PT PFIZER INDONESIA
LOCAL PRODUCT DOCUMENT

Generic Name: Etanercept
Trade Name: ENBREL
CDS Effective Date: December 18, 2023
Supersedes: August 05, 2022

1. NAME OF THE MEDICINAL PRODUCT
Enbrel 50 mg solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each pre-filled syringe contains 50 mg of etanercept.

Etanercept is a human tumour necrosis factor receptor (TNFR) p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. Etanercept is a dimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. This Fc component contains the hinge, CH2 and CH3 regions but not the CH1 region of IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. The potency is determined by measuring the ability of etanercept to neutralise the TNFα-mediated growth inhibition of A375 cells. The specific activity of etanercept is 1.7×10^6 units/mg.

For excipients, see section 6.1.

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

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Rheumatoid arthritis
Enbrel can be used alone or in combination with methotrexate for the treatment of active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate. Used in combination with methotrexate, Enbrel has been shown to halt disease-associated structural damage.

Enbrel is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

In patients with rheumatoid arthritis, Enbrel used alone or in combination with methotrexate has been shown to slow the progression of disease-associated structural damage as measured by X-ray.

Juvenile idiopathic arthritis
Treatment of active polyarticular-course juvenile chronic arthritis in children aged 4 to 17 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Enbrel has not been studied in children aged less than 4 years.

Psoriatic arthritis
Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate.

Ankylosing spondylitis
Etanercept is indicated for treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to previous disease-modifying antirheumatic drug therapy.

Plaque psoriasis
Etanercept is indicated for treatment of adults (18 years or older) with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA (see section 5.1).

4.2 Posology and method of administration
Enbrel treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or psoriasis.

Adults (18-64 years)
Rheumatoid arthritis
25 mg Enbrel administered twice weekly is the recommended dose, alternatively, 50 mg administered once weekly has been shown to be safe and effective (see section 5.1).

Psoriatic arthritis and ankylosing spondylitis
The recommended dose is 25 mg Enbrel administered twice weekly, or 50 mg administered once weekly.

Plaque psoriasis
The recommended dose of Enbrel is 25 mg administered twice 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.

Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

If re-treatment with Enbrel is indicated, the above guidance on treatment duration should be followed. The dose should be 25 mg twice weekly. A 25 mg strength of Enbrel is available, and should be used for administration of 25 mg doses.

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

Elderly (≥65 years)
No dose adjustment is required. Posology and administration are the same as for adults 18-64 years of age.

Children and adolescents (≥4 to <18 years)
0.4 mg/kg (up to a maximum of 25 mg per dose) after reconstitution of 25 mg Enbrel in 1 mL of water for injection, given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses.

Enbrel has not been studied in children <4 years of age.

Renal and hepatic impairment
No dose adjustment is required.

Method of administration
Administer Enbrel as subcutaneous injections in the thigh, abdomen, or upper arm.

Give each new injection at least 3 cm from a previous site. Do NOT inject into areas where the skin is tender, bruised, red, or hard.

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

Before injection, Enbrel single-use pre-filled syringe should be allowed to reach room temperature (approximately 15 to 30 minutes). The needle cover should not be removed while allowing the pre-filled syringe to reach room temperature. The solution should be clear to opalescent, colorless to yellow or pale brown, and liquid may contain trace levels of translucent to white amorphous particles.

Missed doses
If a dose is missed, patients should be advised to administer the dose as soon as they remember, unless the next scheduled dose is the next day, in which case the missed dose should be skipped. Patients should continue to inject the medicine on their usual day(s). If a

patient does not remember until the day that the next injection is due, instruct the patient not to take a double dose.

4.3 Contraindications

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

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

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

4.4 Special warnings and special precautions for use

Infections

Serious infections, including sepsis and tuberculosis (TB), have been reported with the use of Etanercept (see section 4.8). Some of these infections have been fatal. These infections were due to bacteria, mycobacteria, fungi, viruses and parasites (including protozoa). Opportunistic infections have also been reported (including listeriosis and legionellosis). Patients who develop a new infection while undergoing treatment with Enbrel should be monitored closely. Administration of Enbrel should be discontinued if a patient develops a serious infection. Physicians should exercise caution when considering the use of Enbrel in patients with a history of recurring or chronic infections or with underlying conditions which may pre-dispose patients to infections such as advanced or poorly controlled diabetes (see sections 4.3 and 4.8).

