Enercept™

[Etanercept]

Lyophilized Powder for Injection

25mg

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DESCRIPTION

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

QUALITATIVE AND QUANTITATIVE COMPOSITION

Enercept (Etanercept) Lyophilized Powder for Injection is available for administration as:

Enercept Lyophilized Powder for Injection 25mg
Each vial contains:
Etanercept…25mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Tumor Necrosis Factor (TNF) is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. 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. Biological activity of TNF is dependent upon binding to either cell surface TNFR.
Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind TNF molecules. Etanercept inhibits binding of TNF-α and TNF-β (lymphotoxin alpha [LT-α]) to cell surface TNFRs, 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.

Pharmacokinetics

Absorption

Etanercept is slowly absorbed from the site of subcutaneous injection, reaching maximum concentration approximately 48 hours after a single dose. The absolute bioavailability is 76%. With twice-weekly doses, it is anticipated that steady-state concentrations are approximately twice as high as those observed after single doses. After a single subcutaneous dose of 25mg Etanercept, the average maximum serum concentration observed in healthy volunteers was 1.65 ± 0.66 µg/ml and the area under the curve was 235 ± 96.6 µg.hr/ml.
Mean serum concentration profiles at steady state in treated RA patients were C_{max} of 2.4mg/l vs. 2.6mg/l, C_{min} of 1.2mg/l vs. 1.4mg/l, and partial AUC of 297mgh/l vs. 316mgh/l for 50mg Etanercept once weekly vs. 25mg Etanercept twice weekly, respectively.
In a population pharmacokinetics analysis in ankylosing spondylitis patients, the Etanercept steady state AUCs were 466 µg.hr/ml and 474 µg.hr/ml for 50mg Etanercept once weekly and 25mg twice weekly, respectively.

Distribution

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

Elimination

Etanercept is cleared slowly from the body. The half-life is long, approximately 70 hours. Clearance is approximately 0.066l/hr in patients with rheumatoid arthritis, somewhat lower than the value of 0.11l/hr observed in healthy volunteers.

THERAPEUTIC INDICATIONS

Rheumatoid Arthritis

Enercept (Etanercept) is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis (RA). Etanercept can be initiated in combination with methotrexate (MTX) or used alone.

Polyarticular Juvenile Idiopathic Arthritis

Enercept (Etanercept) is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients ages 2 and older.

Psoriatic Arthritis

Enercept (Etanercept) is indicated for reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (PsA). Enercept (Etanercept) can be used with or without methotrexate.

Ankylosing Spondylitis

Enercept (Etanercept) is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis (AS).

Non-radiographic axial spondyloarthritis

Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to non steroidal anti-inflammatory drugs (NSAIDs).

Plaque Psoriasis

Enercept (Etanercept) is indicated for the treatment of patients 4 years or older with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy.

DOSAGE & ADMINISTRATION

Enercept (Etanercept) treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis.

Adult Patients

Rheumatoid Arthritis

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

Psoriatic Arthritis, Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis

The recommended dose is 25mg Enercept (Etanercept) administered twice weekly, or 50mg administered once weekly.
For all of the above indications, available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Plaque Psoriasis

The recommended dose of Enercept (Etanercept) is 25mg administered twice weekly or 50mg administered once weekly. Alternatively, 50mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25mg twice weekly or 50mg once weekly. Treatment with Enercept (Etanercept) should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Enercept (Etanercept) is indicated, the same guidance on treatment duration should be followed. The dose should be 25mg twice weekly or 50mg once weekly.

Pediatric Patients

Juvenile Idiopathic Arthritis

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

Plaque Psoriasis

The recommended dose is 0.8mg/kg (up to a maximum of 50mg 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 Enercept (Etanercept) is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8mg/kg (up to a maximum of 50mg per dose) once weekly.

Special Population

Renal and Hepatic Impairment

No dose adjustment is required.

Elderly

No dose adjustment is required.

