For the use of a Registered Rheumatologist and Orthopedicians only

INTACEPT
Etanercept solution for injection 25 mg/0.5 mL or 50 mg/1.0 mL

DECSRIPTION AND COMPOSITION
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, CH2 and CH3 regions, but not the CH1 region of IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. The specific activity of etanercept is 1.7×10^6 units/mg.

Etanercept is a sterile, clear, colorless or pale yellow, preservative-free liquid solution for injection. Etanercept is supplied at a concentration of 25 mg/0.5 mL or 50 mg/1.0 mL in single-use pre-filled syringe.

INTACEPT 25
Each 0.5 mL single use pre-filled syringe contains:
Etanercept 25 mg

INTACEPT 50
Each 1.0 mL single use pre-filled syringe contains:
Etanercept 50 mg
The pH of the solution is 6.3±0.3.

Contents	**INTACEPT 25**	**INTACEPT 50**
Etanercept	25 mg	50 mg
Sucrose	10.0 mg	20.0 mg
L-Lysine Monohydrate	0.75 mg	1.50 mg
DL-Aspartic acid	0.65 mg	1.30 mg
Sodium Chloride	2.9 mg	5.8 mg
Polysorbate 20	0.1 mg	0.2 mg
Disodium EDTA	0.185 mg	0.370 mg
Sodium Phosphate monobasic	0.75 mg	1.50 mg
Potassium phosphate dibasic	1.65 mg	3.30 mg
Ortho phosphoric acid	*q.s.* to pH 6.3	*q.s.* to pH 6.3
Sodium hydroxide	*q.s.* to pH 6.3	*q.s.* to pH 6.3
WFI	*q.s.* to 0.5 mL	*q.s.* to 1.0 mL

DOSAGE FORM
Solution for injection 25 mg/0.5 mL or 50 mg/1.0 mL single-use prefilled syringe

PRECLINICAL PHARMACOLOGY
The biological activity of etanercept manufactured by Intas Pharmaceuticals Limited against Enbrel® manufactured by John Wyeth & Brother Limited was assessed in an in-vitro cell based assay. When compared with the reference standard, it was found comparable and equipotent.

Single dose comparative pharmacokinetic study of etanercept manufactured by Intas Pharmaceuticals Limited against Enbrel® manufactured by John Wyeth & Brother Limited was conducted by Intas in Swiss Albino mice. This study concluded that Pharmacokinetic parameters Cmax, Tmax, volume of distribution, clearance and t1/2 for the test formulation Etanercept manufactured by Intas were not significantly different from the reference formulation Enbrel®.

Acute & sub acute toxicity studies of etanercept manufactured by Intas Pharmaceuticals Ltd. were conducted to evaluate its safety profile. Single Dose Toxicity Studies of Etanercept in Wistar rats & Swiss Albino mice were performed following Intravenous & Subcutaneous administration. In these studies, the Maximum Tolerated Dose (MTD) of etanercept was found to be > 52mg/kg body weight in Wistar rats and > 103 mg/kg in Swiss Albino mice. 4-Week Sub-Acute Subcutaneous Toxicity Studies of Etanercept in Wistar rats & New Zealand White rabbits were also performed with 14 Days recovery period. Results of the sub acute studies indicated that the test item etanercept has no adverse effect on body weight, feed Consumption, hematological, clinical chemistry parameters, organ weights and gross and histopathology at and up to the dose of 52 mg/kg & 26 mg/kg body weight of Wistar rats & New Zealand white rabbits, respectively, compared to control group. Further no incidence of delayed toxicity was observed in satellite animals which were observed 14 days after main group necropsy.

Based on the findings of this subacute studies, the No Observed Adverse Effect Level (NOAEL) of Etanercept in New Zealand White rabbits, following weekly subcutaneous administration was found to be >52 mg for wistar rats & > 26 mg/kg body weight for Rabbits.

Primary skin irritation test of etanercept manufactured by Intas Pharmaceuticals Ltd. was performed in New Zealand White rabbits to evaluate the dermal irritation potential if any, by applying Etanercept to intact naked skin of rabbits. From this study, it was concluded that the test item Intas etanercept was found to be 'non-irritant' to the skin of rabbits.