Patients should be evaluated for infections before, during and after treatment with Enbrel, taking into consideration that the mean elimination half-life of etanercept is 80 hours (standard deviation of 28 hours; range from 7 to 300 hours).

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

Wegener's granulomatosis

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

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

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

Allergic reactions associated with Enbrel administration have been reported commonly. Allergic reactions have included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, Enbrel therapy should be discontinued immediately and appropriate therapy initiated (see section 4.8).

Immunosuppression
The possibility exists for anti-TNF therapies, including Enbrel, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. Whether treatment with Enbrel might influence the development and course of malignancies and active and/or chronic infections is unknown.

Malignancies and lymphoproliferative disorders

Solid and hematopoietic malignancies
Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the post-marketing 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. Cases of leukemia have been reported in patients treated with TNF-antagonist. There is an increased background risk for lymphoma and leukemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. *Post-hoc* analyses of rheumatoid arthritis clinical trials with etanercept have neither confirmed nor excluded an increased risk for malignancies. In a study of 49 patients with rheumatoid arthritis treated with Enbrel, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. The safety and

efficacy of Enbrel in patients with immunosuppression or chronic infections have not been evaluated.

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

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

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

Skin cancers
Melanoma and non-melanoma skin cancer (NMSC) has been reported in patients treated with TNF-antagonists including etanercept. Post-marketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with etanercept. Combining the results of controlled portions of clinical trials of etanercept, more cases of NMSC were observed in patients receiving etanercept compared with control patients, particularly in patients with psoriasis. Periodic skin examination is recommended for all patients who are at increased risk for skin cancer.

Vaccinations
In a double-blind, placebo-controlled, randomized clinical study in patients with psoriatic arthritis, 184 patients also received a multivalent pneumococcal polysaccharide vaccine at week 4. In this study most psoriatic arthritis patients receiving Enbrel were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had two-fold rises in titers compared to patients not receiving Enbrel. The clinical significance of this is unknown. Live vaccines should not be given concurrently with Enbrel. No data are available on the secondary transmission of infection by live vaccines in patients receiving Enbrel. It is recommended that juvenile chronic arthritis patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Enbrel therapy.

Autoantibody formation
Treatment with Enbrel may be associated with 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 Enbrel. Caution should be exercised in patients being treated with Enbrel who have a previous history of blood dyscrasias. All patients should be advised that if they develop signs and symptoms suggestive of blood dyscrasias or infections (e.g. persistent fever, sore throat, bruising, bleeding, paleness) whilst on Enbrel, they should seek immediate medical advice. Such patients should be evaluated urgently, including full blood count; if blood dyscrasias are confirmed, Enbrel should be discontinued.

Neurological disorders
Although no clinical trials have been performed evaluating Enbrel therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. There have been rare reports of central nervous system (CNS) demyelinating disorders in patients treated with Enbrel (see section 4.8). Additionally, there have been rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome). A careful risk/benefit evaluation, including a neurological assessment, is recommended when prescribing Enbrel to patients with pre-existing or recent onset of CNS 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 one year duration in rheumatoid arthritis patients, the combination of Enbrel and methotrexate did not result in unexpected safety findings, and the safety profile of Enbrel when given in combination with methotrexate was similar to the profiles reported in studies of Enbrel and methotrexate alone. Long-term studies to assess the safety of the combination are ongoing. The long-term safety of Enbrel in combination with other disease-modifying antirheumatic drugs has not been established.

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

Renal and hepatic impairment
Based on pharmacokinetic data (see section 5.2), no dosage 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 Enbrel in patients who also have CHF. There have been post-marketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking Enbrel. There have also been rare (<0.1%) reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. Two large clinical trials evaluating the use of Enbrel in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data from one of these trials suggest a possible tendency toward worsening CHF in those patients assigned to Enbrel treatment. In addition, a clinical trial evaluating the use

of infliximab (a monoclonal antibody that binds to TNF-alpha) in the treatment of CHF was terminated early due to an increase in mortality among infliximab treated patients.

