

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ETANERCEPT safely and effectively. See full prescribing information for ETANERCEPT.

ETANERCEPT injection, for subcutaneous use
ETANERCEPT for injection, for subcutaneous use
Initial U.S. Approval: 1998

This product is Enbrel® (etanercept).

WARNING: SERIOUS INFECTIONS and MALIGNANCIES See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS

- Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. (5.1)
- Etanercept should be discontinued if a patient develops a serious infection or sepsis during treatment. (5.1)
- Perform test for latent TB; if positive, start treatment for TB prior to starting Etanercept. (5.1)
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)

MALIGNANCIES

- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF-blockers, including Etanercept. (5.3)

INDICATIONS AND USAGE

Etanercept is a tumor necrosis factor (TNF) blocker indicated for the treatment of:

Adult patients with:

- Rheumatoid Arthritis (RA) (1.1)
- Psoriatic Arthritis (PsA) (1.3)
- Ankylosing Spondylitis (AS) (1.4)
- Plaque Psoriasis (PsO) (1.5)

Pediatric patients with:

- Polyarticular Juvenile Idiopathic Arthritis (pJIA), 2 years of age or older (1.2)
- Juvenile Psoriatic Arthritis, 2 years of age or older (JPsA) (1.6)
- Plaque Psoriasis, 4 years of age or older (1.5)

DOSAGE AND ADMINISTRATION

Etanercept is administered by subcutaneous injection.

Patient Population	Recommended Dose and Frequency
Adult RA and PsA (2.3)	50 mg once weekly with or without methotrexate (MTX)
AS (2.3)	50 mg once weekly
Adult PsO (2.3)	50 mg twice weekly for 3 months, followed by 50 mg once weekly
pJIA, Pediatric PsO and JPsA (2.4)	0.8 mg/kg weekly, with a maximum of 50 mg per week

DOSAGE FORMS AND STRENGTHS

- Injection: 25 mg/0.5 mL and 50 mg/mL solution in a single-dose prefilled syringe (3)
- Injection: 50 mg/mL solution in single-dose prefilled SureClick® autoinjector (3)
- Injection: 25 mg/0.5 mL solution in a single-dose vial (3)

CONTRAINDICATIONS

Etanercept is contraindicated in patients with sepsis. (4)

WARNINGS AND PRECAUTIONS

- Do not start Etanercept during an active infection. If an infection develops, monitor carefully and stop Etanercept if infection becomes serious. (5.1)
- Consider empiric anti-fungal therapy for patients at risk for invasive fungal infections who develop a severe systemic illness on Etanercept (those who reside or travel to regions where mycoses are endemic). (5.1)
- Demyelinating disease, exacerbation or new onset, may occur. (5.2)
- Cases of lymphoma have been observed in patients receiving TNF-blocking agents. (5.3)
- Congestive heart failure, worsening or new onset, may occur. (5.4)
- Advise patients to seek immediate medical attention if symptoms of pancytopenia or aplastic anemia develop, and consider stopping Etanercept. (5.5)
- Monitor patients previously infected with hepatitis B virus for reactivation during and several months after therapy. If reactivation occurs, consider stopping Etanercept and beginning anti-viral therapy. (5.6)
- Anaphylaxis or serious allergic reactions may occur. (5.7)
- Stop Etanercept if lupus-like syndrome or autoimmune hepatitis develops. (5.9)

ADVERSE REACTIONS

Most common adverse reactions (incidence > 5%): infections and injection site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Live vaccines – Avoid concurrent administration with Etanercept (5.8, 7.1)
- Anakinra – Increased risk of serious infection (5.12, 7.2)
- Abatacept – Increased risk of serious adverse events, including infections (5.12, 7.2)
- Cyclophosphamide – Not recommended for use with Etanercept. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2026

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS and MALIGNANCIES

SERIOUS INFECTIONS

Patients treated with Etanercept are at increased risk for developing serious infections that may lead to hospitalization or death [see *Warnings and Precautions (5.1) and Adverse Reactions (6)*]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Etanercept should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Test patients for latent tuberculosis before Etanercept use and during therapy. Initiate treatment for latent infection prior to Etanercept 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. Consider empiric anti-fungal therapy 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 Etanercept should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with Etanercept, 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

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

1.2 Polyarticular Juvenile Idiopathic Arthritis

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

1.3 Psoriatic Arthritis

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

1.4 Ankylosing Spondylitis

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

1.5 Plaque Psoriasis

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

1.6 Juvenile Psoriatic Arthritis

Etanercept is indicated for the treatment of active juvenile psoriatic arthritis (JPsA) in pediatric patients 2 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Testing and Procedures Prior to Treatment Initiation

Perform the following evaluations and procedures prior to initiating treatment with Etanercept:

- Prior to initiating Etanercept and periodically during therapy, evaluate patients for active tuberculosis and test for latent infection [see *Warnings and Precautions (5.1)*].
- Complete all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with Etanercept [see *Warnings and Precautions (5.8)*].

