SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ENBREL® 25 mg powder and solvent for solution for injection

ENBREL® 25 mg PS solution for injection in pre-filled syringe

ENBREL® 50 mg PS solution for injection in pre-filled syringe or pre-filled MYCLIC pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder and solvent for solution for injection

Each single-use vial of ENBREL contains 25 mg etanercept.

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

Contains sugar (mannitol and sucrose).

Solution for injection

Each pre-filled syringe of ENBREL PS contains 25 mg or 50 mg etanercept.

Each pre-filled pen of ENBREL PS contains 50 mg etanercept.

Contains sugar (sucrose).

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. The Fc component of etanercept contains the hinge, CH2 and CH3 regions, but not the CH1 region of IgG1.

Excipients with known effect

Powder and solvent for solution for injection

Each vial of ENBREL 25 mg contains 40 mg of mannitol and 10 mg of sucrose.

Solution for injection

Each 1 mL of ENBREL 25 mg PS contains 10 mg of sucrose.

Each 1 mL of ENBREL 50 mg PS contains 10 mg of sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ENBREL 25 mg powder and solvent for solution for injection

Powder for solution for injection.

Before reconstitution the powder forms a white cake. After reconstitution the solution is a colourless to slightly yellow or pale brown liquid, clear to slightly opalescent.

ENBREL 25 mg and 50 mg PS solution for injection in pre-filled syringe and pre-filled pen (MYCLIC)

Solution for injection.

Clear colourless, yellow or pale brown solution. The liquid may contain trace levels of translucent to white amorphous particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

ENBREL can be used alone or in combination with methotrexate to reduce the signs and symptoms and inhibit the progression of structural damage as measured by X-ray of active rheumatoid arthritis (RA) in adults when the response to one or more disease modifying antirheumatic medicines has proven inadequate.

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

Juvenile idiopathic arthritis

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

ENBREL is indicated for treatment of active polyarticular-course juvenile idiopathic arthritis and extended oligoarthritis in children and adolescents from the age of 2 years who have had inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

Psoriatic arthritis

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

Axial spondylarthritis

Ankylosing spondylitis (AS)

ENBREL is indicated to reduce signs and symptoms in patients with ankylosing spondylitis.

Non-radiographic axial spondyloarthritis

ENBREL is indicated for the treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence, who have had an inadequate response to, or are intolerant to, conventional therapy.

Plaque psoriasis

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

Paediatric plaque psoriasis

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

4.2 Posology and method of administration

Posology

Use in adults

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

The recommended dose of ENBREL for adult patients 18 years and older with rheumatoid arthritis is 25 mg reconstituted in 1,0 mL of water for injection administered twice weekly (72 to 96 hours apart) as a subcutaneous injection. 50 mg per week provides the optimal therapeutic response in rheumatoid arthritis. ENBREL can be administered as follows:

- once weekly (two 25 mg subcutaneous injections reconstituted in 1,0 mL of water for injection or two ENBREL 25 mg PS pre-filled syringes) administered subcutaneously at approximately the same time or
- one single 25 mg subcutaneous injection reconstituted in 1,0 mL of water for injection or one ENBREL 25 mg PS pre-filled syringe administered twice weekly, 3 – 4 days apart (i.e. two 25 mg single dose vials or two 25 mg PS pre-filled syringes per week) or
- ENBREL 50 mg PS pre-filled syringe or pre-filled pen administered once weekly as a subcutaneous

injection.

In psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondylarthritis, the recommended dose is 50 mg per week (given as one single 25 mg injection reconstituted in 1,0 mL of water for injection or as one ENBREL 25 mg PS pre-filled syringe given twice weekly, 3 – 4 days apart). Doses other than 25 mg administered twice weekly have not been studied.

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

Plaque psoriasis

In plaque psoriasis, the dose of ENBREL is 50 mg per week given as one single 25 mg injection reconstituted in 1,0 mL water for injection or as one ENBREL 25 mg PS pre-filled syringe administered twice weekly, 3 – 4 days apart or ENBREL 50 mg PS pre-filled syringe or pre-filled pen administered once weekly. Higher responses may be achieved from initial treatment up to 12 weeks with a dose of 50 mg given twice weekly.