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

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

Hepatitis B reactivation
Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant anti-TNF agents including Enbrel has been reported. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to hepatitis B reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating anti-TNF therapy.

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

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

Concurrent treatment with anakinra
Concurrent administration of Enbrel and anakinra has been associated with an increased risk of serious infections and neutropenia. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.5).

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

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent Enbrel and anakinra treatment

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

Concurrent treatment with sulfasalazine

In a clinical study of patients who were receiving established doses of sulfasalazine, to which Enbrel was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with Enbrel or sulfasalazine alone. The clinical significance of this interaction is unknown.

Non-interactions

In clinical trials with adult rheumatoid arthritis patients, no interactions have been observed when Enbrel was administered with glucocorticoids, salicylates (except sulfasalazine), non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate. No data are available on the effects of vaccination in patients receiving Enbrel. See section 4.4 for vaccination advice.

Methotrexate has no effect on the pharmacokinetics of Enbrel.

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

4.6 Fertility, pregnancy and lactation

Use during pregnancy

The effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. One pregnancy registry compared rates of major birth defects in liveborn infants of mothers with rheumatic diseases or psoriasis exposed to Enbrel in the first trimester (n=319) versus those unexposed to Enbrel during pregnancy (n=144). The all-inclusive adjusted odds ratio for major birth defects was 2.77 (95% CI 1.04-7.35) and when chromosomal and known genetic disorders were removed was 2.49 (95% CI 0.92-6.68). The findings showed no increased rate of minor malformations, and no pattern of major or minor malformations. In addition, there was no increase in rates of intrauterine or postnatal growth deficits or delayed postnatal development. In a second observational multi-country registry study comparing the risk of adverse pregnancy outcomes in women exposed to etanercept (n = 522) to those exposed to non-biologic drugs (n = 3508), there was no observed increased risk of major birth defects (adjusted odds ratio 0.96, 95% CI: 0.58-1.60). This study also showed no increased risks of minor birth defects, preterm birth, stillbirth or infections in the first year of life for infants born to women exposed to etanercept during pregnancy. Enbrel

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

Preclinical data about peri- and post-natal toxicity of Enbrel and of effects of Enbrel on fertility and general reproductive performance are not available. Developmental toxicity studies have been performed in rats and rabbits. The AUC-based systemic exposures of Enbrel in rats and rabbits are 21- to 25-times higher than in humans at the usual human therapeutic dose of 50 mg weekly, and are approximately 10- to 13-times higher than in humans at the maximum recommended human dose of 50 mg twice weekly (for psoriasis). No evidence of harm to the fetus in rats or rabbits or neonatal rats due to Enbrel was observed. Animal reproduction studies are not always predictive of human response.

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

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

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

Pediatric use
Etanercept has not been studied in children <4 years of age (see section 4.2). For pediatric specific safety information concerning malignancies and vaccinations, see sections 4.4 and 4.8.

Geriatric use
No specific dosage adjustments of etanercept are recommended based on patient age.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Adult patients

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

The following list of adverse reactions is based on experience from clinical trials in adults and on post-marketing experience.

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

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

Adverse Reactions Table

Adverse Drug Reactions (ADRs) by System Organ Class (SOC) and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC.

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from available data)
Infections and infestations	Infection (including upper respiratory tract infection, bronchitis, cystitis, skin infection)		Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis, and parasitic infection)	Tuberculosis, opportunistic infection (including invasive fungal, bacterial, atypical mycobacterial, viral infections, and Legionella) (see section 4.4)		Hepatitis B reactivation*, Listeria*
Neoplasms benign,			Non-melanoma	Malignant melanoma		Merkel cell carcinoma*

Adverse Reactions Table

Adverse Drug Reactions (ADRs) by System Organ Class (SOC) and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC.