In the Skin Sensitization Study (GPMT) of etanercept manufactured by Intas Pharmaceuticals Ltd., the test item Intas etanercept was found as non-sensitizer to the skin of Guinea pigs under the experimental conditions.

CLINICAL PHARMACOLOGY

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.

CLINICAL PHARMACODYANAMIC PROPERTIES

Etanercept can modulate biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (eg, E-selectin, and to a lesser extent, intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (eg, IL-6), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin). Etanercept has been shown to affect several animal models of inflammation, including murine collagen-induced arthritis.

CLINICAL PHARMACOKINETIC PROPERTIES

After administration of 25 mg of etanercept by a single SC injection to 25 patients with rheumatoid arthritis (RA), a mean ± standard deviation half-life of 102 ± 30 hours was observed with a clearance of 160 ± 80 mL/hr. A maximum serum concentration (Cmax) of 1.1 ± 0.6 mcg/mL and time to Cmax of 69 ± 34 hours was observed in these patients following a single 25 mg dose. After 6 months of twice weekly 25 mg doses in these same RA patients, the mean Cmax was 2.4 ± 1.0 mcg/mL (N = 23). Patients exhibited a 2- to 7-fold increase in peak serum concentrations and approximately 4-fold increase in AUC_{0-72} hr (range 1- to 17-fold) with repeated dosing. Serum concentrations in patients with RA have not been measured for periods of dosing that exceed 6 months.

In another study, serum concentration profiles at steady state were comparable among patients with RA treated with 50 mg etanercept once weekly and those treated with 25 mg etanercept twice weekly. The mean (± standard deviation) Cmax, Cmin, and partial AUC were 2.4 ± 1.5 mcg/mL, 1.2 ± 0.7 mcg/mL, and 297 ± 166 mcg•h/mL, respectively, for patients treated with 50 mg etanercept once weekly (N = 21); and 2.6 ± 1.2 mcg/mL, 1.4 ± 0.7 mcg/mL, and 316 ± 135 mcg•h/mL for patients treated with 25 mg etanercept twice weekly (N = 16).

In clinical studies with etanercept, pharmacokinetic parameters were not different between men and women and did not vary with age in adult patients. The pharmacokinetics of etanercept were unaltered by concomitant methotrexate (MTX) in RA patients. No formal pharmacokinetic studies have been conducted to examine the effects of renal or hepatic impairment on etanercept disposition.

CLINICAL TRIAL OF ETANERCEPT IN INDIAN PATIENTS

The efficacy and safety of etanercept of Intas was evaluated in comparison with innovator's etanercept in multi-centric, randomized phase III trial in patients with active rheumatoid arthritis. Primary objective of the study was to compare the efficacy of etanercept manufactured by Intas versus innovator's etanercept in patients with active rheumatoid arthritis. Secondary objective was to compare the pharmacokinetic of etanercept manufactured by Intas versus innovator's etanercept and to evaluate safety of the patients who are exposed to the investigational medicinal products.

Adult men and women with age ≥ 18 with active rheumatoid arthritis diagnosed according to the revised 1987 American College of Rheumatology (ACR) criteria for the classification of rheumatoid arthritis were included in study.

Out of a total of 107 patients 82 were randomized to Intas etanercept and 25 randomized to innovator's etanercept. The primary efficacy endpoint was the proportion of patient achieving at least 20% improvement in ACR core criteria for assessment of rheumatoid arthritis (ACR20) in intention-to-treat population. The results of the present study demonstrated that ACR20 was achieved in 83.95% patient in treatment arm of Intas etanercept as compared to 84% in treatment arm of innovator's etanercept at the end of 12 week of treatment period (p value > 0.5). Further detailed analysis of the result showed that both group had comparable with secondary efficacy endpoint of ACR50 (53.09% vs. 36%, p values= 0.1716), mean change in DAS-28 score (2.08 vs. 2.00, p value= 0.7737) and change in Health Assessment Questionnaire score (0.69 vs. 0.71, p values= 0.8939) in intention-to-treat population. Per-protocol analysis also revealed the similar results. Result of the study indicates that etanercept solution for subcutaneous use manufactured by Intas has equivalent efficacy compare to innovator's etanercept in treatment of patients with active rheumatoid arthritis.