2.2 Important Administration Instructions

Administration of one 50 mg Etanercept single-dose prefilled syringe or one Etanercept single-dose prefilled SureClick autoinjector provides a dose equivalent to two 25 mg Etanercept single-dose prefilled syringes or two 25 mg Etanercept single-dose vials.

2.3 Recommended Dosage in Adult Patients with Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, and Plaque Psoriasis

Etanercept is administered by subcutaneous injection (Table 1).

Table 1. Recommended Dosage for Adult Patients with RA, AS, PsA and PsO

Patient Population	Recommended Dosage
Adult RA, AS, and PsA	50 mg weekly
Adult PsO	<u>Starting Dose:</u> 50 mg twice weekly for 3 months <u>Maintenance Dose:</u> 50 mg once weekly

See the Etanercept “Instructions for Use” insert for detailed information on injection site selection and dose administration [see *Dosage and Administration (2.3)* and *Patient Counseling Information (17)*].

Adult Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis Patients

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

Based on a study of 50 mg Etanercept 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.

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 Etanercept dosage [see *Clinical Studies (14.5)*].

2.4 Recommended Dosage for Pediatric Patients with Polyarticular Juvenile Idiopathic Arthritis, Plaque Psoriasis, and Juvenile Psoriatic Arthritis

The recommended weight-based dosage for pediatric patients is administered by subcutaneous injection (Table 2).

Table 2. Recommended Dosage for Pediatric Patients with pJIA, PsO and JPsA

Body Weight	Recommended Dosage
63 kg (138 pounds) or more	50 mg weekly
Less than 63 kg (138 pounds)	0.8 mg/kg weekly

To achieve pediatric doses other than 25 mg or 50 mg, use Etanercept solution in a single-dose vial.

Dosages of Etanercept higher than those described in Table 2 have not been studied in pediatric patients.

In pJIA patients, glucocorticoids, NSAIDs, or analgesics may be continued during treatment with Etanercept.

2.5 Preparation Instructions for Etanercept

Etanercept 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. Administer injections subcutaneously in the thigh, abdomen or outer area of the upper arm.

The Etanercept devices are not made with natural rubber latex.

The Etanercept “Instructions for Use” insert for each presentation contains more detailed instructions on injection site selection and the preparation of Etanercept.

Preparation of Etanercept Single-dose Prefilled Syringe

For a more comfortable injection, leave Etanercept prefilled syringes 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.

Inspect 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 Etanercept single-dose 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.

Preparation of Etanercept Single-dose Prefilled SureClick Autoinjector

Leave the autoinjector at room temperature for at least 30 minutes before injecting. DO NOT remove the needle cover while allowing the prefilled syringe to reach room temperature.

Inspect 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.

Preparation of Etanercept Single-dose Vial

For a more comfortable injection, leave Etanercept vial(s) at room temperature for at least 30 minutes before injecting. DO NOT remove the vial cap while allowing the vial to reach room temperature.

Inspect 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 Etanercept single-dose vial, administer the correct dose of solution using the following recommended materials:

- A 1 mL Luer-Lock syringe.
- A withdrawal needle with Luer-Lock connection, sterile, 22-gauge, length 1 ½ inch.
- An injection needle with Luer-Lock connection, sterile, 27-gauge, length ½ inch.

Two vials may be required to administer the total prescribed dose. Use the same syringe for each vial. The vial does not contain preservatives; therefore, discard unused portions.

3 DOSAGE FORMS AND STRENGTHS

- Injection: 25 mg/0.5 mL and 50 mg/mL clear, colorless solution in a single-dose prefilled syringe
- Injection: 50 mg/mL clear, colorless solution in a single-dose prefilled SureClick autoinjector
- Injection: 25 mg/0.5 mL clear, colorless solution in a single-dose vial

4 CONTRAINDICATIONS

Etanercept is contraindicated in patients with sepsis.

5 WARNINGS AND PRECAUTIONS

5.1 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 [see *Adverse Reactions (6.1)*].

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. Tests for latent tuberculosis infection may be falsely negative while on therapy with Etanercept.

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 *Bacillus 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.

5.2 Neurologic Reactions

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-Barre 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 [*see Postmarketing Experience (6.3)*].

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 Etanercept trials in adult patients with RA, AS, and PsA, 2 lymphomas were observed among 3306 Etanercept-treated patients versus 0 among 1521 control patients (duration of controlled treatment ranged from 3 to 36 months).

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. 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 Etanercept in 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 Etanercept- or 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 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. 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 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 versus 0.37 cases per 100 patient-years among 1521 control-treated patients representing 1077 patient-years. Among 1245 adult PsO 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 versus 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.

5.4 New Onset or Worsening of 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 [see *Adverse Reactions (6.2)*]. 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.

5.5 Hematologic Reactions

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 ($ANC < 1 \times 10^9/L$). 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 requiring 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.

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, discontinue administration of Etanercept and initiate appropriate therapy immediately.

5.8 Immunizations

Avoid concurrent administration of live vaccines with Etanercept. It is recommended that patients, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating Etanercept therapy [see *Drug Interactions (7.1)* and *Use in Specific Populations (8.4)*].