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from available data)
malignant and unspecified (including cysts and polyps)			skin cancers (see section 4.4)	(see section 4.4), lymphoma,* leukaemia*		(see section 4.4)
Blood and lymphatic system disorders			Thrombocytopenia, anaemia, leukopenia, neutropenia	Pancytopenia (see section 4.4)	Aplastic anaemia* (see section 4.4)	Histiocytosis haematophagic (macrophage activation syndrome)*
Immune system disorders		Allergic reactions (*see Skin and subcutaneous tissue disorders, below*), autoantibody formation	Vasculitis (including ANCA positive vasculitis)	Serious allergic/anaphylactic reactions (including bronchospasm), sarcoidosis		
Nervous system disorders	Headache*			CNS demyelinating events, including multiple sclerosis and localized demyelinating conditions such as optic neuritis and transverse myelitis (see section 4.4), peripheral demyelinating events,		

Adverse Reactions Table

Adverse Drug Reactions (ADRs) by System Organ Class (SOC) and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC.

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from available data)
				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	New onset cardiac failure congestive		
Respiratory, thoracic, and mediastinal disorders				Interstitial lung disease (including pulmonary fibrosis and pneumonitis)		
Gastrointestinal disorders			Inflammatory bowel disease*			

Adverse Reactions Table

Adverse Drug Reactions (ADRs) by System Organ Class (SOC) and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC.

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from available data)
Hepatobiliary disorders			Elevated liver enzymes (*see Elevated liver enzymes above*)	Autoimmune hepatitis		
Skin and subcutaneous tissue disorders		Pruritus, rash	Angioedema, psoriasis (new onset or exacerbation, including all subtypes), urticaria, psoriasiform rash*	Stevens-Johnson syndrome,* cutaneous vasculitis (including hypersensitivity vasculitis), erythema multiforme*	Toxic epidermal necrolysis*	
Musculoskeletal and connective tissue disorders				Cutaneous lupus erythematosus,* subacute cutaneous lupus erythematosus,* lupus-like syndrome		
Renal and urinary disorders				Glomerulonephritis*		

Adverse Reactions Table

Adverse Drug Reactions (ADRs) by System Organ Class (SOC) and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC.

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from available data)
General disorders and administration site conditions	Injection site reactions (including bleeding, bruising, erythema, itching, pain, and swelling)	Pyrexia				

* ADR identified post-marketing.

Additional information

Serious adverse events reported in clinical trials

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

Malignancies and lymphoproliferative disorders

Thirty-eight new malignancies of various types were observed in 2,680 rheumatoid arthritis patients treated in clinical trials with Enbrel for up to 48 months, including 231 patients treated with Enbrel in combination with methotrexate in the 1-year active-controlled study. No psoriatic arthritis patients developed malignancies in the double-blind placebo-controlled studies of up to 6 months duration involving 131 Enbrel-treated patients. Twenty-three malignancies were reported in plaque psoriasis patients treated with Enbrel in double-blind and open-label studies of up to 15 months involving 1,261 Enbrel-treated patients.

Reports of malignancies affecting various sites have been received in the post-marketing period (see section 4.4).

There have been reports of malignancies in a clinical trial of patients being treated for Wegener's granulomatosis.

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

In controlled trials in patients with plaque psoriasis, approximately 14% of patients treated with Enbrel developed injection site reactions compared with 6% of placebo-treated patients during the first 12 weeks of treatment.

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

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

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

Serious and fatal infections have been reported during use of Enbrel; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Opportunistic infections have also been reported including invasive fungal, parasitic (including protozoal), viral (including herpes zoster), bacterial (including Listeria and Legionella), and atypical mycobacterial infections (see section 4.4). The most commonly reported invasive fungal infections included *Candida, Pneumocystis, Aspergillus,* and *Histoplasma*.

Some have occurred within a few weeks after initiating treatment with Enbrel in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see section 4.4). Data from a

sepsis clinical trial not specifically in patients with rheumatoid arthritis suggest that Enbrel treatment may increase mortality in patients with established sepsis.

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

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

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

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

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

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).

Laboratory evaluations

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

Concurrent Enbrel and anakinra treatment
In studies when patients received concurrent treatment with Enbrel plus anakinra, a higher rate of serious infections compared to Enbrel alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count <1000/mm^3). While neutropenic, one patient developed cellulitis that resolved after hospitalization (see sections 4.4 and 4.5).

Undesirable effects in pediatric patients with juvenile chronic arthritis
In general, the adverse events in pediatric patients were similar in frequency and type to those seen in adult patients.