In pharmacokinetic assessment in subgroup of patients (n=20, 10 in each group), median Tmax in both the groups was 72 h. AUC_{0-168} values were 545485.46 ± 141357.91 ng·h/mL and 568740.27 ± 185718.84 ng·h/mL in test arm-A and reference arm-B, respectively. Cmax values were 4596.74 ± 1285.35 ng/mL and 4734.08 ± 1575.65 ng/mL in test arm-A and reference arm-B, respectively.
Pharmacokinetic parameters (i.e. Cmax and AUC_{0-168}) were comparable after single dose administration of Test Product-A and Reference Product-B in patients with active rheumatoid arthritis.

Out of 107 randomized patients, total 28 adverse events (21 in Intas etanercept arm and 7 in innovator's etanercept arm) were reported during the conduct of the study. Total of 28 adverse events were reported during conduct of this study. More frequent adverse events reported were fever, headache and upper respiratory tract infection. Majority of the adverse events reported during the conduct of the study were mild in nature. Approximately 80.95% of the adverse events reported in Intas etanercept arm and 42.86% of the adverse events reported in innovator's etanercept arm were mild in severity. Only 9.52% of the patients in Intas etanercept arm had severe adverse events during the conduct of the study compared to 14.29% in innovator's etanercept arm.
There were total three serious adverse events reported in the study. Out of the three SAEs, 1 was in Intas etanercept group, while two SAEs were in innovator's etanercept group.
No adverse event was associated with abnormal laboratory value. All laboratory parameters were within acceptable range and clinically not significant. All the vital parameters were also within acceptable range during the study in both the treatment groups.
Overall both the study drugs, etanercept manufactured by Intas as well as innovator's etanercept, were found safe and well tolerated in the study population. The overall tolerability of etanercept manufactured by Intas is comparable with innovator's etanercept, at intended therapeutic doses in rheumatoid arthritis patients. Etanercept manufactured by Intas was demonstrated to be safe and well tolerated in the study population.
It can be concluded that, compared to innovator's etanercept, etanercept manufactured by Intas has equivalent safety and efficacy profile in treatment of rheumatoid arthritis patients.

INDICATION
Etanercept is indicated for the treatment of:
Rheumatoid Arthritis

- Etanercept in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.
- Etanercept can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.
- Etanercept is also indicated in the treatment of severe, active & progressive rheumatoid arthritis in adults not previously treated with methotrexate.
- Etanercept, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Psoriatic arthritis

- Treatment of active and progressive psoriatic arthritis in adults when the response to previous diseasemodifying antirheumatic drug therapy has been inadequate. Etanercept has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by Xray in patients with polyarticular symmetrical subtypes of the disease.

Ankylosing spondylitis (AS)

- Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy

Juvenile idiopathic arthritis

- Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an 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.
- Etanercept has not been studied in children aged less than 2 years

DOSE AND METHOD OF ADMINISTRATION

Rheumatoid arthritis

- 25 mg Etanercept administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective.

Psoriatic arthritis, Ankylosing spondylitis

- The recommended dose is 25 mg Etanercept administered twice weekly, or 50 mg 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.

Juvenile idiopathic arthritis

- The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose) 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. Discontinuation of treatment should be considered in patients who show no response after 4 months.
- No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously

CONTRAINDICATIONS

Etanercept should not be administered to patients with sepsis.

WARNINGS AND PRECAUTIONS

Serious Infections

Patients treated with etanercept are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease. Treatment with etanercept should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- With chronic or recurrent infection;
- Who have been exposed to tuberculosis;
- With a history of an opportunistic infection;
- Who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, Coccidioidomycosis, or blastomycosis; or With underlying conditions that may predispose them to infection, such as advanced or poorly controlled diabetes.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with etanercept.
Etanercept should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with etanercept should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

Tuberculosis
Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving etanercept, including patients who have previously received treatment for latent or active tuberculosis. Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with etanercept than with TNF-blocking monoclonal antibodies. Nonetheless, postmarketing cases of tuberculosis reactivation have been reported for TNF blockers, including etanercept. Tuberculosis has developed in patients who tested negative for latent tuberculosis prior to initiation of therapy. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating etanercept and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF-blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating etanercept, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).
Anti-tuberculosis therapy should also be considered prior to initiation of etanercept in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.
Tuberculosis should be strongly considered in patients who develop a new infection during etanercept treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

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. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric anti-fungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of anti-fungal therapy. In 38 etanercept clinical trials and 4 cohort studies in all approved

indications representing 27,169 patient-years of exposure (17,696 patients) from the United States and Canada, no histoplasmosis infections were reported among patients treated with etanercept.