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

Special populations

Use in elderly patients

No dosage adjustment is required.

Use in patients with renal impairment

No dosage adjustment is required.

Use in patients with hepatic impairment

No dosage adjustment is required.

Paediatric population

The dosage of ENBREL 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 ENBREL 25 mg/mL powder and solvent for solution for injection (see below for dosing for specific indications). Patients weighing 62,5 kg or more may be dosed using a fixed-dose pre-filled syringe or pre-filled pen.

Juvenile idiopathic arthritis (age 2 years and above)

Children (≥ 2 to < 18 years)

0,4 mg/kg (up to a maximum of 25 mg per dose) after reconstitution of 25 mg ENBREL in 1,0 mL of water for injection or ENBREL 25 mg PS pre-filled syringe, 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.

Glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with ENBREL in children. ENBREL has not been studied in children < 2 years of age.

Paediatric plaque psoriasis (age 6 years and above)

Children (≥ 6 to < 18 years)

0,8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

If re-treatment with ENBREL is indicated, the above guidance on treatment duration should be followed. The dose should be 0,8 mg/kg (up to a maximum of 50 mg per dose) once weekly.

Method of administration

For subcutaneous injection.

Preparation of ENBREL

ENBREL is intended for use under the guidance and supervision of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in injection technique.

Administration

Administer ENBREL as subcutaneous injections in the thigh, abdomen, or upper arm. Alternate injection sites. New injections should be given at least 3 cm from a previous site. Do NOT inject into areas where the skin is tender, bruised, red, or hard.

4.3 Contraindications

- ENBREL should not be administered to patients with known hypersensitivity to etanercept or to any of the excipients of ENBREL listed in section 6.1.
- ENBREL should not be administered to patients with sepsis or risk of sepsis.
- Treatment with ENBREL should not be initiated in patients with serious active infections, including chronic or localised infections.

4.4 Special warnings and precautions for use

Infections

SERIOUS INFECTIONS INCLUDING SEPSIS AND TUBERCULOSIS (TB) HAVE BEEN REPORTED WITH THE USE OF ENBREL (SEE SECTION 4.8). SOME OF THESE INFECTIONS HAVE BEEN FATAL. THESE INFECTIONS WERE DUE TO BACTERIA, MYCOBACTERIA, FUNGI, VIRUSES, AND PARASITES (INCLUDING PROTOZOA). OPPORTUNISTIC INFECTIONS HAVE ALSO BEEN REPORTED (INCLUDING LISTERIOSIS AND LEGIONELLOSIS). PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH ENBREL SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF ENBREL SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS

INFECTION. CAUTION SHOULD BE EXERCISED WHEN CONSIDERING THE USE OF ENBREL IN PATIENTS WITH A HISTORY OF RECURRING OR CHRONIC INFECTIONS OR WITH UNDERLYING CONDITIONS WHICH MAY PREDISPOSE PATIENTS TO INFECTIONS (SEE SECTIONS 4.3 AND 4.8).

Patients should be evaluated for infections, including active or latent tuberculosis, hepatitis B and C before, during and after treatment with ENBREL (see below). ENBREL treatment should be discontinued if a patient develops life-threatening infection. Caution should be exercised in patients at high risk of developing serious infection, including patients undergoing major surgeries.

Opportunistic infections, including invasive fungal infections, have been reported in patients receiving ENBREL. In some cases, fungal and other opportunistic infections are not recognised, 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, health care providers should consider the patient's risk for relevant opportunistic infections (e.g. exposure to endemic mycoses).

TREATMENT WITH ENBREL SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALISED INFECTIONS. HEALTH CARE PROVIDERS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF ENBREL IN PATIENTS WITH A HISTORY OF RECURRING INFECTIONS OR WITH UNDERLYING CONDITIONS WHICH MAY PREDISPOSE PATIENTS TO INFECTIONS, SUCH AS ADVANCED OR POORLY CONTROLLED DIABETES.