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

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

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

The most frequent non-infectious adverse events seen in each age group were as follows:
4-8 years: abdominal pain (29%); 9-12 years: vomiting and accidental injury (27% each); and 13-17 years: headache (27%). Five events occurred in more than 10% of the patients: abdominal pain, headache, rhinitis, vomiting, rash. The majority of patients (53%) who experienced adverse events had events considered unrelated to drug.

4.9 Overdose
The maximum tolerated dose of Enbrel has not been established in humans. Single intravenous doses up to 60 mg/m^2 have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities. The highest dose level evaluated in rheumatoid arthritis patients has been an intravenous loading dose of 32 mg/m^2 followed by subcutaneous doses of 16 mg/m^2 (~25 mg) administered twice weekly.

Enbrel did not induce lethality or notable signs of toxicity in mice or rats following a single subcutaneous dose of 2000 mg/kg or a single intravenous dose of 1000 mg/kg. Enbrel did not elicit dose-limiting or target organ toxicity in cynomolgus monkeys following twice weekly subcutaneous administration for 4 or 26 consecutive weeks at a dose (15 mg/kg) that resulted in AUC-based serum drug concentrations that were over 27-fold higher than that obtained in humans at the recommended human dose of 25 mg.

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

There is no known antidote to Enbrel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
TNF-alpha Inhibitor
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.

Mechanism of action

Etanercept is a dimeric soluble form of the p75 TNF (tumor necrosis factor) receptor that can bind to two TNF molecules. Etanercept inhibits binding of both TNF (TNF_α) and lymphotoxin alpha [LT_α] (TNF_β) to cell surface TNF receptors, thus rendering TNF biologically inactive and preventing TNF-mediated cellular responses. TNF is a dominant cytokine in the inflammatory process of adult rheumatoid arthritis patients. TNF and LT_α are expressed in patients with juvenile idiopathic arthritis. Elevated levels of TNF are found in the synovial fluid of patients with rheumatoid arthritis and juvenile idiopathic arthritis.

Clinical efficacy

This section presents data from four randomised controlled trials in rheumatoid arthritis, 3 studies in juvenile idiopathic arthritis, 1 study in psoriatic arthritis, 4 studies in adults with ankylosing spondylitis and 3 studies in plaque psoriasis.

Adult patients with rheumatoid arthritis
The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid arthritis who had failed therapy with at least one but no more than four, DMARDs. Doses of 10 mg or 25 mg Enbrel or placebo were administered subcutaneously (SC) twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria.

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

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

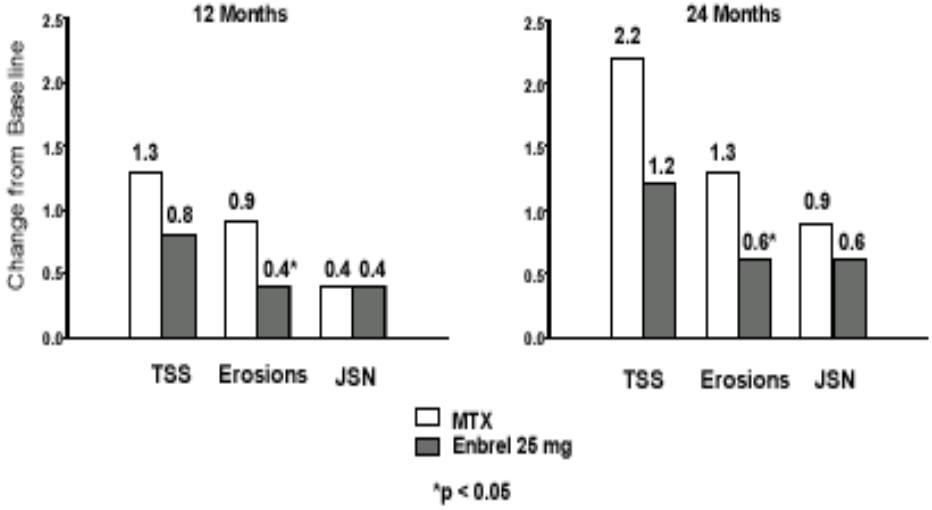
After discontinuation of Enbrel, symptoms of arthritis generally returned within a month. Reintroduction of treatment with Enbrel after discontinuation of up to 24 months resulted in the same magnitudes of responses as patients who received Enbrel without interruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 10 years in open-label extension treatment trials when patients received Enbrel without interruption.