Neurologic Events

Treatment with TNF-blocking agents, including etanercept, has been associated with rare (< 0.1%) 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. Cases of transverse myelitis, optic neuritis, multiple sclerosis, Guillain-Barré syndromes, other peripheral demyelinating neuropathies, and new onset or exacerbation of seizure disorders have been reported in postmarketing experience with etanercept therapy. Prescribers should exercise caution in considering the use of etanercept in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders.

Malignancies

Lymphomas

In the controlled portions of clinical trials of TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared to control patients.
Among 6543 adult rheumatology (RA, PsA, AS) patients treated with etanercept in controlled and uncontrolled portions of clinical trials, representing approximately 12,845 patient-years of therapy, the observed rate of lymphoma was 0.10 cases per 100 patient-years. An increased rate of lymphoma up to several-fold has been reported in the RA patient population, and may be further increased in patients with more severe disease activity.

Leukemia

Cases of acute and chronic leukemia have been reported in association with postmarketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at higher risk (approximately 2-fold) than the general population for the development of leukemia.
During the controlled portions of etanercept trials, 2 cases of leukemia were observed among 5445 (0.06 cases per 100 patient-years) etanercept-treated patients versus 0 among 2890 (0%) control patients (duration of controlled treatment ranged from 3 to 48 months).
Among 15,401 patients treated with etanercept in controlled and open portions of clinical trials representing approximately 23,325 patient-years of therapy, the observed rate of leukemia was 0.03 cases per 100 patient-years.

Other Malignancies

Information is available from 10,953 adult patients with 17,123 patient-years and 696 pediatric patients with 1282 patient-years of experience across 45 etanercept clinical studies.

For malignancies other than lymphoma and non-melanoma skin cancer, there was no difference in exposure-adjusted rates between the etanercept and control arms in the controlled portions of clinical studies for all indications.
Whether treatment with etanercept might influence the development and course of malignancies in adults is unknown.

Melanoma and Non-melanoma skin cancer (NMSC)

Melanoma and non-melanoma skin cancer has been reported in patients treated with TNF antagonists including etanercept.
Among 15,401 patients treated with etanercept in controlled and open portions of clinical trials representing approximately 23,325 patient-years of therapy, the observed rate of melanoma was 0.043 cases per 100 patient-years.
Among 3306 adult rheumatology (RA, PsA, AS) patients treated with etanercept in controlled clinical trials representing approximately 2669 patient-years of therapy, the observed rate of NMSC was 0.41 cases per 100 patient-years vs 0.37 cases per 100 patient-years among 1521 control-treated patients representing 1077 patient-years. Among 1245 adult psoriasis patients treated with etanercept in controlled clinical trials, representing approximately 283 patient-years of therapy, the observed rate of NMSC was 3.54 cases per 100 patient-years vs 1.28 cases per 100 patient-years among 720 control-treated patients representing 156 patient-years.
Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with etanercept.
Periodic skin examinations should be considered for all patients at increased risk for skin cancer.

Pediatric Patients
Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy at ≤ 18 years of age), including etanercept. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported postmarketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports.
In clinical trials of 1140 pediatric patients representing 1927.2 patient-years of therapy, no malignancies, including lymphoma or NMSC, have been reported.
Postmarketing Use
In global postmarketing adult and pediatric use, lymphoma and other malignancies have been reported.

Patients With Heart Failure

Two clinical trials evaluating the use of etanercept in the treatment of heart failure were terminated early due to lack of efficacy. One of these studies suggested higher mortality in etanercept-treated patients compared to placebo. There have been postmarketing reports of worsening of congestive heart failure (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 preexisting cardiovascular disease. Some of these patients have been under 50 years of age. Physicians should exercise caution when using etanercept in patients who also have heart failure, and monitor patients carefully.