5.9 Autoimmunity

Treatment with Etanercept may result in the formation of autoantibodies [see *Adverse Reactions (6.1)*] and, rarely (< 0.1%), in the development of a lupus-like syndrome or autoimmune hepatitis [see *Adverse Reactions (6.2)*], 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, discontinue treatment and evaluate the patient.

5.10 Immunosuppression

TNF mediates inflammation and modulates cellular immune responses. TNF-blocking agents, including Etanercept, 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 [see *Warnings and Precautions (5.1, 5.3)* and *Adverse Reactions (6.1)*].

5.11 Not Recommended for Use in Patients with Granulomatosis with Polyangiitis Receiving Immunosuppressants

The use of Etanercept in patients with granulomatosis with polyangiitis receiving immunosuppressive agents is not recommended. In a study of patients with granulomatosis with polyangiitis, 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 [see *Drug Interactions (7.3)*].

5.12 Not Recommended for Use with Anakinra or Abatacept

Use of Etanercept with anakinra or abatacept is not recommended [see *Drug Interactions (7.2)*].

5.13 Increased Mortality 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious Infections [see *Warnings and Precautions (5.1)*]
- Neurologic Reactions [see *Warnings and Precautions (5.2)*]
- Malignancies [see *Warnings and Precautions (5.3)*]
- Patients with Heart Failure [see *Warnings and Precautions (5.4)*]
- Hematologic Reactions [see *Warnings and Precautions (5.5)*]
- Hepatitis B Reactivation [see *Warnings and Precautions (5.6)*]
- Allergic Reactions [see *Warnings and Precautions (5.7)*]
- Autoimmunity [see *Warnings and Precautions (5.9)*]
- Immunosuppression [see *Warnings and Precautions (5.10)*]

6.1 Clinical Trials Experience

Across clinical studies and postmarketing experience, the most serious adverse reactions with Etanercept were infections, neurologic events, CHF, and hematologic events [see *Warnings and Precautions (5)*]. The most common adverse reactions with Etanercept were infections and injection site reactions.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Adult Patients with Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, or Plaque Psoriasis

The data described below reflect exposure to Etanercept in 2219 adult patients with RA followed for up to 80 months, in 182 patients with PsA for up to 24 months, in 138 patients with AS for up to 6 months, and in 1204 adult patients with PsO for up to 18 months.

In controlled trials, the proportion of Etanercept-treated patients who discontinued treatment due to adverse events was approximately 4% in the indications studied.

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 [see *Warnings and Precautions (5)*, *Use in Specific Populations (8.4)*, and *Clinical Studies (14.2, 14.6)*].

In a 48-week clinical study in 211 children aged 4 to 17 years with pediatric PsO, the adverse reactions reported were similar to those seen in previous studies in adults with PsO. Long-term safety profile for up to 264 additional weeks was assessed in an open-label extension study and no new safety signals were identified.

In open-label clinical studies of children with JIA, adverse reactions reported in those ages 2 to 4 years were similar to adverse reactions reported in older children.

Infections

Infections, including viral, bacterial, and fungal infections, have been observed in adult and pediatric patients. Infections have been noted in all body systems and have been reported in patients receiving Etanercept alone or in combination with other immunosuppressive agents.

In controlled portions of trials, the types and severity of infection were similar between Etanercept and the respective control group (placebo or MTX for RA and PsA patients) in RA, PsA, AS and PsO patients. Rates of infections in RA and adult PsO patients are provided in Table 3 and Table 4, respectively. Infections consisted primarily of upper respiratory tract infection, sinusitis and influenza.

In controlled portions of trials in RA, PsA, AS and PsO, the rates of serious infection were similar (0.8% in placebo, 3.6% in MTX, and 1.4% in Etanercept/Etanercept + MTX-treated groups). In clinical trials in 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 clinical trials in adult PsO patients, serious infections experienced by patients have included, but are not limited to, pneumonia, cellulitis, gastroenteritis, abscess and osteomyelitis. The rate of serious infections was not increased in open-label extension trials and was similar to that observed in Etanercept- and placebo-treated patients from controlled trials.

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 [see *Warnings and Precautions (5.1)*].

The types of infections reported in pediatric patients with PsO and JIA were generally mild and consistent with those commonly seen in the general pediatric population. Two JIA patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae.

Injection Site Reactions

In placebo-controlled trials in rheumatologic indications, approximately 37% of patients treated with Etanercept developed injection site reactions. In controlled trials in patients with PsO, 15% of adult patients and 7% of pediatric patients treated with Etanercept developed injection site reactions during the first 3 months of treatment. 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.

Other Adverse Reactions

Table 3 summarizes adverse reactions reported in adult RA patients. The types of adverse reactions seen in patients with PsA or AS were similar to the types of adverse reactions seen in patients with RA.