The efficacy of Enbrel was compared to methotrexate in a 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 Enbrel were administered SC twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement including onset of action within 2 weeks with Enbrel 25 mg was similar to that

seen in the previous trials, and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with Enbrel 25 mg resulted in substantial improvement at 12 months, with about 44% of patients achieving a normal HAQ score (less than 0.5). This benefit was maintained in Year 2 of this study.

In this study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score (JSN). Radiographs of hands/wrists and feet were read at baseline and 6, 12, and 24 months. The 10 mg Enbrel dose had consistently less effect on structural damage than the 25 mg dose. Enbrel 25 mg was significantly superior to methotrexate for erosion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between methotrexate and Enbrel 25 mg. The results are shown in the figure below.

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



In another active-controlled, double-blind, randomised study, clinical efficacy, safety, and radiographic progression in RA patients treated with Enbrel alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg), and of the combination of Enbrel and methotrexate initiated concurrently were compared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least 1 DMARD other than methotrexate.

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

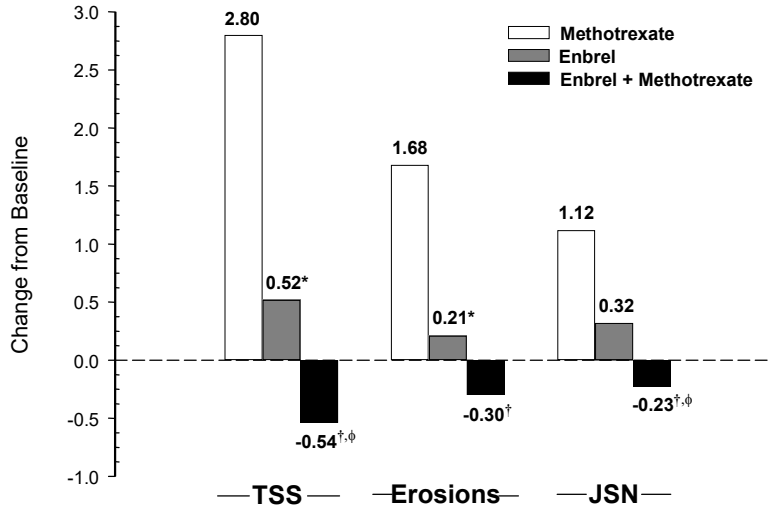
CLINICAL EFFICACY RESULTS AT 12 MONTHS: COMPARISON OF ENBREL VS. METHOTREXATE VS. ENBREL IN COMBINATION WITH METHOTREXATE IN PATIENTS WITH RA OF 6 MONTHS TO 20 YEARS DURATION

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

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

Radiographic progression at week 52 was significantly less in the Enbrel group than in the methotrexate group, while the combination was significantly better than either monotherapy at slowing radiographic progression (see figure below).

RADIOGRAPHIC PROGRESSION: COMPARISON OF ENBREL VS. METHOTREXATE VS. ENBREL IN COMBINATION WITH METHOTREXATE IN PATIENTS WITH RA OF 6 MONTHS TO 20 YEARS DURATION (52 WEEK 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.

In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤0.5) at 24 months was higher in the Enbrel in combination with methotrexate group compared with the Enbrel alone and methotrexate alone groups (62%, 50%, and 36%, respectively; $p<0.05$). The difference between Enbrel alone and methotrexate alone was also significant ($p<0.05$). Among patients who completed a full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively.

Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the significant advantages for Enbrel monotherapy compared with methotrexate monotherapy were also observed after 24 months.

The safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg Enbrel once weekly, and 153 patients received 25 mg Enbrel twice weekly. The safety and efficacy profiles of the two Enbrel treatment regimens were comparable at week 8 in their effect on signs and symptoms of RA; data at week 16 did not show comparability (non-inferiority) between the

two regimens. A single 50 mg/mL injection of Enbrel was found to be equivalent to two simultaneous injections of 25 mg/mL.