Hematologic Events

Rare (< 0.1%) reports of pancytopenia, including very rare (< 0.01%) reports of aplastic anemia, some with a fatal outcome, have been reported in patients treated with etanercept. The causal relationship to etanercept therapy remains unclear. Although no high-risk group has been identified, caution should be exercised in patients being treated with etanercept who have a previous history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they

develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on etanercept. Discontinuation of etanercept therapy should be considered in patients with confirmed significant hematologic abnormalities.
Two percent of patients treated concurrently with etanercept and anakinra developed neutropenia (ANC < 1 x 10^9/L). While neutropenic, one patient developed cellulitis that resolved with antibiotic therapy.

Hepatitis B Reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-blocking agents, including very rare cases (< 0.01%) with etanercept, has been reported. In some instances, hepatitis B reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to hepatitis B reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF-blocker therapy. Prescribers should exercise caution in prescribing TNF blockers in patients previously infected with HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-blocker therapy to prevent HBV reactivation. Patients previously infected with HBV and require treatment with etanercept should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, consideration should be given to stopping etanercept and initiating anti-viral therapy with appropriate supportive treatment. The safety of resuming etanercept therapy after HBV reactivation is controlled is not known. Therefore, prescribers should weigh the risks and benefits when considering resumption of therapy in this situation.

Allergic Reactions

Allergic reactions associated with administration of etanercept during clinical trials have been reported in < 2% of patients. If an anaphylactic reaction or other serious allergic reaction occurs, administration of etanercept should be discontinued immediately and appropriate therapy initiated.

Immunizations

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 therapy.

Autoimmunity

Treatment with etanercept may result in the formation of autoantibodies and, rarely (< 0.1%), in the development of a lupus-like syndrome or autoimmune hepatitis, which may resolve following withdrawal of etanercept. 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.

Use in Wegener's Granulomatosis Patients

The use of etanercept in patients with Wegener's granulomatosis receiving immunosuppressive agents is not recommended. In a study of patients with Wegener's granulomatosis, the addition of etanercept to standard therapy (including cyclophosphamide) was associated with a higher incidence of non-cutaneous solid malignancies and was not associated with improved clinical outcomes when compared with standard therapy alone.

Use with Anakinra or Abatacept

Use of etanercept with anakinra or abatacept is not recommended.

Use in Patients with Moderate to Severe Alcoholic Hepatitis

In a study of 48 hospitalized patients treated with etanercept or placebo for moderate to severe alcoholic hepatitis, the mortality rate in patients treated with etanercept was similar to patients treated with placebo at 1 month but significantly higher after 6 months. Physicians should use caution when using etanercept in patients with moderate to severe alcoholic hepatitis.

USE IN SPECIAL POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well controlled studies in pregnant women. Based on limited data, etanercept concentration in cord blood at the time of delivery showed that etanercept crossed the placenta in small amounts.

Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to etanercept. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Human Data

Three case reports showed that cord blood levels of etanercept at delivery in infants, born to mothers administered etanercept during pregnancy, were between 3 and 32% of the maternal serum level.

Nursing Mothers

Limited data from published literature show that etanercept is present in low levels in human milk and minimally absorbed by a breastfed infant. Caution should be exercised when etanercept is administered to a nursing woman. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for etanercept and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Pediatric Use

Etanercept has not been studied in children < 2 years of age with juvenile idiopathic arthritis (JIA). The safety and efficacy of etanercept in pediatric patients with psoriasis have not been studied.

Rare (< 0.1%) cases of IBD have been reported in JIA patients receiving etanercept, which is not effective for the treatment of IBD.

The clinical significance of infant exposure to etanercept *in utero* is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to exposed infants.