Table 3. Percent of Adult RA Patients Experiencing Adverse Reactions in Controlled Clinical Trials

Adverse Reaction	Placebo-Controlled ^a (Studies I, II, and a Phase 2 Study)		Active-Controlled ^b (Study III)	
	Placebo (N = 152)	Etanercept ^c (N = 349)	MTX (N = 217)	Etanercept ^c (N = 415)
	Percent of Patients		Percent of Patients	
Infection ^d (total)	39	50	86	81
Upper Respiratory Infections ^e	30	38	70	65
Non-upper Respiratory Infections	15	21	59	54
Injection Site Reactions	11	37	18	43
Diarrhea	9	8	16	16
Rash	2	3	19	13
Pruritus	1	2	5	5
Pyrexia	-	3	4	2

Adverse Reaction	Placebo-Controlled ^a (Studies I, II, and a Phase 2 Study)		Active-Controlled ^b (Study III)	
	Placebo (N = 152)	Etanercept ^c (N = 349)	MTX (N = 217)	Etanercept ^c (N = 415)
	Percent of Patients		Percent of Patients	
Urticaria	1	-	4	2
Hypersensitivity	-	-	1	1

^a Includes data from the 6-month study in which patients received concurrent MTX therapy in both arms.

^b Study duration of 2 years.

^c Any dose.

^d Includes bacterial, viral and fungal infections.

^e Most frequent Upper Respiratory Infections were upper respiratory tract infection, sinusitis and influenza.

In placebo-controlled adult PsO trials, the percentages of patients reporting adverse reactions in the 50 mg twice a week dose group were similar to those observed in the 25 mg twice a week dose group or placebo group.

Table 4 summarizes adverse reactions reported in adult PsO patients from Studies I and II.

Table 4. Percent of Adult PsO Patients Experiencing Adverse Reactions in Placebo-Controlled Portions of Clinical Trials (Studies I & II)

Adverse Reaction	Placebo (N = 359)	Etanercept ^a (N = 876)
	Percent of Patients	
Infection ^b (total)	28	27
Non-upper Respiratory Infections	14	12
Upper Respiratory Infections ^c	17	17
Injection Site Reactions	6	15
Diarrhea	2	3
Rash	1	1
Pruritus	2	1
Urticaria	-	1
Hypersensitivity	-	1
Pyrexia	1	-

^a Includes 25 mg subcutaneous (SC) once weekly (QW), 25 mg SC twice weekly (BIW), 50 mg SC QW, and 50 mg SC BIW doses.

^b Includes bacterial, viral and fungal infections.

^c Most frequent Upper Respiratory Infections were upper respiratory tract infection, nasopharyngitis and sinusitis.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etanercept in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Immunogenicity

Patients with RA, PsA, AS or PsO were tested at multiple time points for antibodies to etanercept. 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, PsA, AS or PsO. These antibodies were all non-neutralizing. Results from JIA patients were similar to those seen in adult RA patients treated with Etanercept.

In adult PsO studies that evaluated the exposure of etanercept for up to 120 weeks, the percentage of patients testing positive at the assessed time points of 24, 48, 72 and 96 weeks ranged from 3.6%-8.7% and were all non-neutralizing. The percentage of patients testing positive increased with an increase in the duration of study; 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.

In pediatric PsO studies, approximately 10% of subjects developed antibodies to etanercept by Week 48 and approximately 16% of subjects developed antibodies to etanercept by Week 264. All of these antibodies were non-neutralizing. However, because of the limitations of the immunogenicity assays, the incidence of binding and neutralizing antibodies may not have been reliably determined.

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.

Autoantibodies

Patients with RA had serum samples tested for autoantibodies at multiple time points. In RA Studies I and II, the percentage of patients evaluated for antinuclear antibodies (ANA) who developed new positive ANA (titer \geq 1:40) was higher in patients treated with Etanercept (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with Etanercept compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of patients treated with Etanercept compared to none of placebo-treated patients). The proportion of patients treated with Etanercept who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. In RA Study III, no pattern of increased autoantibody development was seen in Etanercept patients compared to MTX patients [see *Warnings and Precautions (5.9)*].

6.3 Postmarketing Experience

The following adverse reactions have been identified 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 [see <i>Warnings and Precautions (5.5)</i>]
Cardiac disorders:	congestive heart failure [see <i>Warnings and Precautions (5.4)</i>]
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 [see <i>Warnings and Precautions (5.3)</i>]
Nervous system disorders:	convulsions, multiple sclerosis, demyelination, optic neuritis, transverse myelitis, paresthesias, headache [see <i>Warnings and Precautions (5.2)</i>]
Ocular disorders:	uveitis, scleritis
Renal and urinary disorders:	glomerulonephritis
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.

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

7 DRUG INTERACTIONS

Specific drug interaction studies have not been conducted with Etanercept.

7.1 Vaccines

Most PsA 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 [see *Warnings and Precautions* (5.8, 5.10)].

7.2 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%) [see *Warnings and Precautions* (5.12)] 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 < $1 \times 10^9/L$).

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 [see *Warnings and Precautions* (5.12)].

7.3 Cyclophosphamide

The use of Etanercept in patients receiving concurrent cyclophosphamide therapy is not recommended [see *Warnings and Precautions* (5.11)].