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

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

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

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

Long-term safety of Enbrel monotherapy (n=103), Enbrel plus methotrexate (n=294), or methotrexate monotherapy (n=197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years

of age. Overall, infections were more commonly reported in patients treated with Enbrel compared to methotrexate alone (3.8% versus 2%), and the infections associated with Enbrel use were of a more severe nature.

Adult patients with Psoriatic Arthritis

The efficacy of Enbrel was assessed in a 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 MTX therapy (stable for ≥2 months) could continue at a stable dose of ≤25 mg/week MTX. Doses of 25 mg of Enbrel (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered SC twice a week for 6 months. At the end of the double-blind study, patients could enter a long-term open-label extension study for a total duration of up to 2 years.

The results 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 PLACEBO-CONTROLLED TRIAL

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

a: 25 mg Enbrel SC twice weekly
b: p <0.001, Enbrel vs. placebo
c: p <0.01, Enbrel vs. placebo

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

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

Mean (SE) Annualized Change from Baseline in Total Sharp Score (TSS)

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

SE = standard error
a: p = 0.0001

Enbrel treatment resulted in improvement in physical function during the double-blind period, and this benefit was maintained during the longer-term exposure of up to 2 years.

There is insufficient evidence of the efficacy of Enbrel in patients with ankylosing spondylitis-like psoriatic arthropathy due to the small number of patients studied.

No study has been performed in patients with psoriatic arthritis using the 50 mg, once-weekly dosing regimen. Evidence of efficacy for the once-weekly dosing regimen in this patient population has been based on data from the study in patients with ankylosing spondylitis.

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

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

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

RESPONSES OF PATIENTS WITH ANKYLOSING SPONDYLITIS IN A PLACEBO-CONTROLLED TRIAL		
	Percent of Patients	
Ankylosing Spondylitis Response	**Placebo n = 139**	**Enbrel n = 138**
ASAS 20		
2 weeks	22	46[a]

3 months	27	60[a]
6 months	23	58[a]
ASAS 50		
2 weeks	7	24[a]
3 months	13	45[a]
6 months	10	42[a]
ASAS 70		
2 weeks	2	12[b]
3 months	7	29[b]
6 months	5	28[b]
a: p<0.001, Enbrel vs. placebo		
b: p = 0.002, Enbrel vs. placebo		

Among patients with ankylosing spondylitis who received Enbrel, the clinical responses were apparent at the time of the first visit (2 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant therapies at baseline.

Similar results were obtained in the 2 smaller ankylosing spondylitis trials.

In a fourth study, the safety and efficacy of 50 mg Enbrel (two 25 mg SC injections) administered once weekly vs. 25 mg Enbrel administered twice weekly were evaluated in a double-blind, placebo-controlled study of 356 patients with active ankylosing spondylitis. The safety and efficacy profiles of the 50 mg once-weekly and 25 mg twice-weekly regimens were similar.

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

Study 1 was a Phase 2 study in patients with active but clinically stable plaque psoriasis involving ≥10% of the body surface area that were ≥18 years old. One hundred and twelve (112) patients were randomized to receive a dose of 25 mg of Enbrel (n=57) or placebo (n=55) twice a week for 24 weeks.

Study 2 evaluated 652 patients with chronic plaque psoriasis using the same inclusion criteria as study 1 with the addition of a minimum psoriasis area and severity index (PASI) of 10 at screening. Enbrel was administered at doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week for 6 consecutive months. During the first 12 weeks of the double-blind treatment period, patients received placebo or one of the above three Enbrel doses. After 12 weeks of treatment, patients in the placebo group began treatment with blinded Enbrel (25 mg twice a week); patients in the active treatment groups continued to week 24 on the dose to which they were originally randomized.

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

In study 1, the Enbrel-treated group had a significantly higher proportion of patients with a PASI 75 response at week 12 (30%) compared to the placebo-treated group (2%) ($p<0.0001$). At 24 weeks, 56% of patients in the Enbrel-treated group had achieved the PASI 75 compared to 5% of placebo-treated patients. Key results of studies 2 and 3 are shown below.

Responses of patients with Psoriasis in Studies 2 and 3

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

*p ≤0.0001 compared with placebo.
a. No statistical comparisons to placebo were made at week 24 in Study 2 because the original placebo group began receiving Enbrel 25 mg BIW from week 13 to week 24.
b. Dermatologist Static Global Assessment. Clear or almost clear defined as 0 or 1 on a 0 to 5 scale.