Geriatric Use

Around 480 RA patients ages 65 years or older have been studied in clinical trials. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

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

DRUG INTERACTIONS
Specific drug interaction studies have not been conducted with etanercept.
1. Vaccines
Most Psoriatic arthritis patients receiving etanercept were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had 2-fold rises in titers compared to patients not receiving etanercept. The clinical significance of this is unknown. Patients receiving etanercept may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving etanercept. Patients with a significant exposure to varicella virus should temporarily discontinue etanercept therapy and be considered for prophylactic treatment with varicella zoster immune globulin.
2. Immune-Modulating Biologic Products
In a study in which patients with active RA were treated for up to 24 weeks with concurrent etanercept and anakinra therapy, a 7% rate of serious infections was observed, which was higher than that observed with etanercept alone (0%) and did not result in higher ACR response rates compared to etanercept alone.
The most common infections consisted of bacterial pneumonia (4 cases) and cellulitis (4 cases). One patient with pulmonary fibrosis and pneumonia died due to respiratory failure. Two percent of patients treated concurrently with etanercept and anakinra developed neutropenia (ANC < 1 x 10^9/L).
In clinical studies, concurrent administration of abatacept and etanercept resulted in increased incidences of serious adverse events, including infections, and did not demonstrate increased clinical benefit.
3. Cyclophosphamide
The use of etanercept in patients receiving concurrent cyclophosphamide therapy is not recommended.
4. Sulfasalazine
Patients in a clinical study who were on established therapy with sulfasalazine, to which etanercept was added, were noted to develop a mild decrease in mean neutrophil counts in comparison to groups treated with either etanercept or sulfasalazine alone. The clinical significance of this observation is unknown.

UNDESIRABLE EFFECTS

Across clinical studies and postmarketing experience, the most serious adverse reactions with etanercept were infections, neurologic events, CHF, and hematologic events. The most common adverse reactions with etanercept were infections and injection site reactions.
Clinical trial results
Infections
Infections, including viral, bacterial, and fungal infections, have been observed in adult and pediatric patients.
Infections consisted primarily of upper respiratory tract infection, sinusitis and influenza.
In clinical trials with rheumatologic indications, serious infections experienced by patients have included, but are not limited to, pneumonia, cellulitis, septic arthritis, bronchitis, gastroenteritis, pyelonephritis, sepsis, abscess and osteomyelitis. In 66 global clinical trials of 17,505 patients (21,015 patient-years of therapy), tuberculosis was observed in approximately 0.02% of patients. In 17,696 patients (27,169

patient-years of therapy) from 38 clinical trials and 4 cohort studies in the U.S. and Canada, tuberculosis was observed in approximately 0.006% of patients. These studies include reports of pulmonary and extrapulmonary tuberculosis

Injection Site Reactions

Injection site reactions generally occurred in the first month and subsequently decreased in frequency. In placebo-controlled trials in rheumatologic indications, approximately 37% of patients treated with etanercept developed injection site reactions. All injection site reactions were described as mild to moderate (erythema, itching, pain, swelling, bleeding, bruising) and generally did not necessitate drug discontinuation. Injection site reactions generally occurred in the first month and subsequently decreased in frequency. The mean duration of injection site reactions was 3 to 5 days. Seven percent of patients experienced redness at a previous injection site when subsequent injections were given.

Immunogenicity

Antibodies to the TNF receptor portion or other protein components of the etanercept drug product were detected at least once in sera of approximately 6% of adult patients with RA. These antibodies were all non-neutralizing. However, the clinical significance of this finding is unknown. No apparent correlation of antibody development to clinical response or adverse events was observed. The immunogenicity data of etanercept beyond 120 weeks of exposure are unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to etanercept in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of any antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to etanercept with the incidence of antibodies to other products may be misleading.

Autoantibodies

In RA clinical study, no pattern of increased autoantibody development was seen in etanercept patients compared to MTX patients.

Others

Upper respiratory tract infections and sinusitis, discoid lupus and necrotising vasculitis, urticaria, rash, malignancy, GI upset. Rarely, blood dyscrasias, CNS demyelinating disorders, SLE and lupus-like syndrome.

Adverse Reactions in Pediatric Patients

In general, the adverse reactions in pediatric patients were similar in frequency and type as those seen in adult patients. The types of infections reported in pediatric patients were generally mild and consistent with those commonly seen in the general pediatric population.

Postmarketing Experience of innovator's etanercept

Adverse reactions have been reported during post approval use of etanercept in adults and pediatric patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to etanercept exposure.