Tuberculosis (TB)

Tuberculosis (including disseminated or extrapulmonary presentation) has been observed in patients receiving TNF-blocking medicines, 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. HEALTH CARE PROVIDERS 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 (HBV) reactivation

REACTIVATION OF HEPATITIS B IN PATIENTS WHO WERE PREVIOUSLY INFECTED WITH THE HEPATITIS B VIRUS (HBV) AND HAD RECEIVED CONCOMITANT ANTI-TNF MEDICINES INCLUDING ENBREL HAS BEEN REPORTED. THE MAJORITY OF THESE REPORTS HAVE OCCURRED IN PATIENTS CONCOMITANTLY RECEIVING OTHER MEDICINES 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 FOR 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.

Concurrent treatment with anakinra

CONCURRENT ADMINISTRATION OF ENBREL AND ANAKINRA HAS BEEN ASSOCIATED WITH AN INCREASED RISK OF SERIOUS INFECTIONS AND NEUTROPENIA. THE COMBINATION HAS NOT DEMONSTRATED INCREASED CLINICAL BENEFIT; SUCH USE IS NOT RECOMMENDED (SEE

SECTION 4.5).

Concurrent treatment with abatacept

IN CLINICAL STUDIES, CONCURRENT ADMINISTRATION OF ABATACEPT AND ENBREL THERAPY RESULTED IN INCREASED INCIDENCES OF SERIOUS ADVERSE EVENTS. THIS COMBINATION HAS NOT DEMONSTRATED INCREASED CLINICAL BENEFIT; SUCH USE IS NOT RECOMMENDED (SEE SECTION 4.5).

Wegener's granulomatosis

IN A PLACEBO-CONTROLLED STUDY OF 180 PATIENTS WITH WEGENER'S GRANULOMATOSIS, THE ADDITION OF ENBREL TO STANDARD TREATMENT (INCLUDING CYCLOPHOSPHAMIDE AND HIGH-DOSE STEROIDS) WAS NO MORE EFFICACIOUS THAN STANDARD TREATMENT ALONE. THE GROUP OF PATIENTS WHO RECEIVED ENBREL EXPERIENCED MORE NON-CUTANEOUS MALIGNANCIES OF VARIOUS TYPES THAN THE PATIENT GROUP RECEIVING STANDARD TREATMENT ALONE. THE USE OF ENBREL FOR TREATMENT OF WEGENER'S GRANULOMATOSIS IS NOT RECOMMENDED.

Alcoholic hepatitis

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

Allergic reactions

Parenteral administration of any biologic medicine should be attended by appropriate precautions in case an allergic or untoward reaction occurs. Allergic reactions associated with ENBREL administration have

been reported. If any serious allergic or anaphylactic reaction occurs, ENBREL therapy should be discontinued immediately and appropriate therapy initiated.

ENBREL 25 mg powder and solvent for solution for injection

The rubber closure of the solvent syringe contains latex (dry natural rubber). Patients or caregivers should contact their health care provider before using ENBREL if the rubber closure of the solvent syringe will be handled by or if ENBREL will be given to someone with a known or possible hypersensitivity (allergy) to latex.

ENBREL 25 mg and 50 mg PS solution for injection in pre-filled syringe or pre-filled pen

The needle cover of the pre-filled syringe and the needle cap of the pre-filled pen contain latex (dry natural rubber). Patients or caregivers should contact their health care provider before using ENBREL PS if the needle cover will be handled by or if ENBREL PS will be given to someone with a known or possible hypersensitivity (allergy) to latex.

Immunosuppression

Anti-TNF therapies including ENBREL may affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses.

Malignancies and lymphoproliferative disorders

Solid and haematopoietic malignancies (excluding skin cancers)

Reports of malignancies affecting various sites have been received in the post-marketing period. In the controlled portions of clinical trials of TNF-antagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period for placebo patients was shorter than for patients receiving TNF-antagonist therapy. Cases of 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 the risk estimation. Post hoc analyses of rheumatoid

arthritis clinical trials with ENBREL have neither confirmed nor excluded an increased risk for malignancies.

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

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

Skin cancers

Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists including ENBREL. Post-marketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with ENBREL. Periodic skin examination is recommended for all patients who are at increased risk for skin cancer.

Combining the results of controlled portions of clinical trials of ENBREL, more cases of NMSC were observed in patients receiving ENBREL compared with control patients, particularly in patients with psoriasis. Periodic skin examination is recommended for all patients who are at increased risk for NMSC.

