PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

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

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

ETERAPEXT 50 mg Prefill Pen solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ETERAPEXT 25 mg PS:

Each pre-filled syringe contains 25 mg of etanercept.

ETERAPEXT 50 mg PS:

Each pre-filled syringe contains 50 mg of etanercept.

ETERAPEXT 50 mg Prefill Pen:

Each pre-filled pen contains 50 mg of etanercept.

Contains sugar: sucrose 10,0 mg per ml.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian 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, CH_2 and CH_3 regions, but not the CH_1 region of IgG1. Etanercept contains 934 amino acids and has an apparent

molecular weight of approximately 150 kilodaltons.

The specific activity of etanercept is $1,7 \times 10^6$ units/mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

The solution is clear to opalescent, colourless to yellow and is formulated at pH 6,3 ± 0,2. The osmolality of the solution is 310 ± 30 mOsm/kg.

The solution is free of visible particulate matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis:

ETERAPEXT 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. ETERAPEXT 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 ETERAPEXT 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:

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

Axial spondylarthritis:

Ankylosing spondylitis (AS):

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

Non-radiographic axial spondyloarthritis:

ETERAPEXT 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:

ETERAPEXT 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:

ETERAPEXT 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 ETERAPEXT for adult patients 18 years and older with rheumatoid arthritis is 25 mg administered twice weekly (72 to 96 hours apart) as a subcutaneous injection. 50 mg per week provides the optimal therapeutic response in rheumatoid arthritis. ETERAPEXT can be administered as follows:

a) Two ETERAPEXT 25 mg PS Pre-filled Syringes) administered subcutaneously at approximately the same time or

b) One ETERAPEXT 25 mg PS Pre-filled Syringe administered subcutaneously 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

c) ETERAPEXT 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, one ETERAPEXT 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 (NSAID's), or analgesics may be continued during treatment with ETERAPEXT in adults.

Plague psoriasis:

In plaque psoriasis, the dose of ETERAPEXT is 50 mg per week, as one ETERAPEXT 25 mg PS Pre-filled Syringe administered twice weekly, 3 – 4 days apart or ETERAPEXT 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 doctor's 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.

Use in children:

The dosage of ETERAPEXT is based on body weight for paediatric patients.

ETERAPEXT is available as 25 mg pre-filled syringe, 50 mg prefilled syringe and 50 mg pre-filled pen. Thus, it is only suitable to administer ETERAPEXT to paediatric patients that require a full 25 mg or 50 mg dose.

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) of ETERAPEXT 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 ETERAPEXT in children. ETERAPEXT 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 ETERAPEXT 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.

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.

Method of administration

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

ETERAPEXT 25 mg & 50 mg PS Solution for Injection in Pre-filled Syringe or Pre-filled Pen:

Before injection, ETERAPEXT 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 doctor before using ETERAPEXT PS if the needle cover will be handled by or if ETERAPEXT PS will be given to someone with a known or possible hypersensitivity (allergy) to latex.

Administration:

Administer ETERAPEXT 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

- Hypersensitivity to etanercept or to any of the excipients (see section 6.1).
- Sepsis or risk of sepsis.
- Treatment with ETERAPEXT should not be initiated in patients with active infections, including chronic or localised infections.

4.4 Special warnings and precautions for use

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

A diagnosis of any form of active tuberculosis should be explicitly excluded in patients considered for treatment with ETERAPEXT. Furthermore, a history of previous tuberculosis, HIV-infection, or a diagnosis of latent tuberculosis infection pose a risk for reactivation of tuberculosis disease and appropriate preventative therapy is indicated, regardless of HIV-status. Diagnosis and treatment of latent infection, following national guidelines, should be initiated prior to use of ETERAPEXT.

People initiating ETERAPEXT treatment, who initially tested negative for active or latent tuberculosis, should be systematically tested for latent TB infection during treatment with ETERAPEXT, and preventative treatment instituted if indicated.

Infections

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

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

Patients who develop a new infection while undergoing treatment with

ETERAPEXT should be monitored closely. Administration of ETERAPEXT should be discontinued if a patient develops a serious infection. The safety and efficacy of etanercept in patients with chronic infections have not been evaluated. Clinical practitioners should exercise caution when considering the use of ETERAPEXT in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections, such as advanced or poorly controlled diabetes.