Adverse reactions are listed by body system below:

Blood and lymphatic system disorders: pancytopenia, anemia, leukopenia, neutropenia, thrombocytopenia, lymphadenopathy, aplastic anemia
Cardiac disorders: congestive heart failure
Gastrointestinal disorders: inflammatory bowel disease (IBD)
General disorders: angioedema, chest pain
Hepatobiliary disorders: autoimmune hepatitis, elevated transaminases, hepatitis B reactivation
Immune disorders: macrophage activation syndrome, systemic vasculitis, sarcoidosis
Musculoskeletal and connective tissue disorders:
lupus-like syndrome
Neoplasms benign, malignant, and unspecified: melanoma and non-melanoma skin cancers, Merkel cell carcinoma
Nervous system disorders: convulsions, multiple sclerosis, demyelination, optic neuritis, transverse myelitis, paresthesias
Ocular disorders: uveitis, scleritis
Respiratory, thoracic and mediastinal disorders: interstitial lung disease
Skin and subcutaneous tissue disorders: cutaneous lupus erythematosus, cutaneous vasculitis (including leukocytoclastic vasculitis), erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, subcutaneous nodule, new or worsening psoriasis (all sub-types including pustular and palmoplantar)
Opportunistic infections, including atypical mycobacterial infection, herpes zoster, aspergillosis and Pneumocystis jiroveci pneumonia, and protozoal infections have also been reported in postmarketing use.

OVERDOSE
Toxicology studies have been performed in monkeys at doses up to 30 times the human dose with no evidence of dose-limiting toxicities. No dose-limiting toxicities have been observed during clinical trials of etanercept. Single IV doses up to 60 mg/m^2 (approximately twice the recommended dose) have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities.

INCOMPATIBILITIES
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

SHELF LIFE: 24 Months

PACKING INFORMATION
Etanercept is supplied in a 0.5 mL single-use prefilled syringe containing 25 mg etanercept.
Etanercept is supplied in a 1.0 mL single-use prefilled syringe containing 50 mg etanercept.

STORAGE AND HANDLING INSTRUCTION
Store refrigerated between 2 °C to 8 °C (36 °F to 46 °F) in the carton to protect from light. Do not shake. The preparation should not be allowed to freeze. Keep out of reach and sight of children.

INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION OF INTACEPT

This section is divided into the following subsections:

Introduction

Step 1: Setting up for an injection

Step 2: Choosing an injection site

Step 3: Injecting the Intacept solution

Step 4: Disposing of supplies

Introduction

The following instructions explain how to prepare and inject Intacept. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or his/her assistant on the techniques of self-injection. Do not attempt to administer an injection until you are sure that you understand how to prepare and give the injection.

The Intacept solution should not be mixed with any other medicine before use.

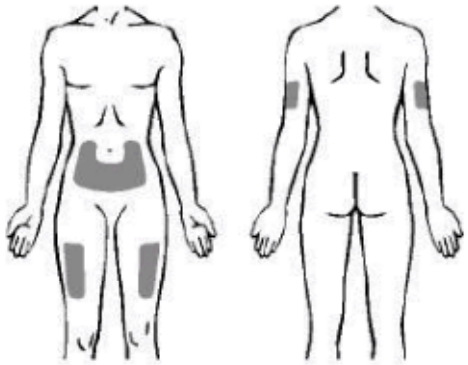
Step 1: Setting up for an injection

1. Select a clean, well-lit, flat working surface.
2. Take the Intacept carton containing the pre-filled syringes out of the refrigerator and place it on a flat work surface. Starting from one of the top corners, pull back the paper cover from the top and sides of the tray. Remove pre-filled syringe and alcohol swab and place them on your work surface. Do not shake the pre-filled syringe of Intacept.
   If you have any questions about storage, contact your doctor, nurse, or pharmacist for further instructions.
3. **You should allow 15 to 30 minutes for the Intacept solution in the syringe to reach room temperature. DO NOT** remove the needle cover while allowing it to reach room temperature. Waiting until the solution reaches room temperature may make the injection more comfortable for you. Do not warm Intacept in any other way (for example, do not warm it in a microwave or in hot water).
4. Assemble the additional supplies you will need for your injection. These include the alcohol swab from the Intacept carton and a cotton ball or gauze.
5. Wash your hands with soap and warm water.
6. Inspect the solution in the syringe. It should be clear or slightly opalescent, colourless or pale yellow, and may contain small white or almost transparent particles of protein. This appearance is normal for Intacept. Do not use the solution if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

Step 2: Choosing an injection site

1. Three recommended injection sites for Intacept using a pre-filled syringe include: (1) the front of the middle thighs; (2) the abdomen, except for the 5 cm area right around the navel; and (3) the outer area of the upper arms (see Diagram 1). If you are self injecting, you should not use the outer area of the upper arms.

