Altebrel™ (Etanercept)

Health Care Professional Information

Manufactured by:

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Warnings: serious infections and malignancies

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Serious Infections

Patients treated with Altebrel™ 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.

Altebrel™ should be dis continued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before Altebrel™ use and during therapy. Treatment for latent infection should be initiated prior to Altebrel™ use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with Altebrel™ should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Altebrel™, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Malignancies

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

1. Indications and Usage

1.1 Rheumatoid Arthritis

Altebrel™ 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). Altebrel™ can be initiated in combination with methotrexate (MTX) or used alone.

1.2 Polyarticular Juvenile Idiopathic Arthritis

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

1.3 PSOriatic arthritis

Altebrel™ 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). Altebrel™ can be used with or without MTX.

1.4 Ankylosing Spondylitis

Altebrel™ is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis (A.S).

1.5 Plaque PSOriasis

Altebrel™ is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque PSOriasis (PSO) who are candidates for systemic therapy or phototherapy.**2. Dosage and Administration**

Table 1. Dosing and administration for adult patients

patient population	**recommended dosage strength and frequency**
adult RA, A.S, and PSA patients	50 mg weekly
adult PSO patients	starting dose:50 mg twice weekly for 3 months maintenance dose:50 mg once weekly

2.1 adult rheumatoid arthritis, ankylosing spondylitis, and PSOriatic arthritis patients

MTX, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with Altebrel™.

based on a study of 50 mg Altebrel™ twice weekly in patients with RA that suggested higher incidence of adverse reactions but similar *American College of Rheumatology* (ACR) response rates, doses higher than 50 mg per week are not recommended.

2.2 adult plaque PSOriasis patients

In addition to the 50 mg twice weekly recommended starting dose, starting doses of 25 mg or 50 mg per week were shown to be efficacious. The proportion of responders was related to Altebrel™ dosage.

2.3 JIA patients

Table 2. Dosing and administration for juvenile idiopathic arthritis

pediatric patients weight	recommended dose
63 kg (138 pounds) or more	50 mg weekly
less than 63 kg (138 pounds)	0.8 mg/kg weekly

In JIApatients, glucocorticoids, NSAIDs, or analgesics may be continued during treatment with Altebrel™.

Higher doses of Altebrel™ have not been studied in pediatric patients.

2.4 preparation of Altebrel™

Altebrel™ is intended for use under the guidance and supervision of a physician. Patients may self-inject when deemed appropriate and if they receive medical follow-up, as necessary. Patients should not self-administer until they receive proper training in how to prepare and administer the correct dose. Injections should occur in the thigh, abdomen or outer area of the upper arm.

Patients can be advised to get in touch with OrchidPharmed Patient Support Center for Free injection education.

Phone: +982122382641

24/7 hotline: +989363094949

Also, there is a card in the Altebrel packaging, mentions all patient support centers and the name of educated nurses all over IRAN.

preparation of Altebrel™ using the single-use prefilled syringe

For a more comfortable injection, leave Altebrel™ at room temperature for about 15 to 30 minutes before injecting. Do not remove the needle cover while allowing the prefilled syringe to reach room temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. There may be small white particles of protein in the solution. This is not unusual for proteinaceous solutions. The solution should not be used if discolored or cloudy, or if foreign particulate matter is present.

When using the Altebrel™ single-use prefilled syringe, check to see if the amount of liquid in the prefilled syringe falls between the two purple fill level indicator lines on the syringe. If the syringe does not have the right amount of liquid, do not use that syringe.

2.5 monitoring to assess safety

Prior to initiating Altebrel™ and periodically during therapy, patients should be evaluated for active tuberculosis and tested for latent infection.

3. Dosage forms and strengths

- 50 mg single-use prefilled syringe

1 ml of a 50 mg/ml solution of Etanercept

- 25 mg single-use prefilled syringe

0.5 ml of a 50 mg/ml solution of Etanercept

4. Contraindications

Altebrel™ should not be administered to patients with sepsis.

5. Warnings and precautions

5.1 serious infections

Patients treated with Altebrel™ 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 Altebrel™ 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 Altebrel™.