Tuberculosis

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

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

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

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

Hepatitis B reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-antagonists, including etanercept, has been reported. This includes reports of reactivation of hepatitis B in patients who were anti-HBc positive but HBsAg negative.

Patients should be tested for HBV infection before initiating treatment with ETERAPEXT. For patients who test positive for HBV infection, consultation with a clinical medical practitioner with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when administering ETERAPEXT in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy. Adequate data from treating patients infected with HBV with anti-viral therapy in conjunction with TNF-antagonist therapy are not available. In patients who develop HBV infection, ETERAPEXT should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Worsening of hepatitis C

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

Concurrent treatment with anakinra

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

Concurrent treatment with abatacept

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

Allergic reactions

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

Immunosuppression

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

Two juvenile idiopathic arthritis patients developed varicella infection and signs

and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue ETERAPEXT therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin. The safety and efficacy of ETERAPEXT in patients with immunosuppression have not been evaluated.

Malignancies and lymphoproliferative disorders

Solid and haematopoietic malignancies (excluding skin cancers)

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the 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 less frequent, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. In the post-marketing setting, cases of leukaemia have been reported in patients treated with TNF-antagonists. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.

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

Malignancies, some fatal, have been reported among children, adolescents and

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

Skin cancers

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

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

Vaccinations

Live vaccines should not be given concurrently with ETERAPEXT. No data are available on the secondary transmission of infection by live vaccines in patients receiving etanercept. In a double-blind, placebocontrolled, randomised clinical study in adult patients with psoriatic arthritis, 184 patients also received a multivalent pneumococcal polysaccharide vaccine at week 4. In this study, most psoriatic arthritis patients receiving etanercept were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titres in

aggregate were moderately lower, and few patients had two-fold rises in titres compared to patients not receiving etanercept. The clinical significance of this is unknown.

Autoantibody formation

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

Haematologic reactions

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

Neurological disorders

There have been rare reports of CNS demyelinating disorders in patients treated with etanercept (see section 4.8). Additionally, there have been less frequent reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating etanercept therapy in patients with multiple sclerosis, clinical trials of other TNF-antagonists in patients with multiple sclerosis have

shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing ETERAPEXT to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

Combination therapy

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

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

Renal and hepatic impairment

Based on pharmacokinetic data (see section 5.2), no dose adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited.

Congestive heart failure

Clinical medical practitioners should use caution when using ETERAPEXT in patients who have congestive heart failure (CHF). There have been post-marketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking etanercept. There have also been rare (< 0,1 %) reports of new onset CHF, including CHF in patients without known pre-existing

cardiovascular disease. Some of these patients have been under 50 years of age. Two large clinical trials evaluating the use of etanercept in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data from one of these trials suggest a possible tendency toward worsening CHF in those patients assigned to etanercept treatment.

Alcoholic hepatitis

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

Wegener's granulomatosis

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

Hypoglycaemia in patients treated for diabetes

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

Special populations

Elderly

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

Paediatric population

Vaccinations

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

Inflammatory bowel disease (IBD) and uveitis in patients with juvenile idiopathic arthritis (JIA)

There have been reports of IBD and uveitis in JIA patients being treated with etanercept (see section 4.8).

ETERAPEXT contains sucrose

ETERAPEXT contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as

fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not use ETERAPEXT.

4.5 Interaction with other medicines and other forms of interaction

Concurrent treatment with anakinra

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

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

Concurrent treatment with abatacept

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

Concurrent treatment with sulfasalazine

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

significance of this interaction is unknown. Clinical practitioners should use caution when considering combination therapy with sulfasalazine.

Non-interactions

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

The safe use of ETERAPEXT during pregnancy and lactation has not been established. No fertility or long-term perinatal/ postnatal studies are available. Use ETERAPEXT during pregnancy only if clearly needed.

Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with etanercept during pregnancy. The clinical impact of this is unknown, however, infants may be at increased risk of infection.

Administration of live vaccines to infants for 16 weeks after the mother's last dose of ETERAPEXT is generally not recommended.