Diagram 1



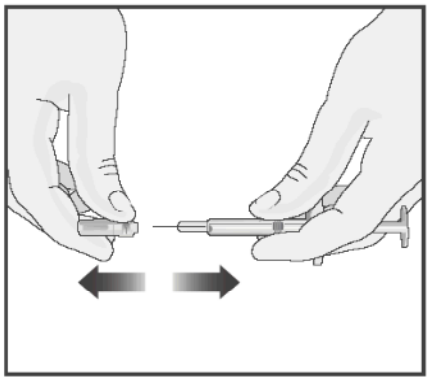
2. A different site should be used for each new injection. Each new injection should be given at least 3 cm from an old site. Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks. (It may be helpful to keep notes on the location of the previous injections.)
3. If you have psoriasis, you should try not to inject directly into any raised, thick, red, or scaly skin patches (" psoriasis skin lesions ").

Step 3: Injecting the Intacept solution

1. Wipe the site where Intacept is to be injected with the alcohol swab, using a circular motion. **Do NOT** touch this area again before giving the injection.
2. Pick up the pre-filled syringe from the flat work surface. Remove the needle cover by firmly pulling it straight off the syringe (see Diagram 2). **Be careful not to bend or twist the cover during removal to avoid damage to the needle.**

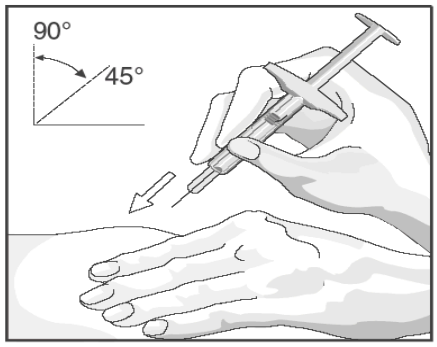
   When you remove the needle cover, there may be a drop of liquid at the end of the needle; this is normal. Do not touch the needle or allow it to touch any surface. Do not touch or bump the plunger. Doing so could cause the liquid to leak out.

Diagram 2



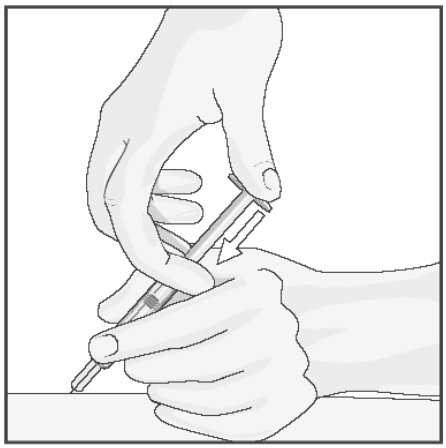
3. When the cleaned area of skin has dried, pinch and hold it firmly with one hand. With the other hand, hold the syringe like a pencil.
4. With a quick, short motion, push the needle all the way into the skin at an angle between 45 ° and 90 ° (see Diagram 3). With experience, you will find the angle that is most comfortable for you. Be careful not to push the needle into the skin too slowly, or with great force.

Diagram 3



5. When the needle is completely inserted into the skin, release the skin that you are holding. With your free hand, hold the syringe near its base to stabilise it. Then push the plunger to inject all of the solution at a **slow**, steady rate (see Diagram 4).

Diagram 4



6. When the syringe is empty, pull the needle out of the skin, being careful to keep it at the same angle as inserted. There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site for 10 seconds. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

Step 4: Disposing of supplies

The pre-filled syringe is for single-use administration only. The syringe and needle should **NEVER** be reused. **NEVER** recap a needle. Dispose of the needle and syringe as instructed by your doctor, nurse or pharmacist.

If you have any questions, please talk to a doctor, nurse or pharmacist who is familiar with Intacept.

Manufactured & Marketed by:

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