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

Risk Summary

Available studies with use of etanercept during pregnancy do not reliably support an association between etanercept and major birth defects. Clinical data are available from the Organization of Teratology Information Specialists (OTIS) Etanercept Pregnancy Registry in women with rheumatic diseases or psoriasis and a Scandinavian study in pregnant women with chronic inflammatory disease. Both the OTIS Registry and the Scandinavian study showed the proportion of liveborn infants with major birth defects was higher for women exposed to etanercept compared to diseased etanercept unexposed women. However, the lack of pattern of major birth defects is reassuring and differences between exposure groups (e.g., disease severity) may have impacted the occurrence of birth defects (*see Data*).

Reports of etanercept use during the third trimester of pregnancy demonstrated that placental transfer of etanercept was low in infants at birth (*see Data*). There are risks to the mother and fetus associated with active rheumatoid arthritis. The theoretical risks of administration of live or live-attenuated vaccines to the infants exposed *in utero* to Etanercept should be weighed against the benefits of vaccinations (*see Clinical Considerations*).

In animal reproduction studies with pregnant rats and rabbits, no fetal harm or malformations were observed with subcutaneous administration of etanercept during the period of organogenesis at doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg Etanercept once weekly (*see Data*).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the United States, about 2-4% of liveborn babies have a major birth defect and about 15-20% of pregnancies end in miscarriage, regardless of drug exposure.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that the risk of adverse pregnancy outcomes in women with rheumatoid arthritis is correlated with maternal disease activity and that active disease increases the risk of adverse pregnancy outcomes, including fetal loss, preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) and small for gestational age birth.

Fetal/Neonatal Adverse Reactions

The risk of fetal/neonatal adverse reactions with *in utero* exposure to Etanercept is unknown. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to Etanercept *in utero* [*see Warnings and Precautions (5.8) and Drug Interactions (7.1)*].

Data

Human Data

A prospective cohort pregnancy registry conducted by OTIS in the US and Canada between 2000 and 2012 compared the risk of major birth defects in liveborn infants of women with rheumatic diseases or psoriasis exposed to etanercept in the first trimester. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N = 319) and diseased etanercept unexposed cohorts (N = 144) was 9.4% and 3.5%, respectively. The findings showed no statistically significant increased risk of minor birth defects and no pattern of major or minor birth defects.

A Scandinavian study compared the risk of major birth defects in liveborn infants of women with chronic inflammatory disease (CID) exposed to TNF-inhibitors during early pregnancy. Women were identified from the Danish (2004-2012) and Swedish (2006-2012) population-based health registers. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N = 344) and CID etanercept unexposed cohorts (N = 21,549) was 7.0% and 4.7%, respectively.

Overall, while both the OTIS Registry and Scandinavian study show a higher proportion of major birth defects in etanercept-exposed patients compared to diseased etanercept unexposed patients, the lack of pattern of birth defects is reassuring and differences between exposure groups (e.g., disease severity) may have impacted the occurrence of birth defects.

Reports from the literature showed that cord blood levels of etanercept at delivery, in infants born to women administered etanercept during pregnancy, varied from undetectable to 32% of the maternal serum level. In a cohort study of 30 pregnant women with RA, 29 were treated with etanercept until 30 weeks of gestation and 1 was treated until 36 weeks of gestation. Etanercept was not detected in the cord blood sample from any infant at delivery. In three published case reports, etanercept was detected in cord blood at levels of 3.3, 3.6, and 7.4% of the maternal concentration, when etanercept was administered at 50 mg every 7-12 days in pregnancy until 4 days prior to delivery, 25 mg twice weekly until 36 weeks of gestation, and 25 mg subcutaneous every week through the third trimester, respectively. There was one post-marketing safety report of a pregnant woman who received etanercept 25 mg once to twice weekly throughout pregnancy, and etanercept was detected in cord blood at 32% of the maternal concentration.

Animal Data

In embryofetal development studies with etanercept administered during the period of organogenesis to pregnant rats from gestation day (GD) 6 through 20 or pregnant rabbits from GD 6 through 18, there was no evidence of fetal malformations or embryotoxicity in rats or rabbits at respective doses that achieved systemic exposures 48 to 58 times the exposure in patients treated with 50 mg Etanercept once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day in rats and 40 mg/kg/day in rabbits). In a peri- and post-natal development study with pregnant rats that received etanercept during organogenesis and the later gestational period from GD 6 through 21, development of pups through post-natal day 4 was unaffected at doses that achieved exposures 48 times the exposure in patients treated with 50 mg Etanercept once weekly (on an AUC basis with maternal subcutaneous doses up to 30 mg/kg/day).

8.2 Lactation

Risk Summary

Data from published literature show that etanercept is present in low levels in human milk but is not detected in the plasma of breastfed infants (*see Data*). There are no data on the effects of etanercept on milk production. There have been no consistent reports of adverse events in breastfed infants over decades of use. The developmental 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.

Data

In three case reports, etanercept was detected in breast milk at levels ranging from < 2 to 7.5 ng/mL after lactating women had received doses of etanercept of 25 mg weekly or twice weekly. Although etanercept was detected in breast milk in these cases, etanercept was not detected in the serum of the breastfed infants.

