PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

Erelzi® 25 mg (solution for injection)

Erelzi® 50 mg (solution for injection)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ERELZI 25 mg: Each pre-filled syringe contains 25 mg etanercept.

ERELZI 50 mg: Each pre-filled syringe/pen contains 50 mg etanercept.

ERELZI 25 mg contains sugar (5,00 mg sucrose per 0,5 ml pre-filled syringe).

ERELZI 50 mg contains sugar (10,00 mg sucrose per 1,0 ml pre-filled syringe/pen).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

The solution is a colourless to slightly yellowish solution, practically free from extraneous particles.

4 CLINICAL PARTICULARS

4.1. Therapeutic indications

Rheumatoid arthritis:

ERELZI 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.

ERELZI 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.

ERELZI 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:

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

Axial spondyloarthritis:

Ankylosing spondylitis (AS):

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

Non-radiographic axial spondyloarthritis:

ERELZI 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:

ERELZI 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:

ERELZI 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 spondyloarthritis:

The recommended dose of ERELZI 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.

ERELZI can be administered as follows:

a) two ERELZI 25 pre-filled syringes administered subcutaneously at approximately the same time once weekly or
b) one single ERELZI 25 pre-filled syringe administered twice weekly, 3 to 4 days apart (i.e. two ERELZI 25 pre-filled syringes per week) or
c) ERELZI 50 pre-filled syringe or pre-filled pen administered once weekly as a subcutaneous injection.

In psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis, the recommended dose is 50 mg per week (given as one ERELZI 25 pre-filled syringe given twice weekly, 3 to 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 ERELZI in adults.

Plaque psoriasis:

In plaque psoriasis, the dose of ERELZI is 50 mg per week (given as one ERELZI 25 pre-filled syringe administered twice weekly, 3 to 4 days apart or ERELZI 50 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 medical practitioner 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 ERELZI is based on body weight for paediatric patients.

As ERELZI is only available as 25 mg pre-filled syringe and 50 mg pre-filled syringe and pre-filled pen, paediatric patients weighing less than 62,5 kg and that require less than a full 25 mg or 50 mg dose, should not receive ERELZI.

Patients weighing 62,5 kg or more may be dosed using a fixed-dose pre-filled syringe or pre-filled pen.

The safety and efficacy of ERELZI in children aged less than 2 years has not been established.

No data are available.

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 ERELZI 25 pre-filled syringe, given twice weekly as a subcutaneous injection with an interval of 3 to 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 ERELZI in children. ERELZI 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 ERELZI 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.

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.

Method of administration:

Preparation of ERELZI:

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

Before injection, ERELZI single use pre-filled syringes or pre-filled pen should be allowed to reach room temperature (approximately 15 to 30 minutes). The needle cover should not be removed while allowing the pre-filled syringe 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 ERELZI if the needle cover will be handled by or if ERELZI will be given to someone with a known or possible hypersensitivity (allergy) to latex.

Administration:

Administer ERELZI 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 listed in section 6.1.
- Sepsis or risk of sepsis.
- Treatment with ERELZI 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.

Infections:

SERIOUS INFECTIONS INCLUDING SEPSIS AND TUBERCULOSIS (TB) HAVE BEEN REPORTED WITH THE USE OF ETANERCEPT (SEE SECTION 4.8). SOME OF THESE INFECTIONS HAVE BEEN FATAL. THESE INFECTIONS WERE DUE TO BACTERIA, MYCOBACTERIA, FUNGI, VIRUSES, AND PARASITES (INCLUDING PROTOZOA). OPPORTUNISTIC INFECTIONS HAVE ALSO BEEN REPORTED (INCLUDING LISTERIOSIS AND LEGIONELLOSIS). PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH ERELZI SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF ERELZI SHOULD BE DISCOUNTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION. CAUTION SHOULD BE EXERCISED WHEN CONSIDERING THE USE OF ERELZI 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 ERELZI taking into consideration that the mean elimination half-life of etanercept is approximately 70 hours (range 7 to 300 hours) (see below). ERELZI 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 ERELZI. 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 ERELZI SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALISED INFECTIONS. MEDICAL PRACTITIONERS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF ERELZI 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 agents, such as etanercept. Tuberculosis may be due to reactivation of latent TB infection or to new infection.