Breast-feeding

Etanercept has been reported to be excreted in human milk following subcutaneous administration. In lactating rats following subcutaneous administration, etanercept was excreted in the milk and detected in the serum of pups. Because immunoglobulins, in common with many medicines, can be excreted in human milk, a decision must be made whether to discontinue breast-feeding or to discontinue ETERAPEXT therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

a. Summary of the safety profile

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

Serious adverse reactions have also been reported for etanercept. TNF-antagonists, such as etanercept, affect the immune system and their use may affect the body's defenses against infection and cancer.

Serious infections affect fewer than 1 in 100 patients treated with etanercept. Reports have included fatal and life-threatening infections and sepsis. Various malignancies have also been reported with use of etanercept, including cancers of the breast, lung, skin and lymph glands (lymphoma).

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

b. Tabulated summary of adverse reactions

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

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Infection (including upper respiratory tract infection, bronchitis, cystitis, skin infection)*
	Less frequent	Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis and parasitic

MedDRA system organ class	**Frequency**	**Adverse reactions**
		infection)*, tuberculosis, opportunistic infection (including invasive fungal, protozoal, bacterial, atypical mycobacterial, viral infections, and Legionella)*
	Frequency unknown	Hepatitis B reactivation, listeria
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Less frequent	Non-melanoma skin cancers*, malignant melanoma (see section 4.4), lymphoma, leukaemia
	Frequency unknown	Merkel cell carcinoma (see section 4.4), Kaposi's sarcoma
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia, anaemia, leukopenia, neutropenia, pancytopenia*, aplastic anaemia*
	Frequency unknown	Histiocytosis haematophagic (macrophage activation syndrome)*
Immune system disorders	Frequent	Allergic reactions (see Skin and subcutaneous tissue disorders), autoantibody formation*
	Less frequent	Vasculitis (including antineutrophilic cytoplasmic antibody positive

MedDRA system organ class	**Frequency**	**Adverse reactions**
		vasculitis), serious allergic/anaphylactic reactions (including angioedema, bronchospasm), sarcoidosis
	Frequency unknown	Worsening of symptoms of dermatomyositis
Metabolism and nutrition disorders	Frequent	Hyperglycaemia, hypoglycaemia
	Less frequent	Metabolic acidosis, hypoalbuminaemia
Nervous system disorders	Frequent	Headache
	Less frequent	CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis (see section 4.4), peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy (see section 4.4), seizure

MedDRA system organ class	**Frequency**	**Adverse reactions**
Eye disorders	Less frequent	Uveitis, scleritis
Cardiac disorders	Less frequent	Worsening of cardiac failure congestive, new onset cardiac failure congestive (see section 4.4)
Respiratory, thoracic and mediastinal disorders	Less frequent	Interstitial lung disease (including pneumonitis and pulmonary fibrosis)*
Gastrointestinal disorders	Less frequent	Inflammatory bowel disease
Hepatobiliary disorders		Elevated liver enzymes*, autoimmune hepatitis*
Skin and subcutaneous tissue disorders	Frequent	Pruritus, rash
	Less frequent	Angioedema, psoriasis (including new onset or worsening and pustular, primarily palms and soles), urticaria, psoriasiform rash, Stevens-Johnson syndrome, cutaneous vasculitis (including hypersensitivity vasculitis), erythema multiforme, lichenoid reactions, toxic epidermal necrolysis

MedDRA system organ class	Frequency	Adverse reactions
Musculoskeletal and connective tissue disorders	Less frequent	Cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus, lupus-like syndrome
General disorders and Administrative site conditions	Frequent	Injection site reactions (including bleeding, bruising, erythema, itching, pain, swelling)*, pyrexia

***** see Description of selected adverse reactions, below.

c. Description of selected adverse reaction

Malignancies and lymphoproliferative disorders

One hundred and twenty-nine (129) new malignancies of various types were observed in 4 114 rheumatoid arthritis patients treated in clinical trials with etanercept for up to approximately 6 years, including 231 patients treated with etanercept in combination with methotrexate in the 2-year active controlled study. The observed rates and incidences in these clinical trials were similar to those expected for the population studied. A total of 2 malignancies were reported in clinical studies of approximately 2 years duration involving 240 etanercept-treated psoriatic arthritis patients. In clinical studies conducted for more than 2 years with 351 ankylosing spondylitis patients, 6 malignancies were reported in etanercept-treated patients. In a group of 2 711 plaque psoriasis patients treated with etanercept in double-blind and open-label studies of up to 2,5 years, 30 malignancies and 43 nonmelanoma skin cancers were reported.