8.4 Pediatric Use

Polyarticular Juvenile Idiopathic Arthritis

The safety and effectiveness of Etanercept have been established in pediatric patients 2 years of age and older with pJIA. Etanercept has been studied in 69 children with moderately to severely active polyarticular JIA 2 to 17 years of age.

The safety and effectiveness of Etanercept in pediatric patients less than 2 years of age with pJIA have not been established.

Juvenile Psoriatic Arthritis

The safety and effectiveness of Etanercept have been established in pediatric patients 2 years to 17 years old with JPsA. Use of Etanercept in JPsA is supported by evidence from adequate and well controlled studies of Etanercept in adults with PsA; pharmacokinetic data from adult patients with PsA, RA, and PsO; and pharmacokinetic data from pediatric patients with active JIA and PsO. Safety of Etanercept in JPsA is supported by a clinical study in

69 pediatric patients with moderately to severely active JIA aged 2 to 17 years; a clinical study in 211 pediatric patients with moderate to severe PsO aged 4 to 17 years; and an open-label extension study in 182 pediatric patients with moderate to severe PsO aged 4 to 17 years.

The observed pre-dose (trough) concentrations are generally comparable between adults with RA and PsA and pediatric patients with active JIA, as well as adults with PsO and pediatric patients with PsO. The PK exposure is expected to be comparable between adults with PsA and pediatric patients with JPsA [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14.1, 14.2, 14.3, 14.5, 14.6)*].

The safety and effectiveness in pediatric patients below the age of 2 years have not been established in JPsA.

Plaque Psoriasis

The safety and effectiveness of Etanercept for plaque psoriasis have been established in pediatric patients 4 years of age and older. Etanercept has been studied in 211 pediatric patients with moderate to severe PsO aged 4 to 17 years.

The safety and effectiveness of Etanercept in pediatric patients below the age of 4 years with PsO have not been established.

Malignancies in 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 [see *Warnings and Precautions (5.3)*].

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 Patients with Diabetes

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.

10 OVERDOSAGE

No dose-limiting toxicities have been observed during clinical trials of Etanercept. Single IV doses up to 60 mg/m² (approximately twice the recommended dose) have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities.

11 DESCRIPTION

Etanercept, a tumor necrosis factor (TNF) blocker, is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of etanercept contains the C_H2 domain, the C_H3 domain and hinge region, but not the C_H1 domain of IgG1. Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

Etanercept injection in the single-dose prefilled syringe, the single-dose prefilled SureClick autoinjector and the single-dose vial is clear and colorless, sterile, preservative-free solution, and is formulated at pH 6.3 \pm 0.2.

Table 5. Contents of Etanercept

Presentation	Active Ingredient Content	Inactive Ingredients Content
Etanercept 50 mg prefilled syringe and prefilled SureClick autoinjector	50 mg etanercept in 1 mL	25 mM L-arginine hydrochloride 120 mM sodium chloride 1% sucrose
Etanercept 25 mg prefilled syringe	25 mg etanercept in 0.5 mL	25 mM L-arginine hydrochloride 120 mM sodium chloride 1% sucrose
Etanercept 25 mg single-dose vial	25 mg etanercept in 0.5 mL	25 mM L-arginine hydrochloride 120 mM sodium chloride 1% sucrose

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacodynamics

Etanercept can modulate biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (e.g., E-selectin, and to a lesser extent, intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (e.g., 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.

12.3 Pharmacokinetics

After administration of 25 mg of Etanercept by a single SC injection to 25 patients with RA, a mean \pm standard deviation half-life of 102 ± 30 hours was observed with a clearance of 160 ± 80 mL/hr. A maximum serum concentration (C_{\max}) of 1.1 ± 0.6 mcg/mL and time to C_{\max} 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_{\max} 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 $AUC_{0-72 \text{ hr}}$ (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 (\pm standard

deviation) C_{max} , C_{min} , 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.

The mean (\pm SD) serum steady-state trough concentrations for 50 mg QW dosing in adult PsA subjects were 2.1 ± 1.2 mcg/mL and 2.1 ± 1.4 mcg/mL at weeks 24 and 48, respectively.

The mean (\pm SD) serum steady-state trough concentrations for the 50 mg QW dosing in adult PsO subjects were 1.5 ± 0.7 mcg/mL. Pediatric PsO patients (age 4 to 17 years) were administered 0.8 mg/kg of Etanercept once weekly (up to a maximum dose of 50 mg per week) for up to 48 weeks. The mean (\pm SD) serum steady-state trough concentrations ranged from 1.6 ± 0.8 to 2.1 ± 1.3 mcg/mL at weeks 12, 24, and 48.

Overall, the observed etanercept concentrations in patients with JIA and pediatric PsO were within the range of those observed for adult RA, PsA and PsO after administration of Etanercept.

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.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

14.1 Adult Rheumatoid Arthritis

The safety and efficacy of Etanercept were assessed in four randomized, double-blind, controlled studies. The results of all four trials were expressed in percentage of patients with improvement in RA using ACR response criteria.