Among patients with plaque psoriasis who received Enbrel, significant responses relative to placebo were apparent at the time of the first visit (2 weeks) and were maintained through 24 weeks of therapy.

Study 2 also had a drug withdrawal period during which patients who achieved a PASI improvement of at least 50% at week 24 had treatment stopped. Patients were observed off

treatment for the occurrence of rebound (PASI ≥150% of baseline) and for the time to relapse (defined as a loss of at least half of the improvement achieved between baseline and week 24). During the withdrawal period, symptoms of psoriasis gradually returned with a median time to disease relapse of 3 months. No rebound flare of disease and no psoriasis-related serious adverse events were observed. There was some evidence to support a benefit of re-treatment with Enbrel in patients initially responding to treatment.

In study 3, the majority of patients (77%) who were initially randomised to 50 mg twice weekly and had their Enbrel dose decreased at week 12 to 25 mg twice weekly maintained their PASI 75 response through week 36. For patients who received 25 mg twice weekly throughout the study, the PASI 75 response continued to improve between weeks 12 and 36.

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

Antibodies to Enbrel
Antibodies to Enbrel, all non-neutralising, were detected in 4 out of 96 rheumatoid arthritis patients who received Enbrel at a dose of 25 mg twice a week for up to 3 months in a placebo-controlled trial. In the active-controlled trial, 11 (2.8%) of 400 etanercept-treated patients had at least one positive result but none of these patients had a positive neutralising antibody test. Results from JCA patients were similar to those seen in adult RA patients treated with Enbrel. Of 98 patients with psoriatic arthritis who have been tested, no patient has developed antibodies to Enbrel at 24 weeks. Among 175 ankylosing spondylitis patients treated with Enbrel, 3 patients were reported with antibodies to Enbrel, none were neutralising. In double-blind studies up to 6 months duration in plaque psoriasis, about 1% of the 1,084 patients developed antibodies to Enbrel, none were neutralising.

Although the experience does not exclude the possibility that a clinically relevant effect might occur, no apparent correlation of antibody development to clinical response or adverse events was seen.

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

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 Enbrel, the average maximum serum concentration observed in healthy volunteers was 1.65 ± 0.66 μg/mL, and the area under the curve was 235 ± 96.6 μg•hr/mL. Dose

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

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

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 mgh/L vs. 316 mgh/L for 50 mg Enbrel once weekly (n=21) vs. 25 mg Enbrel twice weekly (n=16), respectively.

Although there is elimination of radioactivity in urine after administration of radiolabeled etanercept to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal or hepatic failure. The presence of renal and hepatic impairment should not require a change in dosage. There is no apparent pharmacokinetic difference between men and women.

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

Elderly patients
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.

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

Gender
There is no apparent pharmacokinetic difference between men and women.

Concentration-effect Relationship
Steady-state serum concentrations of 1 to 2 mg/L of etanercept are associated with optimal effect, and are obtained with doses of 25 mg twice weekly. In an open-label, single-dose, two-treatment, crossover study in 28 healthy volunteers, Enbrel, administered as a single

50 mg/mL injection, was found to be bioequivalent to two simultaneous injections of 25 mg/mL.

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

5.3 Preclinical safety data

Carcinogenicity
In the toxicological studies with Enbrel, no dose-limiting or target organ toxicity was evident. Enbrel 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 Enbrel due to the development of neutralising antibodies in rodents, which is a human protein.

Enbrel did not induce lethality or notable signs of toxicity in mice or rats following a single subcutaneous dose of 2000 mg/kg or a single intravenous dose of 1000 mg/kg. Enbrel 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.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store at 2°C - 8°C before reconstitution. Do not freeze. Keep the pre-filled syringes in the outer carton in order to protect from light.

6.5 Nature and contents of container
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).

Cartons contain 2 single-use pre-filled syringes of Enbrel with 2 alcohol swabs.

6.6 Instructions for use, handling, and disposal
The needle cover of pre-filled syringe contains latex (dry natural rubber). Patient 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.

Any unused product or waste material should be disposed of in accordance with local requirements.

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