Method of Administration

Enercept (Etanercept) is administered by subcutaneous injection. Enercept (Etanercept) Lyophilized Powder for Injection must be reconstituted in 1ml Sterile Water for Injection prior to administration.
Enercept (Etanercept) contains no antibacterial preservative and therefore, solutions prepared with Sterile Water for Injection should be administered as soon as possible and within 6 hours following reconstitution when stored at temperature of up to 25°C. The solution should be clear and colourless to pale yellow or pale brown with no lumps, flakes or particles. Some white foam may remain in the vial – this is normal. Enercept (Etanercept) should not be used if all the powder in the vial is not dissolved within 10 minutes. If this is the case, start again with another vial.

ADVERSE REACTIONS

Very Common: Infection (including upper respiratory tract infection, bronchitis, cystitis, skin infection) and injection site reactions (including bleeding, bruising, erythema, itching, pain, swelling).

Common: Allergic reactions, autoantibody formation, pruritus, rash and pyrexia.

Uncommon: Serious infections (including pneumonia, cellulitis, arthritis bacterial, sepsis and parasitic infection), non-melanoma skin cancers, thrombocytopenia, anaemia, leukopenia, neutropenia, vasculitis (including anti-neutrophilic cytoplasmic antibody positive vasculitis), uveitis, scleritis, worsening of cardiac failure congestive, elevated liver enzymes, angioedema, psoriasis (including new onset or worsening and pustular, primarily palms and soles), urticaria and psoriasiform rash.

Rare: Tuberculosis, opportunistic infection (including invasive fungal, protozoal, bacterial, atypical mycobacterial, viral infections, and legionella), malignant melanoma, lymphoma, leukaemia, pancytopenia, serious allergic/anaphylactic reactions (including angioedema, bronchospasm), sarcoidosis, CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis, peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy and multifocal motor neuropath, seizure, new onset cardiac failure congestive, interstitial lung disease (including pneumonitis and pulmonary fibrosis), autoimmune hepatitis, Stevens-Johnson syndrome, cutaneous vasculitis (including hypersensitivity vasculitis), erythema multiforme, lichenoid reactions, cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus and lupus-like syndrome.

Very Rare: Aplastic anaemia and toxic epidermal necrolysis.

Frequency Not Known: Hepatitis B reactivation, listeria, merkel cell carcinoma, histiocytosis haematophagic (macrophage activation syndrome) and worsening of symptoms of dermatomyositis.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS

Etanercept is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipient of the product.
- Sepsis or risk of sepsis.
- Active infections, including chronic or localised infections.
- Concurrent treatment with Interleukin-1 antagonists.

WARNING: SERIOUS INFECTIONS & MALIGNANCIES

Serious Infections

Patients treated with Etanercept are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Etanercept should be discontinued if a patient develops a serious infection or sepsis. The risks and benefits of treatment with Etanercept should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Malignancies

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including Etanercept.

PRECAUTIONS

Infections

Patients should be evaluated for infections before, during, and after treatment with Etanercept. Serious infections, sepsis, tuberculosis, and opportunistic infections, including invasive fungal infections, listeriosis and legionellosis, have been reported with the use of Etanercept. Patients who develop a new infection while undergoing treatment with Etanercept should be monitored closely. Administration of Etanercept should be discontinued if a patient develops a serious infection.

Tuberculosis

Cases of active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary location, have been reported in patients treated with Etanercept. Before starting treatment with Etanercept, all patients must be evaluated for both active and inactive ('latent')

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

Interstitial Lung Disease
There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Invasive Fungal Infections
Cases of serious and sometimes fatal fungal infections, including histoplasmosis, have been reported with TNF blockers, including Etanercept. For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric anti-fungal therapy should be considered while a diagnostic workup is being performed.

Hepatitis B Reactivation
Patients should be tested for HBV infection before initiating treatment with Etanercept. Caution should be exercised when administering Etanercept in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy. In patients who develop HBV infection, Etanercept should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

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

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

Immunosuppression
The possibility exists for TNF-antagonists, including Etanercept, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. Patients with a significant exposure to varicella virus should temporarily discontinue Etanercept therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

Solid and Hematopoietic Malignancies (excluding skin cancers)
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.