Haematologic reactions

Cases of pancytopenia and 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.

Auto-antibody formation

Treatment with ENBREL may be associated with the formation of autoimmune antibodies (see section 4.8). The impact of long-term treatment with ENBREL on the development of autoimmune disease is unknown.

Immunogenicity

Antibodies to ENBREL, all non-neutralising, were detected at least once in sera of 16 % of rheumatoid arthritis patients. No apparent correlation of antibody development to clinical response or adverse events was seen. The long-term immunogenicity of ENBREL is unknown.

Vaccinations

Pneumococcal vaccine response information is not available for patients with rheumatoid arthritis. In a double-blind placebo-controlled randomised clinical study in patients with psoriatic arthritis, 184 patients received a multivalent polysaccharide vaccine at week 4. In this study most psoriatic arthritis patients receiving ENBREL were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had two-fold rises in titers compared to patients not receiving ENBREL. The clinical significance of this is unknown. Live vaccines should not be given concurrently with ENBREL. If possible, bring paediatric patients up to date with immunisations according to current local guidelines before beginning ENBREL therapy.

Neurological disorders

Although no clinical trials have been performed evaluating ENBREL therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. There have been reports of 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). ENBREL is not recommended for 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.

Congestive heart failure (Congestive cardiac failure)

There have been post-marketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking ENBREL. There have also been rare (< 0,1 %) reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age (see section 4.8).

Health care providers should use caution when using ENBREL in patients who also have CHF.

Hypoglycaemia in patients treated for diabetes

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

Special populations

Use in elderly patients

The impact of advanced age was studied in the population pharmacokinetic analysis of ENBREL 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.

Greater sensitivity of some older individuals cannot be ruled out.

No specific dose adjustments of ENBREL are recommended based on patient age.

4.5 Interaction with other medicines and other forms of interaction

Concurrent treatment with anakinra

Patients treated with ENBREL and anakinra were observed to have a higher rate of serious infection when compared with patients who were treated with ENBREL alone (historical data). In addition, in a double-blind placebo-controlled trial in patients receiving background methotrexate, patients treated with ENBREL and anakinra were observed to have a higher rate of serious infections and neutropenia than patients treated

with ENBREL alone (see section 4.4.)

Concurrent treatment with abatacept

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

Concurrent treatment with sulfasalazine

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

Non-interactions

Methotrexate has no effect on the pharmacokinetics of ENBREL and may therefore be administered in combination with methotrexate. Interactions between ENBREL and other medicines have not been evaluated in formal studies. No confirmed medicine interactions have been reported with the use of ENBREL.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safe use of ENBREL during pregnancy and lactation has not been established.

Use ENBREL during pregnancy only if clearly needed.

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

Breastfeeding

The safe use of ENBREL during lactation has not been established. In lactating rats following subcutaneous administration, ENBREL was excreted in the milk and detected in the serum of pups. Limited information from the published literature indicates ENBREL has been detected at low levels in human milk. ENBREL could be considered for use during breastfeeding if clearly needed, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

While systemic exposure in a breastfed infant is expected to be low because ENBREL is largely degraded in the gastrointestinal 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 ENBREL could be considered 16 weeks after stopping breastfeeding (or at an earlier timepoint if the infant etanercept serum levels are undetectable).

Fertility

No fertility or long-term perinatal/ postnatal studies are available.

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

Summary of the safety profile

Adult patients

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

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

Tabulated summary of adverse reactions

The following list of adverse reactions is based on experience from clinical trials in adults. Within the system organ 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	**Frequency**	**Adverse reaction**
Infections and infestations	Very common	Infection (including upper respiratory tract infections, bronchitis, cystitis, skin infections)
	Uncommon	Serious infections (including pneumonia, cellulitis, bacterial arthritis, sepsis and parasitic infection)
	Rare	Tuberculosis, opportunistic infection (including invasive fungal, bacterial, atypical mycobacterial, viral