Altebrel™ should be discontinued if a patient develops a serious infection or sepsis. a patient who develops a new infection during treatment with Altebrel™ should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

<u>Tuberculosis</u>

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, post marketing 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 Altebrel™ and periodically during therapy. Tests for latent tuberculosis infection may be falsely negative while on therapy with Altebrel™.

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 Altebrel™, even for patients previously vaccinated with bacille calmette-guerin (BCG).

Anti-tuberculosis therapy should also be considered prior to initiation of Altebrel™ 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 Altebrel™ 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 Etanerceptclinical 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.

5.2 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 Altebrel™ in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders.

5.3 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. during the controlled portions of Etanercepttrials in adult patients with RA, A.S, and PSA, 2 lymphomas were observed among 3306 Etanercepttreated patients versus 0 among 1521 control patients (duration of controlled treatment ranged from 3 to 36 months).

Among 6543 adult rheumatology (RA, PSA, and A.S) patients treated with Etanerceptin 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. This was 3-fold higher than the rate of lymphoma expected in the general u.s. population based on the surveillance, epidemiology, and end results (seer) database. 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.

Among 4410 adult PSO patients treated with Etanerceptin clinical trials up to 36 months, representing approximately 4278 patient-years of therapy, the observed rate of lymphoma was 0.05 cases per 100 patient-years, which is comparable to the rate in the general population. No cases were observed in Etanerceptor placebo-treated patients during the controlled portions of these trials.

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 Etanercepttrials, 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 Etanerceptin 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 Etanerceptclinical studies.

For malignancies other than lymphoma and non-melanoma skin cancer, there was no difference in exposure-adjusted rates between the Etanerceptand control arms in the controlled portions of clinical studies for all indications. Analysis of the malignancy rate in combined controlled and uncontrolled portions of studies has demonstrated that types and rates are similar to what is expected in the general u.s. population based on the seer database and suggests no increase in rates over time. Whether treatment with Emight 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, A.S) 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.

Post marketing 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 post marketing and are derived from a variety of sources, including registries and spontaneous post marketing reports.

In clinical trials of 1140 pediatric patients representing 1927.2 patient-years of therapy, no malignancies, including lymphoma or NMSC, have been reported.

Post marketing use

In global postmarketing adult and pediatric use, lymphoma and other malignancies have been reported.

5.4 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 post marketing 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 Altebrel™ in patients who also have heart failure, and monitor patients carefully.

5.5 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 Altebrel™ 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 Altebrel™. discontinuation of Altebrel™ 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.

5.6 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 Altebrel™ 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 Altebrel™ and initiating anti-viral therapy with appropriate supportive treatment. the safety of resuming Altebrel™ 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.

5.7 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 Altebrel™ should be discontinued immediately and appropriate therapy initiated.

5.8 immunizations

Live vaccines should not be given concurrently with Altebrel™. 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 Altebrel™ therapy.

5.9 autoimmunity

Treatment with Altebrel™ 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 Altebrel™. If a patient develops symptoms and findings suggestive of a lupus-like syndrome or autoimmune hepatitis following treatment with Altebrel™, treatment should be discontinued and the patient should be carefully evaluated.

5.10 immunosuppression

TNF mediates inflammation and modulates cellular immune responses. TNF-blocking agents, including Altebrel™, affect host defenses against infections. The effect of TNF inhibition on the development and course of malignancies is not fully understood. in a study of 49 patients with RA treated with Etanercept, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations.

5.11 use in Wegener's Granulomatosis patients

The use of Altebrel™ 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 no cutaneous solid malignancies and was not associated with improved clinical outcomes when compared with standard therapy alone.

5.12 use with Anakinra or Abatacept

Use of Altebrel™ with Anakinra or Abatacept is not recommended.

5.13 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 Altebrel™ in patients with moderate to severe alcoholic hepatitis.

6. Adverse reactions

6.1 the most common adverse reactions with Altebrel™ were infections and injection site reactions.