Skin Cancers
Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including Etanercept. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Vaccinations
Live vaccines should not be given concurrently with Etanercept. It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating Etanercept.

Autoantibody Formation
Treatment with Etanercept may result in the formation of autoimmune antibodies. If a patient develops symptoms and findings suggestive of a lupus-like syndrome or autoimmune hepatitis following treatment with Etanercept, treatment should be discontinued and the patient should be carefully evaluated.

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

Neurological Disorders
Treatment with TNF-blocking agents, including Etanercept, has been associated with rare cases of new onset or exacerbation of central nervous system demyelinating disorders, some presenting with mental status changes and some associated with permanent disability and with peripheral nervous system demyelinating disorders. Prescribers should exercise caution in considering the use of Etanercept in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders.

Congestive Heart Failure (Cardiac failure congestive)
Physicians should use caution when using Etanercept in patients who have congestive heart failure (CHF) and monitor patients carefully.

Alcoholic Hepatitis
Etanercept should not be used in patients for the treatment of alcoholic hepatitis. Physicians should use caution when using Etanercept in patients who also have moderate to severe alcoholic hepatitis.

Wegener's Granulomatosis
Etanercept is not recommended for the treatment of Wegener's granulomatosis.

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

Inflammatory Bowel Disease (IBD) and Uveitis in patients with Juvenile Idiopathic Arthritis (JIA)
There have been reports of Inflammatory Bowel Disease and Uveitis in Juvenile Idiopathic Arthritis patients being treated with Etanercept.

Elderly
Caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections.

Pregnancy
Women of childbearing potential should consider the use of appropriate contraception to avoid becoming pregnant during Etanercept therapy and for three weeks after discontinuation of therapy. Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with Etanercept during pregnancy.

Nursing Mothers
Etanercept has been reported to be excreted in human milk following subcutaneous administration. A decision must be made whether to discontinue breast-feeding or to discontinue Etanercept therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

DRUG INTERACTIONS
Vaccines
Patients receiving Etanercept may receive concurrent vaccinations, except for live vaccines. Patients with a significant exposure to varicella virus should temporarily discontinue Etanercept therapy and be considered for prophylactic treatment with varicella zoster immune globulin.

Concurrent treatment with anakinra
Adult patients treated with Etanercept and anakinra were observed to have a higher rate of serious infection when compared with patients treated with either Etanercept or anakinra alone. The combination Etanercept and anakinra has not demonstrated increased clinical benefit and is therefore not recommended.

Concurrent treatment with abatacept
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.

Cyclophosphamide
The use of Etanercept in patients receiving concurrent cyclophosphamide therapy is not recommended.

Concurrent treatment with sulfasalazine
In a clinical study of adult patients who were receiving established doses of sulfasalazine, to which Etanercept was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with Etanercept or sulfasalazine alone. The clinical significance of this interaction is unknown. Physicians should use caution when considering combination therapy with sulfasalazine.

Non-interactions
No interactions have been observed when Etanercept was administered with glucocorticoids, salicylates (except sulfasalazine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate.

OVERDOSAGE
No dose-limiting toxicities have been observed with Etanercept. Single IV doses up to 60mg/m^2 (approximately twice the recommended dose) have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities.

STORAGE
Store at 2°C - 8°C in a refrigerator. Do not freeze.
Protect from light, heat and moisture.
Enercept (Etanercept) Lyophilized Powder for Injection 25mg may be stored at temperature up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. Enercept (Etanercept) Lyophilized Powder for Injection 25mg should be discarded if not used within four weeks of removal from refrigeration.
After reconstitution, solution for injection can be used within 6 hours when stored at temperature of up to 25°C. Any unused reconstituted solution should be discarded.

HOW SUPPLIED
Enercept (Etanercept) Lyophilized Powder for Injection 25mg is available in pack of 1 vial along with 1ml Sterile Water for Injection.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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