		infections, and *Legionella*) (see section 4.4)
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	Uncommon	Non-melanoma skin cancers (see section 4.4)
	Rare	Malignant melanoma (see section 4.4)
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia, anaemia, leukopenia, neutropenia
	Rare	Pancytopenia (see section 4.4)
Immune system disorders	Common	Allergic reactions (see *Skin and subcutaneous tissue disorders*, below), auto-antibody formation
	Uncommon	Vasculitis (including ANCA positive vasculitis)
	Rare	Serious allergic/ anaphylactic reactions (including angioedema, bronchospasm), sarcoidosis
Nervous system disorders	Rare	CNS demyelinating events, including multiple sclerosis and localised demyelinating conditions such as optic neuritis and transverse myelitis (see section 4.4), seizure
Eye disorders	Uncommon	Uveitis, scleritis
Cardiac disorders	Uncommon	Worsening of congestive cardiac failure

	Rare	New onset congestive cardiac failure
Respiratory, thoracic and mediastinal disorders	Rare	Interstitial lung disease (including pulmonary fibrosis and pneumonitis)
Hepato-biliary disorders	Uncommon	Elevated liver enzymes
	Rare	Autoimmune hepatitis
Skin and subcutaneous tissue disorders	Common	Pruritus, rash
	Uncommon	Angioedema, psoriasis (new onset or exacerbation including all sub-types), urticaria
	Rare	Cutaneous vasculitis (including hypersensitivity vasculitis
Musculoskeletal, and connective tissue disorders	Rare	Lupus-like syndrome
General disorders and administration site conditions	Very common	Injection site reactions (including bleeding, bruising, erythema, itching, pain and swelling)
	Common	Pyrexia

Post-marketing side effects

System organ class	**Side effect**
Infections and infestations	Hepatitis B reactivation, *Listeria*

Neoplasms benign, malignant and unspecified (including cysts and polyps)	Lymphoma, leukaemia, Merkel cell carcinoma (see section 4.4)
Blood and lymphatic system disorders	Aplastic anaemia (see section 4.4), histiocytosis haematophagic (macrophage activation syndrome)
Nervous system disorders	Headache, peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy and multifocal motor neuropathy (see section 4.4),
Gastrointestinal disorders	Inflammatory bowel disease
Skin and subcutaneous tissue disorders	Psoriasiform rash, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Subacute cutaneous lupus erythematosus, cutaneous lupus erythematosus

*Spontaneous report*s

Malignancies affecting various sites.

Description of selected adverse reactions

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.

Injection site bleeding and bruising have also been observed in conjunction with ENBREL therapy.

In controlled trials in patients with plaque psoriasis, 14 % of patients treated with ENBREL developed injection site reactions during the first three months of treatment.

Infections

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

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

Data from a clinical trial in patients with established sepsis suggest that ENBREL treatment may increase mortality in these patients.

In placebo-controlled psoriatic arthritis and plaque psoriasis trials, there were no differences in rates of infection among patients treated with ENBREL and those treated with placebo. In 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.

Malignancies and lymphoproliferative disorders

Reports of malignancies affecting various sites have been received in the post-marketing period.

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.

There have been reports of malignancies in a clinical trial of patients being treated for Wegener's granulomatosis (see section 4.4).

Interstitial lung disease

In controlled clinical trials of ENBREL across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving ENBREL without concomitant methotrexate was 0,06 % (frequency rare). In the controlled clinical trials that allowed concomitant treatment with ENBREL 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 ENBREL across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving ENBREL without concomitant methotrexate was 0,54 % (frequency uncommon). In the double-blind periods of controlled

clinical trials that allowed concomitant treatment with ENBREL 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 ENBREL across all indications, the frequency (incidence proportion) of autoimmune hepatitis in patients receiving ENBREL without concomitant methotrexate was 0,02 % (frequency rare). In the controlled clinical trials that allowed concomitant treatment with ENBREL and methotrexate, the frequency (incidence proportion) of autoimmune hepatitis was 0,24 % (frequency uncommon).

Auto-antibodies

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.

Reports have described patients, including those with rheumatoid factor positive RA, who have developed additional auto-antibodies in conjunction with a lupus-like syndrome or rashes compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy (see Tabulated summary of adverse reactions above).