Study I evaluated 234 patients with active RA who were ≥ 18 years old, had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs) (e.g., hydroxychloroquine, oral or injectable gold, MTX, azathioprine, D-penicillamine, sulfasalazine), and had ≥ 12 tender joints, ≥ 10 swollen joints, and either erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr, C-reactive protein (CRP) > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg Etanercept or placebo were administered SC twice a week for 6 consecutive months.

Study II evaluated 89 patients and had similar inclusion criteria to Study I except that patients in Study II had additionally received MTX for at least 6 months with a stable dose (12.5 to 25 mg/week) for at least 4 weeks and they had at least 6 tender or painful joints. Patients in Study II received a dose of 25 mg Etanercept or placebo SC twice a week for 6 months in addition to their stable MTX dose.

Study III compared the efficacy of Etanercept to MTX in patients with active RA. This study evaluated 632 patients who were ≥ 18 years old with early (≤ 3 years disease duration) active RA, had never received treatment with MTX, and had ≥ 12 tender joints, ≥ 10 swollen joints, and either ESR ≥ 28 mm/hr, CRP > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg Etanercept were administered SC twice a week for 12 consecutive months. The study was unblinded after all patients had completed at least 12 months (and a median of 17.3 months) of therapy. The majority of patients remained in the study on the treatment to which they were randomized through 2 years, after which they entered an extension study and received open-label 25 mg Etanercept. MTX tablets (escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial) or placebo tablets were given once a week on the same day as the injection of placebo or Etanercept doses, respectively.

Study IV evaluated 682 adult patients with active RA of 6 months to 20 years duration (mean of 7 years) who had an inadequate response to at least one DMARD other than MTX. Forty-three percent of patients had previously received MTX for a mean of 2 years prior to the trial at a mean dose of 12.9 mg. Patients were excluded from this study if MTX had been discontinued for lack of efficacy or for safety considerations. The patient baseline characteristics were similar to those of patients in Study I. Patients were randomized to MTX alone (7.5 to 20 mg weekly, dose escalated as described for Study III; median dose 20 mg), Etanercept alone (25 mg twice weekly), or the combination of Etanercept and MTX initiated concurrently (at the same doses as above). The study evaluated ACR response, Sharp radiographic score, and safety.

Clinical Response

A higher percentage of patients treated with Etanercept and Etanercept in combination with MTX achieved ACR 20, ACR 50, and ACR 70 responses and Major Clinical Responses than in the comparison groups. The results of Studies I, II, and III are summarized in Table 6. The results of Study IV are summarized in Table 7.

**Table 6. ACR Responses in Placebo- and Active-Controlled Trials
(Percent of Patients)**

Response	Placebo-Controlled				Active-Controlled	
	Study I		Study II		Study III	
	Placebo N = 80	Etanercept ^a N = 78	MTX/Placebo N = 30	MTX/Etanercept ^a N = 59	MTX N = 217	Etanercept ^a N = 207
ACR 20						
Month 3	23%	62% ^b	33%	66% ^b	56%	62%
Month 6	11%	59% ^b	27%	71% ^b	58%	65%
Month 12	NA	NA	NA	NA	65%	72%
ACR 50						
Month 3	8%	41% ^b	0%	42% ^b	24%	29%
Month 6	5%	40% ^b	3%	39% ^b	32%	40%
Month 12	NA	NA	NA	NA	43%	49%
ACR 70						
Month 3	4%	15% ^b	0%	15% ^b	7%	13% ^c
Month 6	1%	15% ^b	0%	15% ^b	14%	21% ^c
Month 12	NA	NA	NA	NA	22%	25%

^a 25 mg Etanercept SC twice weekly.

^b $p < 0.01$, Etanercept versus placebo.

^c $p < 0.05$, Etanercept versus MTX.

Table 7. Study IV Clinical Efficacy Results: Comparison of MTX versus Etanercept versus Etanercept in Combination with MTX in Patients with Rheumatoid Arthritis of 6 Months to 20 Years Duration (Percent of Patients)

Endpoint	MTX (N = 228)	Etanercept (N = 223)	Etanercept/MTX (N = 231)
ACR N^{a, b}			
Month 12	40%	47%	63% ^c
ACR 20			
Month 12	59%	66%	75% ^c
ACR 50			
Month 12	36%	43%	63% ^c
ACR 70			
Month 12	17%	22%	40% ^c
Major Clinical Response^d	6%	10%	24% ^c

^a Values are medians.