BEFORE INITIATION OF THERAPY WITH ERELZI, ALL PATIENTSSHOULD BE EVALUATED FOR ACTIVE OR LATENT INFECTION. 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 (APPLICABLE LOCAL GUIDELINES SHOULD BE CONSULTED). IT IS RECOMMENDED THAT THE CONDUCT OF THESE TESTS SHOULD BE RECORDED IN THE PATIENT CARD. PRESCRIBERS ARE REMINDED OF THE RISK OF FALSE NEGATIVE TUBERCULIN SKIN TEST RESULTS, ESPECIALLY IN PATIENTS WHO ARE SEVERELY ILL OR IMMUNOCOMPROMISED. PROPHYLAXIS OF LATENT TB INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH ERELZI. SOME PATIENTS WHO TESTED NEGATIVE FOR LATENT TUBERCULOSIS PRIOR TO RECEIVING ETANERCEPT HAVE DEVELOPED ACTIVE TUBERCULOSIS. MEDICAL PRACTITIONERS SHOULD MONITOR PATIENTS RECEIVING ERELZI 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 INCREASE RATE OF TB INFECTION.

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

People initiating ERELZI / anti-TNF treatment, who initially tested negative for active or latent tuberculosis, should be systematically tested for latent TB infection during treatment with ERELZI, and preventive treatment instituted if indicated.

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 ERELZI treatment.

Hepatitis B (HBV) 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, AS IN ERELZI, HAS BEEN REPORTED. THIS INCLUDES REPORTS OF REACTIVATION OF HEPATITIS B INPATIENTS WHO WERE ANTI-HBc POSITIVE BUT HBsAg NEGATIVE. THE MAJORITY OF THESE REPORTS HAVE OCCURED IN PATIENTS CONCOMITANTLY RECEIVING OTHER MEDICATIONS THAT SUPPRESS THE IMMUNE SYSTEM, WHICH MAY ALSO CONTRIBUTE TO HEPATITIS B REACTIVATION. PATIENTS AT RISK FOR HBV INFECTION SHOULD BE EVALUTED FOR PRIOR EVIDENCE OF HBV INFECTION BEFORE INITIATING ANTI-TNF THERAPY. CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING ERELZI IN PATIENTS PREVIOUSLY INFECTED WITH HBV. THESE PATIENTS SHOULD BE MONITORED FOR SIGNS AND SYMPTOMS OF ACTIVE HBV INFECTION.

Worsening of hepatitis C:

THERE HAVE BEEN REPORTS OF WORSENING OF HEPATITIS C IN PATIENTS RECEIVING ETANERCEPT, AS IN ERELZI. ERELZI SHOULD BE USED WITH CAUTION IN PATIENTS WITH A HISTORY OF HEPATITIS C.

Concurrent treatment with anakinra:

CONCURRENT ADMINISTRATION OF ETANERCEPT, AS IN ERELZI AND ANAKINRA HAS BEEN ASSOCIATED WITH AN INCREASED RISK OF SERIOUS INFECTIONS AND NEUTROPENIA COMPARED TO ETANERCEPT ALONE. THE COMBINATION HAS NOT DEMONSTRATED INCREASED CLINICAL BENEFIT. THUS, THE COMBINED USE OF ERELZI 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, AS IN ERELZI, 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 ETANERCEPT TO STANDARD TREATMENT (INCLUDING CYCLOPHOSPHAMIDE AND HIGH-DOSE STERIODS) WAS NO MORE EFFICACIOUS THAN STANDARD TREATMENT ALONE. THE GROUP OF PATIENTS WHO RECEIVED ETANERCEPT EXPERIENCED MORE NON-CUTANEOUS MALIGNANCIES OF VARIOUS TYPES THAN THE PATIENT GROUP RECEIVING STANDARD TREATMENT ALONE. THE USE OF ERELZI FOR TREATMENT OF WEGENER'S GRANULOMATOSIS IS NOT RECOMMENDED.

Alcoholic hepatitis:

In a study of 48 hospitalised patients treated with etanercept, as in ERELZI, or placebo for moderate to severe alcoholic hepatitis [mean Model of End-stage Liver Disease (MELD) score = 25], etanercept, as in ERELZI, was not efficacious, and the mortality rate in patients treated with etanercept, as in ERELZI, was significantly

higher after 6 months. Consequently, ERELZI should not be used in patients for the treatment of alcoholic hepatitis. Medical practitioners should use caution when using ERELZI in patients who also have moderate to severe alcoholic hepatitis.