Paediatric population

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

Side effects in paediatric patients with juvenile idiopathic arthritis

Infection was the most common adverse event reported in paediatric patients taking ENBREL and occurred at an incidence similar to placebo. The types of infection reported in juvenile idiopathic arthritis patients were

generally mild and consistent with those commonly seen in outpatient paediatric populations.

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

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

Side effects in paediatric patients with plaque psoriasis

In a 48-week study of 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

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 endotoxaemia 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 2 000 mg/kg or a single intravenous dose of 1 000 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 area under the curve (AUC) based serum medicine 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.

In the case of accidental overdosage, treatment should be supportive and symptomatic.

There is no known antidote to ENBREL.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 3.1 Anti-rheumatics (anti-inflammatory agents)

Mechanism of action

Etanercept is a dimeric soluble form of the p75 TNF (tumour 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 (RA) patients.

The efficacy of etanercept was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active RA who had failed therapy with at least one, but no more than four, disease-modifying anti-rheumatic drugs (DMARDs). 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 magnitude 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.

TNF and LT_{α} are expressed in patients with juvenile idiopathic 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.

Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75) exist naturally as monomeric molecules on cell surfaces and in soluble forms. The biological activity of TNF is dependent upon binding to either cell surface receptor.

Etanercept may also modulate biologic responses controlled by additional molecules (e.g. cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

Etanercept inhibits the activity of TNF *in vitro* and has been shown to affect several animal models of inflammation, including collagen-induced arthritis in mice.

5.2 Pharmacokinetic properties

Absorption

Etanercept is slowly absorbed from the site of SC injection, reaching maximum concentration approximately 48 hours after a single dose. The absolute bioavailability is 76 %. With twice weekly doses, it is anticipated that steady-state concentrations are approximately twice as high as those observed after single doses.

Distribution

After a single SC dose of 25 mg etanercept, the average maximum serum concentration observed in healthy volunteers was 1,65 ± 0,66 μg/mL, and area under the curve results were 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 volume of distribution at steady-state after subcutaneous administration is 13,9 ± 9,4 L.

After continued dosing of RA patients (n = 25) with etanercept for 6 months with 25 mg twice weekly, the median observed level was 3,0 μg/mL (range 1,7 to 5,6 μg/mL). Based on the available data, individual patients may undergo a two- to five-fold increase in serum levels with repeated dosing.

Elimination

Etanercept is cleared slowly from the body. The half-life is approximately 80 hours. Clearance is approximately 175 ± 116 mL/hr in patients with rheumatoid arthritis and 131 ± 81 mL/hr in healthy volunteers.

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

Concentration-effect relationship

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

Special populations

Renal impairment or hepatic impairment

Although there is elimination of radioactivity in urine after administration of radiolabelled etanercept to

patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal or hepatic failure. The presence of renal and hepatic impairment should not require a change in dosage.

Gender

There is no apparent pharmacokinetic difference between men and women.

Use in elderly patients

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ENBREL 25 mg powder and solvent for solution for injection

Mannitol

Sucrose

Trometamol

Pre-filled solvent syringe

Water for injection

ENBREL 25 mg PS solution for injection in pre-filled syringe and ENBREL 50 mg PS solution for injection in pre-filled syringe or pre-filled pen

Sucrose

Sodium chloride

L-arginine hydrochloride

6.2 Incompatibilities

In the absence of compatibility studies, ENBREL must not be mixed with other medicines.

6.3 Shelf life

ENBREL 25 mg powder and solvent for solution for injection

36 months

Reconstituted solution

Reconstituted solutions of ENBREL should be administered as soon as possible after reconstitution. If not administered immediately after reconstitution, ENBREL may be stored in the vial at 2 – 8 °C for up to 6 hours.

ENBREL 25 mg PS solution for injection in pre-filled syringe

36 months

ENBREL 50 mg PS solution for injection in pre-filled syringe

36 months

ENBREL 50 mg PS solution for injection in pre-filled MYCLIC pen

36 months

6.4 Special precautions for storage

ENBREL 25 mg powder and solvent for solution for injection

The dose tray containing ENBREL (sterile powder) must be stored in a refrigerator.

DO NOT FREEZE.

ENBREL 25 mg and 50 mg PS solution for injection in pre-filled syringe or pre-filled pen

Store in a refrigerator at 2 – 8 °C. DO NOT FREEZE.