6.1 adverse reactions significant

- >10%:
  - Central nervous system: headache (17% to 19%)
  - Dermatologic: rash (3% to 13%)
  - Gastrointestinal: abdominal pain (5%; children 19%), diarrhea (3% to 16%), vomiting (3%; children 13%)
  - local: injection site reaction (14% to 43%; bleeding, bruising, erythema, itching, pain, or swelling)
  - Respiratory: respiratory tract infection (21% to 54%; upper: 38% to 65%), rhinitis (12%)
  - Miscellaneous: infection (50% to 81%; children 62%), positive antidouble-stranded dna antibodies (15% by ria, 3% by crithidia luciliae assay), positive ana (11%)
- ≥3% to 10%:
  - Central nervous system: dizziness (7%), fever (2% to 3%)
  - Dermatologic: pruritus (2% to 5%)
  - Gastrointestinal: nausea (children 9%), dyspepsia (4%)
  - Neuromuscular & skeletal: weakness (5%)
  - Respiratory: pharyngitis (7%), cough (6%), respiratory disorder (5%), sinusitis (3%)
- <3% (limited to important or life-threatening):
  - abscess, adenopathy, allergic reactions, anemia, angioedema, anorexia, aplastic anemia, appendicitis, aseptic meningitis, aspergillosis, bursitis, cerebral ischemia, cholecystitis, coagulopathy, cutaneous ulcer, deep vein thrombosis, demyelinating

cns disorders (suggestive of multiple sclerosis, transverse myelitis, or optic neuritis), depression, erythema multiforme, esophagitis, gastritis, gastroenteritis, gastrointestinal hemorrhage, heart failure, hepatitis (autoimmune), herpes zoster, hydrocephalus (with normal pressure), hyper-/hypotension, hypersensitivity, inflammatory bowel disease, interstitial lung disease, intestinal perforation, leukemias, leukopenia, lupus erythematous (cutaneous), lupus-like syndrome, lymphadenopathy, lymphomas, malignancies, melanoma, membranous glomerulopathy, merkel cell carcinoma, mi, mouth ulcer, multiple sclerosis, myocardial ischemia, neutropenia, nonmelanoma skin cancer, optic neuritis, pancreatitis, pancytopenia, pneumocystis jiroveci pneumonia, polymyositis, PSOriasis (including new onset, palmoplantar, pustular, or exacerbation), pulmonary disease, pulmonary embolism, renal calculus, sarcoidosis, scleritis, seizure, stroke, stevens-johnson syndrome, subcutaneous nodules, thrombocytopenia, thrombophlebitis, toxic epidermal necrolysis, tuberculosis, tuberculous arthritis, urinary tract infection, uveitis, varicella infection, vasculitis (cutaneous and systemic), weight gain

7. Drug interactions

For a complete list of Drug-Drug interactions please visit Drugs.com.

7.1 vaccines

most PSA patients receiving Altebrel™ 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 Altebrel™. The clinical significance of this is unknown. Patients receiving Altebrel™ may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving Altebrel™.

Patients with a significant exposure to varicella virus should temporarily discontinue Altebrel™ therapy and be considered for prophylactic treatment with varicella zoster immune globulin.

7.2 immune-modulating biologic products

In a study in which patients with active RA were treated for up to 24 weeks with concurrent Etanerceptand Anakinra therapy, a 7% rate of serious infections was observed, which was higher than that observed with Etanercept alone (0%) 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.

7.3 cyclophosphamide

The use of Altebrel™ in patients receiving concurrent cyclophosphamide therapy is not recommended.

7.4 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.

8. use in specific populations

8.1 pregnancy

Pregnancy category B

Risk summary

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.

8.3 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 Altebrel™ is administered to a nursing woman. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Altebrel™ and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

8.4 pediatric use

Etanercept has not been studied in children < 2 years of age with JIA. The safety and efficacy of Etanercept in pediatric patients with PSO 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.

8.5 geriatric use

A total of 480 RA patients' ages 65 years or older have been studied in clinical trials. In PSO randomized clinical trials, a total of 138 out of 1965 patients treated with Etanercept or placebo were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but the number of geriatric PSO patients is too small to determine whether they respond differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

8.6 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.

9. over dosage

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 (approximately twice the recommended dose) have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities.

10. Description

Altebrel™ (Etanercept) 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 IgG_1. The FC component of Etanercept contains the CH2 domain, the CH3 domain and hinge region, but not the CH1 domain of igg1. Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CGO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

The solution of Altebrel™ in the single-use prefilled syringe and the single-use prefilled sureclick autoinjector is clear and colorless, sterile, preservative-free, and is formulated at ph. 6.3 ± 0.2.

reconstitution with 1 ml of the supplied sterile bacteriostatic water for injection, usp (containing 0.9% benzyl alcohol) yields a multiple-use, clear, and colorless solution with a ph of 7.4 ± 0.3.