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

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

Injection site reactions

Compared to placebo, patients with rheumatic diseases treated with etanercept had a significantly higher incidence of injection site reactions (36 % vs. 9 %). Injection site reactions usually occurred in the first month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the etanercept treatment groups, and the majority of patients who were given treatment received topical preparations, such as corticosteroids, or oral antihistamines.

Additionally, some patients developed recall injection site reactions characterised by a skin reaction at the most recent site of injection, along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment.

In controlled trials in patients with plaque psoriasis, approximately 13,6 % of patients treated with etanercept developed injection site reactions compared with 3,4 % of placebo-treated patients during the first 12 weeks of treatment.

Serious infections

In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life-threatening, or requiring hospitalisation or intravenous antibiotics) was

observed. Serious infections occurred in 6,3 % of rheumatoid arthritis patients treated with etanercept for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active controlled study where patients were treated with either etanercept alone, methotrexate alone or etanercept in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of etanercept with methotrexate could be associated with an increase in the rate of infections.

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

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

arthritis (see section 4.4). ETERAPEXT treatment may increase mortality in patients with established sepsis.

Opportunistic infections have been reported in association with etanercept, including invasive fungal, parasitic (including protozoal), viral (including herpes zoster), bacterial (including *Listeria* and *Legionella*), and atypical mycobacterial infections. In a pooled data set of clinical trials, the overall incidence of opportunistic infections was 0,09 % for the 15 402 subjects who received etanercept. The exposure-adjusted rate was 0,06 events per 100 patient-years. In post-marketing experience, approximately half of all of the case reports of opportunistic infections worldwide were invasive fungal infections. The most commonly reported invasive fungal infections included Candida, Pneumocystis, Aspergillus, and Histoplasma. Invasive fungal infections accounted for more than half of the fatalities amongst patients who developed opportunistic infections. The majority of the reports with a fatal outcome were in patients with Pneumocystis pneumonia, unspecified systemic fungal infections, and aspergillosis (see section 4.4).

Auto-antibodies

Adult patients had serum samples tested for autoantibodies at multiple timepoints. Of the rheumatoid arthritis patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥ 1:40) was higher in patients treated with etanercept (11 %) than in placebo-treated patients (5 %). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15 % of patients treated with etanercept compared to 4 % of placebo-treated patients) and by Crithidia luciliae

assay (3 % of patients treated with etanercept compared to none of placebo-treated patients). The proportion of patients treated with etanercept who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. The impact of long-term treatment with etanercept on the development of autoimmune diseases are unknown.

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

Pancytopenia and aplastic anaemia

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

Interstitial lung disease

In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without concomitant methotrexate was 0,06 % (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of interstitial lung disease was 0,47 % (frequency uncommon). There have been post-marketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Concurrent treatment with anakinra

In studies when adult patients received concurrent treatment with etanercept plus anakinra, a higher rate of serious infections compared to etanercept alone was

observed and 2 % of patients (3/139) developed neutropenia (absolute neutrophil count <1 000/mm^3). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see sections 4.4 and 4.5).

Elevated liver enzymes

In the double-blind periods of controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving etanercept without concomitant methotrexate was 0,54 % (less frequent). 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 % (less frequent).

Auto-immune 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 % (less frequent). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of autoimmune hepatitis was 0,24 % (less frequent).

d. Paediatric population

Undesirable effects in paediatric patients with juvenile idiopathic arthritis

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

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

In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62 %) children experienced an infection while receiving etanercept during 3 months of the study (part 1, open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types and proportion of adverse events in juvenile idiopathic arthritis patients were similar to those seen in trials of etanercept in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 69 juvenile idiopathic arthritis patients receiving 3 months of etanercept compared to the 349 adult rheumatoid arthritis patients. These included headache (19 % of patients, 1,7 events per patient year), nausea (9 %, 1,0 event per patient year), abdominal pain (19 %, 0,74 events per patient year), and vomiting (13 %, 0,74 events per patient year).