Before injection, ENBREL PS single pre-filled syringe or pre-filled pen should be allowed to reach room

temperature (approximately 15 to 30 minutes). The needle cover or cap should not be removed while allowing the pre-filled syringe or pre-filled pen to reach room temperature.

6.5 Nature and contents of container

ENBREL 25 mg powder and solvent for solution for injection

ENBREL is supplied in a carton containing two dose trays, each with two divisions. Each division contains one 25 mg single-use vial of ENBREL, a pre-filled clear glass syringe, with a tamper evident seal, a needle-free transfer device (vial adapter) and two alcohol swabs.

ENBREL 25 mg and 50 mg PS solution for injection in pre-filled syringe

ENBREL 25 mg PS pre-filled syringe is supplied in a carton containing four clear glass pre-filled syringes with alcohol swabs.

ENBREL 50 mg PS pre-filled syringe is supplied in a carton containing two clear glass pre-filled syringes with alcohol swabs.

The stainless steel needle is supplied with a rubber needle cover (latex) and plastic cover.

ENBREL 50 mg PS solution for injection in pre-filled pen (MYCLIC)

ENBREL 50 mg PS pre-filled pen is supplied in a carton containing four pre-filled pens with alcohol swabs. The pre-filled pen contains the pre-filled syringe. The stainless steel needle is supplied with a rubber needle cap (latex) and plastic cover.

6.6 Special precautions for disposal and other handling

ENBREL 25 mg powder and solvent for solution for injection

ENBREL should be reconstituted aseptically with 1 mL of the supplied water for injection. During reconstitution of ENBREL, the diluent should be slowly injected into the vial. Some foaming will occur. To avoid excessive foaming, do not shake or vigorously agitate. The contents should be swirled gently during

dissolution. Generally, dissolution of ENBREL takes less than 10 minutes. The reconstituted solution should be clear and colourless.

Visually inspect the solution for particulate matter and discolouration prior to administration. The solution should not be used if discoloured or cloudy, or if particulate matter remains. Withdraw the solution into the syringe, removing as much liquid as possible from the vial. Some foam or bubbles may remain in the vial. The final volume in the syringe will be approximately 1 mL.

No other medicines should be added to solutions containing ENBREL, and ENBREL should not be reconstituted with other diluents. Do not filter reconstituted solution during preparation or administration.

The rubber closure of the solvent syringe contains latex (dry natural rubber). Patients or caregivers should contact the health care provider before using ENBREL if the rubber closure of the solvent syringe will be handled by or if ENBREL will be given to someone with a known or possible hypersensitivity (allergy) to latex.

ENBREL 25 mg and 50 mg PS solution for injection in pre-filled syringe or pre-filled pen

Before injection, ENBREL PS single use pre-filled syringes or pre-filled pen should be allowed to reach room temperature (approximately 15 – 30 minutes). The needle cover should not be removed while allowing the pre-filled syringe or pre-filled pen to reach room temperature. The needle cover of the pre-filled syringe and the needle cap of the pre-filled pen contain latex (dry natural rubber). Patients or caregivers should contact their health care provider before using ENBREL PS if the needle cover will be handled by or if ENBREL PS will be given to someone with a known or possible hypersensitivity (allergy) to latex.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

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South Africa

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8. REGISTRATION NUMBERS

ENBREL 25 mg: 34/3.1/0330

Solvent for ENBREL 25 mg: 34/34/0331

ENBREL 25 mg PS: 41/3.1/0762

ENBREL 50 mg PS: 41/3.1/0763

9. DATE OF FIRST AUTHORISATION

ENBREL 25 mg: 17/05/2002

Solvent for ENBREL 25 mg: 06/02/2004

ENBREL 25 mg PS: 04/03/2011

ENBREL 50 mg PS: 04/03/2011

10. DATE OF REVISION OF THE TEXT

26 May 2025

NAMIBIA: NS2

ENBREL 25 mg Powder and Solvent: 04/3.1/1704

ENBREL 25 mg PS: 16/3.1/0203

ENBREL 50 mg PS: 16/3.1/0204

ENBREL 50 mg PFP: 16/3.1/0205