Table 3. Contents of Altebrel™

presentation	active ingredient content	inactive ingredients content
Altebrel™ 50 mg prefilled syringe	1 ml of a 50 mg/ml solution of Etanercept	1% sucrose 100 mm sodium chloride 25 mm l-arginine hydrochloride 25 mm sodium phosphate
Altebrel™ 25 mg prefilled syringe	0.5 ml of a 50 mg/ml solution of Etanercept	1% sucrose 100 mm sodium chloride 25 mm l-arginine hydrochloride 25 mm sodium phosphate

11. Clinical pharmacology

11.1 mechanism of action

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. it plays an important role in the inflammatory processes of RA, polyarticular JIA, PSA, and as and the resulting joint pathology. In addition, TNF plays a role in the inflammatory process of PSO. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, JIA, PSA, as, and PSO.

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. In in vitro studies, large complexes of Etanercept with TNF-α were not detected and cells expressing transmembrane TNF (that binds Etanercept) are not lysed in the presence or absence of complement.

11.2 pharmacodynamics

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.

11.3 pharmacokinetics

after administration of 25 mg of Etanercept by a single SC injection to 25 patients with 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 (C) of 1.1 ± 0.6 mcg/ml and time to C 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 C 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 auchr. (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. The pharmacokinetic parameters in patients with PSO were similar to those seen in patients with RA.

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) C, C, 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).

Patients with JIA (ages 4 to 17 years) were administered 0.4 mg/kg of Etanercept twice weekly (up to a maximum dose of 50 mg per week) for up to 18 weeks. The mean serum concentration after repeated sc dosing was 2.1 mcg/ml, with a range of 0.7 to 4.3 mcg/ml. limited data suggest that the clearance of Etanercept is reduced slightly in children ages 4 to 8 years. population pharmacokinetic analyses predict that the pharmacokinetic differences between the regimens of 0.4 mg/kg twice weekly and 0.8 mg/kg once weekly in JIA patients are of the same magnitude as the differences observed between twice weekly and weekly regimens in adult RA patients.
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 MTX in RA patients. No formal pharmacokinetic studies have been conducted to examine the effects of renal or hepatic impairment on Etanercept disposition.

12. Nonclinical toxicology

12.1 carcinogenesis, mutagenesis, impairment of fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of Etanercept or its effect on fertility. Mutagenesis studies were conducted in vitro and in vivo, and no evidence of mutagenic activity was observed.

13. Clinical studies

13.1 adult rheumatoid arthritis

The safety and efficacy of Altebrel™ were assessed in four randomized, double-blind, controlled studies.

The results of the trial were expressed in percentage of patients with improvement in RA using ACR response criteria.

jamshidi a. et al. (2013) performed a studyThis to compare the efficacy and safety of a locally developed Etanercept (Altebrel™) and Enbrel ® on the patients with active Rheumatoid Arthritis.

It was a non-inferiority randomized double-blind parallel clinical trial. 128 patients with active rheumatoid arthritis who meet the inclusion/exclusion criteria have been planned to enter to the study and compared the efficacy and safety of 50 mg/week SC administration of Enbrel® and Altebrel™ this was a randomized, double-blind, controlled study to compare the efficacy and safety profile of with enbrel® in patients with active rheumatoid arthritis diagnosed by ACR 20 criteria. The percent of the patients, who have improved according to the *American college of rheumatology* response criteria for 20%, will be measured after 3 and 6 months of treatment beginning and compared between the groups.

The primary endpoint of the study was to compare the percentage of patients who have improved according to criteria of ACR 20. after signing the written informed consents, a total of 128 patients have been planned to randomize and assign to receive enbrel® or Altebrel™ over a six-month period (group a=64, group b=64). 50 mg/week of either of the drugs was administered to each patient subcutaneously. The percentage of improved patients according to ACR 20/50/70 was reported as well as the frequency of adverse events. The data were

coded and entered to SPSS ver.18 and then analyzed, using both parametric and non-parametric tests. $p \leq 0.05$ was considered as a statistically significant value.