Allergic reactions:

Parenteral administration of any biologic product should be attended by appropriate precautions in case an allergic or untoward reaction occurs. Allergic reactions associated with etanercept, as in ERELZI, administration have been reported commonly. Allergic reactions have included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, ERELZI therapy should be discontinued immediately, and appropriate therapy initiated.

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

Immunosuppression:

The possibility exists for TNF-antagonists, including ERELZI, 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, as in ERELZI, 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 ERELZI therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

The safety and efficacy of etanercept, as in ERELZI, 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 rare, 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, as in ERELZI, in the post marketing setting.

Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies typically associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Skin cancers:

Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including etanercept, as in ERELZI. Post-marketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with etanercept, as in ERELZI. 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, as in ERELZI, compared with control patients, particularly in patients with psoriasis.

Vaccinations:

Live vaccines should not be given concurrently with ERELZI. No data are available on the secondary transmission of infection by live vaccines in patients receiving etanercept, as in ERELZI. In a double-blind,

placebo-controlled, randomised clinical study in adult patients with psoriatic arthritis, 184 patients also received a multivalent pneumococcal polysaccharide vaccine at week 4. In this study, most psoriatic arthritis patients receiving etanercept, as in ERELZI, 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, as in ERELZI. The clinical significance of this is unknown.

Autoantibody formation:

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

Haematologic reactions:

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

Neurological disorders:

There have been rare reports of CNS demyelinating disorders in patients treated with etanercept, as in ERELZI (see section 4.8).

Additionally, there have been rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating etanercept, as in ERELZI, therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. ERELZI is not recommended for 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, as in ERELZI, and methotrexate did not result in unexpected safety findings, and the safety profile of etanercept, as in ERELZI, when given in combination with methotrexate was similar to the profiles reported in studies of etanercept, as in ERELZI, and methotrexate alone. Long-term studies to assess the safety of the combination are ongoing. The long-term safety of etanercept, as in ERELZI, in combination with other disease-modifying antirheumatic drugs (DMARD) has not been established.

The use of etanercept, as in ERELZI, 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 (Cardiac failure congestive):

Medical practitioners should use caution when using ERELZI 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, as in ERELZI. 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, as in ERELZI, 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, as in ERELZI, treatment. Medical practitioners should use caution when using ERELZI in patients who also have CHF.

Hypoglycaemia in patients treated for diabetes:

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

Special populations:

Elderly:

In the Phase 3 studies in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, no overall differences in adverse events, serious adverse events, and serious infections in patients age 65 or older who received etanercept, as in ERELZI, 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 ERELZI 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, as in ERELZI (see section 4.8).

Excipients:

ERELZI contains sucrose, Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take ERELZI.

Contains sucrose, which may have an effect on the glycaemic control of patients with diabetes mellitus.

Sodium content:

This medicine contains less than 1 mmol sodium (23 mg) per 25 mg or 50 mg, that is to say essentially ‘sodium-free’.

4.5. Interaction with other medicines and other forms of interaction

Concurrent treatment with anakinra:

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

In addition, in a double-blind, placebo-controlled trial in adult patients receiving background methotrexate, patients treated with etanercept, as in ERELZI, and anakinra were observed to have a higher rate of serious infections (7 %) and neutropenia than patients treated with etanercept, as in ERELZI (see sections 4.4 and 4.8). The combination etanercept, as in ERELZI, 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, as in ERELZI, 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, as in ERELZI, 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, as in ERELZI, or sulfasalazine alone. The clinical significance of this interaction is unknown. Medical practitioners should use caution when considering combination therapy with sulfasalazine.

Non-interactions:

In clinical trials, no interactions have been observed when etanercept, as in ERELZI, 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 ERELZI therapy and for three weeks after discontinuation of therapy.

Pregnancy:

The safe use of ERELZI during pregnancy has not been established.

No fertility or long-term perinatal / postnatal studies are available. Use ERELZI 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 ERELZI is generally not recommended.

Breastfeeding:

The safe use of ERELZI during lactation has not been established.

Etanercept has been reported to be excreted in human milk following subcutaneous administration.

Because immunoglobulins, in common with many medicines, can be excreted in human milk, a decision must be made whether to discontinue breastfeeding or to discontinue ERELZI therapy while breastfeeding.

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

Fertility:

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

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, uveitis and scleritis have been reported.

4.8. Undesirable effects

Summary of the safety profile:

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

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

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

Tabulated list of adverse reactions:

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

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: frequent, less frequent and frequency unknown.