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

There have been reports of inflammatory bowel disease and uveitis in JIA patients being treated with etanercept from post-marketing sources, including a very small number of cases indicating a positive rechallenge (see section 4.4).

Undesirable effects in paediatric patients with plaque psoriasis

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the 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 & Quality Problem Reporting Form**", found online under SAHPRA's publications:

https://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, tumour necrosis factor alpha (TNF-α) inhibitors, ATC code: L04AB01

Pharmacological classification: A 3.1 Anti-rheumatics (anti-inflammatory agents).

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 patients. The efficacy of etanercept was assessed in a randomized, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid arthritis (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 LTα 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 radiolabeled etanercept to patients and volunteers.

Pharmacokinetics in 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

Sodium citrate

Sodium dihydrogen phosphate dihydrate

Glycine

Sucrose

Sodium chloride

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

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

ETERAPEXT may be stored at temperatures up to a maximum of 25 °C for a single period of up to four weeks; after which, it should not be refrigerated again. ETERAPEXT should be discarded if not used within four weeks of removal from refrigeration.

6.5 Nature and contents of container

ETERAPEXT 25 mg PS

The syringe is made from a USP Type 1 clear glass Borosilicate-Barrel with a 27 ½ inch G fixed injection needle and a rigid needle shield and stopper made by grey colour butyl rubber.

ETERAPEXT is available in the outer cardboard carton packs containing 4 pre-filled syringes + 4 alcohol swabs, packs containing 12 pre-filled syringes + 12 alcohol swabs and multipack containing 24 pre-filled syringes and 24 swabs (2 packs of 12 pre-filled syringes + 12 alcohol swabs).

Not all pack sizes may be marketed.

ETERAPEXT 50 mg PS

The syringe is made from a USP Type 1 clear glass Borosilicate Barrel with a 27 ½ inch G fixed injection needle and a rigid needle shield and stopper made by grey colour butyl rubber.

ETERAPEXT is available in the outer cardboard carton packs containing 4 pre-filled syringes + 4 alcohol swabs and packs containing 12 pre-filled syringes + 12 alcohol swabs.

Not all pack sizes may be marketed.

ETERAPEXT 50 mg Prefill Pen

Pre-filled pen containing a pre-filled syringe of ETERAPEXT. The syringe is made from a USP Type 1 clear glass Borosilicate Barrel with a 27 ½ inch G fixed injection needle and a rigid needle shield and stopper made by grey colour butyl rubber.

ETERAPEXT is available in the outer cardboard carton packs containing 4 pre-filled pens + 4 alcohol swabs and packs containing 12 pre-filled pens + 12 alcohol swabs.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Before injection, ETERAPEXT single-use pre-filled syringe should be allowed to reach room temperature (approximately 30 minutes). The solution should not be warmed in any other way. Immediate use is then recommended. The needle cover should not be removed while allowing the pre-filled syringe to reach room temperature. The solution should be clear to opalescent, colourless to yellow and may contain small translucent or white particles of protein.

Comprehensive instructions for administration are given in the patient information leaflet.

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

50 mg solution for injection in pre-filled pen:

Before injection, ETERAPEXT single-use pre-filled pens should be allowed to reach room temperature (approximately 30 minutes). The needle cover should not be removed while allowing the pre-filled pen to reach room temperature. By looking though, the inspection window, the solution should be clear to opalescent, colourless to yellow and may contain small translucent or white particles of protein. Comprehensive instructions for administration are given in the patient information leaflet.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

VIATRIS HEALTHCARE (PTY) LTD

4 Brewery street

Isando

Gauteng

Republic of South Africa

8 REGISTRATION NUMBERS

ETERAPEXT 25 PS: 55/3.1/0527.521

ETERAPEXT 50 PS: 55/3.1/0528.522

ETERAPEXT 50 Prefilled Pen: 55/3.1/0529.523

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 August 2023

10 DATE OF REVISION OF THE TEXT