Evaluating each of the seven parts of ACR 20 criteria in the 3rd and 6th month of the trial showed no significant differences between two groups. Furthermore, ACR 50 and ACR 70 criteria of the American college of rheumatology proved that drug effectiveness for both treatment groups were comparable to each other.

According to the study findings, there is no statistically significant difference in efficacy and safety between Altebrel™ and Enbrel.

Finally it is concluded that these two drugs are similar in safety and efficacy for treatment of patients with active rheumatoid arthritis.

Table 4. comparison of the patients' percentages who met ACR20, 50, 70 after 3 months of treatment in two groups

ACR (%)	Altebrel™ mean ± SD	Enbrel mean ± SD	ci	p-value*
20	80±40	78±40	(-19, 23)	0.85
50	71±46	48±51	(-2, 48)	0.07
70	42±50	33±48	(-16,34)	0.48

* analyzed by z-test approximation

Table 5. comparison of the patients' percentages who met ACR20, 50, 70 after 6 months of treatment in two groups

ACR (%)	Altebrel™ mean ± SD	Enbrel mean ± SD	ci	p-value*
20	75±44	85±36	(-30, 10)	0.34
50	69±47	78±42	(-31, 14)	0.43
70	53±51	59±50	(-31, 19)	0.64

* analyzed by z-test approximation

14. How supplied/storage and handling

Administration of one 50 mg Altebrel™ prefilled syringe provides a dose equivalent to two 25 mg Altebrel™ prefilled syringes, as recommended.

14.1 Altebrel™ single-use prefilled syringe

Each Altebrel™ single-use prefilled syringe contains 50 mg/ml of Etanercept in a single-dose syringe with a 27-gauge, ½-inch needle.

50 mg single-use prefilled syringe	carton of 4
25 mg single-use prefilled syringe	carton of 4

Altebrel™ should be refrigerated at 36°f to 46°f (2°c to 8°c). Do not use Altebrel™ beyond the expiration date stamped on the carton or barrel label. Do not shake. Store Altebrel™ in the original carton to protect from light or physical damage.

for convenience, storage of individual syringes at room temperature at 68°f to 77°f (20°c to 25°c) for a maximum single period of 14 days is permissible, with protection from light and sources of heat. once a syringe has been stored at room temperature, it should not be placed back into the refrigerator. if not used within 14 days at room temperature, the syringe should be discarded.

Do not store Altebrel™ in extreme heat or cold. Do not freeze.

Keep out of the reach of children.

15. Patient counseling information

The healthcare provider should ask the patient questions to determine any risk factors for treatment. Patients developing signs and symptoms of infection should seek medical evaluation immediately.

15.1 patient counseling

Patients should be advised of the potential benefits and risks of Altebrel™. Physicians should instruct their patients to read the medication guide before starting Altebrel™ therapy and to reread each time the prescription is renewed.

Infections

Inform patients that Altebrel™ may lower the ability of their immune system to fight infections. Advise patients of the importance of contacting their doctor if they develop any symptoms of infection, tuberculosis or reactivation of hepatitis b virus infections.

Other medical conditions

Advise patients to report any signs of new or worsening medical conditions, such as central nervous system demyelinating disorders, heart failure or autoimmune disorders, such as lupus-like syndrome or autoimmune hepatitis. Counsel about the risk of lymphoma and other malignancies while receiving Altebrel™. Advise patients to report any symptoms suggestive of a pancytopenia, such as bruising, bleeding, persistent fever or pallor.

15.2 administration of Altebrel™

If a patient or caregiver is to administer Altebrel™, the patient or caregiver should be instructed in injection techniques and how to measure and administer the correct dose. The first injection should be performed under the supervision of a qualified healthcare professional. The patient’s or caregiver’s ability to inject subcutaneously should be assessed. Patients and caregivers should be instructed in the technique, as well as proper syringe and needle disposal, and be cautioned against reuse of needles and syringes.

if the product is intended for multiple use, additional syringes, needles and alcohol swabs will be required.

Patients can be advised to get in touch with OrchidPharmed Patient Support Center for any question or report any Adverse Drug event.

Phone:

24/7 hotline: +989363094949