice a week for up to 12 weeks, followed by 25 mg twice a week or 50 mg once a week.
Your doctor will decide how long you should take Etanercept and whether retreatment is needed based on your response. If Etanercept has no effect on your condition after 12 weeks, your doctor may tell you to stop taking this medicine.

Use in children and adolescents

The appropriate dose and frequency of dosing for the child or adolescent will depend on body weight and disease. Your doctor will determine the correct dose for the child and will prescribe an appropriate strength of Etanercept (25 mg or 50 mg).
For polyarthritis or extended oligoarthritis in patients from the age of 2 years, or enthesitis-related arthritis or psoriatic arthritis in patients from the age of 12 years, the usual dose is 0.4 mg of Etanercept per kg bodyweight (up to a maximum of 25 mg) given twice weekly, or 0.8 mg of Etanercept per kg of bodyweight (up to a maximum of 50 mg) given once weekly.
For psoriasis in patients from the age of 8 years and above, the usual dose is 0.8 mg of Etanercept per kg bodyweight (up to a maximum of 50 mg), and should be given once weekly. If Etanercept has no effect on the child's condition after 12 weeks, your doctor may tell you to stop using this medicine.
The doctor will provide you with detailed directions for preparing and measuring the appropriate dose.

Method and route of administration

Etanercept is administered by an injection under the skin (by subcutaneous injection).
Etanercept can be taken with or without food or drink.
To help you remember, it may be helpful to write in a diary which day(s) of the week Etanercept should be used.

If you use more Etanercept than you should

If you have used more Etanercept than you should (either by injecting too much on a single occasion or by using it too frequently), talk to a doctor or pharmacist immediately. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to inject Etanercept

If you forget a dose, you should inject it as soon as you remember, unless the next scheduled dose is the next day; in which case you should skip the missed dose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

If you stop using Etanercept

Your symptoms may return upon discontinuation.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

3. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

If any of the following happen, do not inject more Etanercept. Tell your doctor immediately, or go to the casualty department at your nearest hospital.

- Trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious allergic reactions are rare. However, any of the above symptoms may indicate an allergic reaction to Etanercept, so you should seek immediate medical attention.

Serious side effects

If you notice any of the following, you or the child may need urgent medical attention.

- Signs of **serious infections**, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints
- Signs of **blood disorders**, such as bleeding, bruising, or paleness
- Signs of **nerve disorders**, such as numbness or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg
- Signs of **heart failure** or **worsening heart failure**, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or coughing, bluish colour of the nails or the lips
- Signs of **cancers:** Cancers may affect any part of the body including the skin and blood, and possible signs will depend on the type and location of the cancer. These signs may include weight loss, fever, swelling (with or without pain), persistent cough, presence of lumps or growths on the skin
- Signs of **autoimmune reactions** (where antibodies are made that may harm normal tissues in the body) such as pain, itching, weakness, and abnormal breathing, thinking, sensation, or vision
- Signs of **lupus or lupus-like syndrome,** such as weight changes, persistent rash, fever, joint or muscle pain, or fatigue
- Signs of **inflammation of the blood vessels** such as pain, fever, redness or warmth of the skin, or itching.

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or visit the casualty department at your nearest hospital.

The known side effects of Etanercept include the following in groups of decreasing frequency:

- **Very common** (may affect more than 1 in 10 people): Infections (including colds, sinusitis, bronchitis, urinary tract infections and skin infections); injection site reactions (including bleeding, bruising, redness, itching, pain, and swelling). Reactions at the injection site (these do not occur as often after the first month of treatment). Some patients have developed a reaction at an injection site that was used before.
- **Common** (may affect up to 1 in 10 people): Allergic reactions; fever; rash; itching; antibodies directed against normal tissue (autoantibody formation).
- **Uncommon** (may affect up to 1 in 100 people): Serious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various

sites); worsening of congestive heart failure; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; low blood platelet count; skin cancer (excluding melanoma); localised swelling of the skin (angioedema); hives (elevated patches of red or pale skin that often itch); eye inflammation; psoriasis (new or worsening); inflammation of the blood vessels affecting multiple organs; elevated liver blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver blood tests is common); abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (signs of bowel problems).

- **Rare** (may affect up to 1 in 1,000 people): Serious allergic reactions (including severe localised swelling of the skin and wheezing); lymphoma (a type of blood cancer); leukaemia (cancer affecting the blood and bone marrow); melanoma (a type of skin cancer); combined low platelet, red, and white blood cell count; nervous system disorders (with severe muscle weakness and signs and symptoms similar to those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord); tuberculosis; new onset congestive heart failure; seizures; lupus or lupus-like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness); skin rash, which may lead to severe blistering and peeling of the skin; lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes); inflammation of the liver caused by the body's own immune system (autoimmune hepatitis; in patients also receiving methotrexate treatment, the frequency is uncommon); immune disorder that can affect the lungs, skin and lymph nodes (sarcoidosis); inflammation or scarring of the lungs (in patients also receiving methotrexate treatment, the frequency of inflammation or scarring of the lungs is uncommon).

- **Very rare** (may affect up to 1 in 10,000 people): failure of the bone marrow to produce crucial blood cells.

- **Not known** (frequency cannot be estimated from the available data): Merkel cell carcinoma (a type of skin cancer); Kaposi's sarcoma (a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appear as purple lesions on the skin); excessive activation of white blood cells associated with inflammation (macrophage activation syndrome); recurrence of hepatitis B (a liver infection); worsening of a condition called dermatomyositis (muscle inflammation and weakness with an accompanying skin rash).

Side effects in children and adolescents

The side effects and their frequencies seen in children and adolescents are similar to those described above.

10. DETAILS OF MANUFACTURER

Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs, Belgium

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

122-A permission - F. No. 12-49/99-DC dt 7 Dec 2001 and subsequent permissions dated 8th Jan 2003, 6th Jul 2004, 13th Sep 2004, 25th Feb 2005, 1st Mar 2007, 22nd Mar 2007, 15th Jul 2009, 22nd Dec 2009, F. No. 4-49/94-DC dt 19th Jun 2006 and Permission No. IMP-228/2014 dt 27th Oct 2014 and 16th March 2020

12. DATE OF REVISION

May 2023