System Organ Class	Frequent	Less frequent	Frequency unknown
Infections and infestations	Infection (including upper respiratory tract	Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis	Hepatitis B reactivation, listeria

System Organ Class	Frequent	Less frequent	Frequency unknown
	infection, bronchitis, cystitis, skin infection)*	and parasitic infection)*, tuberculosis, opportunistic infection (including invasive fungal, protozoal, bacterial, atypical mycobacterial, viral infections, and Legionella)*	
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Non-melanoma skin cancers* (see section 4.4), malignant melanoma (see section 4.4), lymphoma, leukaemia	Merkel cell carcinoma (see section 4.4) Kaposi's sarcoma
Blood and lymphatic system disorders		Thrombocytopenia, anaemia, leukopenia, neutropenia, pancytopenia*, aplastic anaemia*	Histiocytosis haematophagic (macrophage activation syndrome)*
Immune system disorders	Allergic reactions (see Skin and subcutaneous tissue disorders), autoantibody formation*	Vasculitis (including antineutrophilic cytoplasmic antibody positive vasculitis), serious allergic/anaphylactic reactions (including	Worsening of symptoms of dermatomyositis

System Organ Class	Frequent	Less frequent	Frequency unknown
		angioedema, bronchospasm), sarcoidosis	
Nervous system disorders	Headache	CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis (see section 4.4), Peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy (see section 4.4), seizure	
Eye disorders		Uveitis, scleritis	
Cardiac disorders		Worsening of cardiac failure	

System Organ Class	Frequent	Less frequent	Frequency unknown
		congestive (see section 4.4), new onset cardiac failure congestive (see section 4.4)	
Respiratory, thoracic and mediastinal disorders		Interstitial lung disease (including pneumonitis and pulmonary fibrosis)*	
Gastro-intestinal disorders		Inflammatory bowel disease	
Hepatobiliary disorders		Elevated liver enzymes*, autoimmune hepatitis*	
Skin and subcutaneous tissue disorders	Pruritus, rash	Angioedema, psoriasis (including new onset or worsening and pustular, primarily palms and soles), urticaria, psoriasiform rash Stevens-Johnson syndrome, cutaneous vasculitis (including hypersensitivity vasculitis), erythema	Toxic epidermal necrolysis

System Organ Class	Frequent	Less frequent	Frequency unknown
		multiforme, lichenoid reactions	
Musculoskeletal and connective tissue disorders		Cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus, lupus-like syndrome	
Renal and urinary disorders			Glomerulonephritis
General disorders and administration site conditions	Injection Site reactions (including bleeding, bruising, erythema, itching, pain, swelling)*, pyrexia		Thirst

* see Description of selected adverse reactions, below.

Description of selected adverse reactions:

Malignancies and lymphoproliferative disorders:

One hundred and twenty-nine (129) new malignancies of various types were observed in 4,114 rheumatoid arthritis patients treated in clinical trials with etanercept, as in ERELZI, for up to approximately 6 years, including 231 patients treated with etanercept, as in ERELZI, 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, as in ERELZI, 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, as in ERELZI, 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, as in ERELZI, 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, as in ERELZI, 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, as in ERELZI, 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, as in ERELZI, 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, as in ERELZI, alone, methotrexate alone or etanercept, as in ERELZI, 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, as in ERELZI, 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, as in ERELZI, and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by Etanercept, as in ERELZI, 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, as in ERELZI; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Some have occurred within a few weeks after initiating treatment with Etanercept, as in ERELZI, in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see section 4.4). Etanercept, as in ERELZI, treatment may increase mortality in patients with established sepsis.

Opportunistic infections have been reported in association with etanercept, as in ERELZI, 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, as in ERELZI. 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).

Autoantibodies:

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

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

Pancytopenia and aplastic anaemia:

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

Interstitial lung disease:

In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without concomitant methotrexate was 0,06 % (less frequent). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of interstitial lung disease was 0,47 % (less frequent). 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, as in ERELZI, plus anakinra, a higher rate of serious infections compared to Etanercept, as in ERELZI, alone was observed and 2 % of patients (3/139) developed neutropenia (absolute neutrophil count < 1000/mm^3). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see sections 4.4 and 4.5).

Elevated liver enzymes:

In the double-blind periods of controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving etanercept without concomitant methotrexate was 0,54 % (frequency uncommon). In the double-blind periods of controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of adverse events of elevated liver enzymes was 4,18 % (frequency common).

Autoimmune hepatitis:

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

Paediatric population:

Undesirable effects in paediatric patients with juvenile idiopathic arthritis

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

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

In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62 %) children experienced an infection while receiving etanercept, as in ERELZI, 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, as in ERELZI, 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, as in ERELZI, 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, as in ERELZI, 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. Healthcare providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via the link: Sandoz (iqvia.com) or the e-mail address, adverse.event.sac@sandoz.com

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, as in ERELZI, subcutaneously twice weekly for 3 weeks without experiencing undesirable effects.

There is no known antidote to etanercept, as in ERELZI.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

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

ERELZI is a biosimilar medicine.

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

TNF and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-kilodalton (p55) and 75-kilodalton (p75) tumour necrosis factor receptors (TNFRs). Both TNFRs exist naturally in membrane bound and soluble forms. Soluble TNFRs are thought to regulate TNF biological activity.

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

Mechanism of action:

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

5.2. Pharmacokinetic properties

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

Absorption:

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

Distribution:

After a single subcutaneous dose of 25 mg etanercept, the average maximum serum concentration observed in healthy volunteers was 1,65 ± 0,66 µg/ml, and 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 long, approximately 80 hours. Clearance is approximately 175 ± 116 ml/hr in patients with rheumatoid arthritis and 131 ± 81 ml/hr in healthy volunteers. Radioactivity is eliminated in urine after administration of radiolabeled etanercept to patients and volunteers.

Linearity:

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

Special populations:

Renal impairment:

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

Hepatic impairment:

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

Elderly:

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

Paediatric population:

Paediatric patients with juvenile idiopathic arthritis:

In a polyarticular-course juvenile idiopathic arthritis trial with etanercept, 69 patients (aged 4 to 17 years) were administered 0,4 mg etanercept/kg twice weekly for three months. Serum concentration profiles were similar to those seen in adult rheumatoid arthritis patients. The youngest children (4 years of age) had reduced clearance (increased clearance when normalised by weight) compared with older children (12 years of age) and adults. Simulation of dosing suggests that while older children (10–17 years of age) will have serum levels close to those seen in adults, younger children will have appreciably lower levels.

Paediatric patients with plaque psoriasis:

Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered 0,8 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks. The mean serum steady-state trough concentrations ranged from 1,6 to 2,1 µg/ml at weeks 12, 24, and 48. These mean concentrations in patients with paediatric plaque psoriasis were similar to the concentrations observed in patients with juvenile idiopathic

arthritis (treated with 0,4 mg/kg etanercept twice weekly, up to maximum dose of 50 mg per week). These mean concentrations were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice weekly.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Citric acid anhydrous, L-lysine hydrochloride, sodium chloride, sodium citrate dihydrate, sucrose, water for injections.

6.2. Incompatibilities

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

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store in a refrigerator at 2 to 8 °C.

DO NOT FREEZE.

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

After taking a syringe from the refrigerator, wait approximately 15 to 30 minutes to allow the ERELZI solution in the syringe to reach room temperature. Do not warm in any other way. Immediate use is then recommended.

The needle cap should not be removed while allowing the pre-filled syringe to reach room temperature.

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

6.5. Nature and contents of container

ERELZI 25 mg:

Pre-filled syringe: type I glass syringe with a stainless steel needle with a needle guard with finger flange, rubber needle cap and a rubber plunger, containing 0,5 ml of solution.

ERELZI 50 mg:

Pre-filled syringe: type I glass syringe with a stainless steel needle with a needle guard with finger flange, rubber needle cap and a rubber plunger, containing 1,0 ml of solution.

Pre-filled pen: ERELZI is supplied in a single-use pre-filled syringe assembled into a triangular-shaped pen with transparent window and label (SensoReady pen). The syringe inside the pen is made from type I glass with a stainless steel needle and an inner rubber needle cap, containing 1,0 ml of solution.

Cartons contain 1, 2 or 4 pre-filled syringes or pre-filled pens of ERELZI.

Multipacks contain 12 (3 packs of 4) 25 mg or 50 mg pre-filled syringes or pre-filled pens or 8 (2 packs of 4) or 24 (6 packs of 4) 25 mg pre-filled syringes of ERELZI.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

Tel: 010 070 1600

8. REGISTRATION NUMBER

ERELZI 25 mg: 55/3.1/0392

ERELZI 50 mg: 55/3.1/0393

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 August 2021

10. DATE OF REVISION OF THE TEXT

24 July 2025

[1]Company Reg. No.: 1990/001979/07