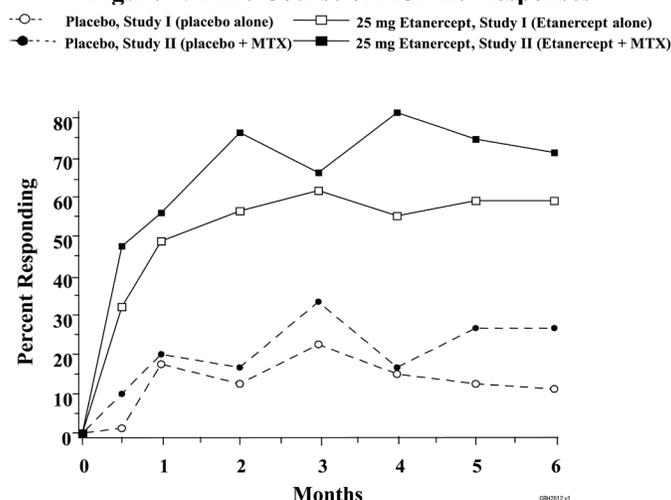
^b ACR N is the percent improvement based on the same core variables used in defining ACR 20, ACR 50, and ACR 70.

^c $p < 0.05$ for comparisons of Etanercept/MTX versus Etanercept alone or MTX alone.

^d Major clinical response is achieving an ACR 70 response for a continuous 6-month period.

The time course for ACR 20 response rates for patients receiving placebo or 25 mg Etanercept in Studies I and II is summarized in Figure 1. The time course of responses to Etanercept in Study III was similar.

Figure 1. Time Course of ACR 20 Responses



Among patients receiving Etanercept, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen in Studies I and III: 25 mg Etanercept was more effective than 10 mg (10 mg was not evaluated in Study II). Etanercept was significantly better than placebo in all components of the ACR criteria as well as other measures of RA disease activity not included in the ACR response criteria, such as morning stiffness.

In Study III, ACR response rates and improvement in all the individual ACR response criteria were maintained through 24 months of Etanercept therapy. Over the 2-year study, 23% of Etanercept patients achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period.

The results of the components of the ACR response criteria for Study I are shown in Table 8. Similar results were observed for Etanercept-treated patients in Studies II and III.

Table 8. Components of ACR Response in Study I

Parameter (median)	Placebo N = 80		Etanercept ^a N = 78	
	Baseline	3 Months	Baseline	3 Months [*]
Number of tender joints ^b	34.0	29.5	31.2	10.0 ^f
Number of swollen joints ^c	24.0	22.0	23.5	12.6 ^f
Physician global assessment ^d	7.0	6.5	7.0	3.0 ^f
Patient global assessment ^d	7.0	7.0	7.0	3.0 ^f
Pain ^d	6.9	6.6	6.9	2.4 ^f
Disability index ^c	1.7	1.8	1.6	1.0 ^f
ESR (mm/hr)	31.0	32.0	28.0	15.5 ^f
CRP (mg/dL)	2.8	3.9	3.5	0.9 ^f

* Results at 6 months showed similar improvement.

^a 25 mg Etanercept SC twice weekly.

^b Scale 0-71.

^c Scale 0-68.

^d Visual analog scale: 0 = best; 10 = worst.

^e Health Assessment Questionnaire: 0 = best; 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

^f $p < 0.01$, Etanercept versus placebo, based on mean percent change from baseline.

After discontinuation of Etanercept, symptoms of arthritis generally returned within a month. Reintroduction of treatment with Etanercept after discontinuations of up to 18 months resulted in the same magnitudes of response as in patients who received Etanercept without interruption of therapy, based on results of open-label studies.

Continued durable responses were seen for over 60 months in open-label extension treatment trials when patients received Etanercept without interruption. A substantial number of patients who initially received concomitant MTX or corticosteroids were able to reduce their doses or discontinue these concomitant therapies while maintaining their clinical responses.

Physical Function Response

In Studies I, II, and III, physical function and disability were assessed using the Health Assessment Questionnaire (HAQ). Additionally, in Study III, patients were administered the SF-36 Health Survey. In Studies I and II, patients treated with 25 mg Etanercept twice weekly showed greater improvement from baseline in the HAQ score beginning in month 1 through month 6 in comparison to placebo ($p < 0.001$) for the HAQ disability domain (where 0 = none and 3 = severe). In Study I, the mean improvement in the HAQ score from baseline to month 6 was 0.6 (from 1.6 to 1.0) for the 25 mg Etanercept group and 0 (from 1.7 to 1.7) for the placebo group. In Study II, the mean improvement from baseline to month 6 was 0.6 (from 1.5 to 0.9) for the Etanercept/MTX group and 0.2 (from 1.3 to 1.2) for the placebo/MTX group. In Study III, the mean improvement in the HAQ score from baseline to month 6 was 0.7 (from 1.5 to 0.7) for 25 mg Etanercept twice weekly. All subdomains of the HAQ in Studies I and III were improved in patients treated with Etanercept.

In Study III, patients treated with 25 mg Etanercept twice weekly showed greater improvement from baseline in SF-36 physical component summary score compared to Etanercept 10 mg twice weekly and no worsening in the SF-36 mental component summary score. In open-label Etanercept studies, improvements in physical function and disability measures have been maintained for up to 4 years.

In Study IV, median HAQ scores improved from baseline levels of 1.8, 1.8, and 1.8 to 1.1, 1.0, and 0.6 at 12 months in the MTX, Etanercept, and Etanercept/MTX combination treatment groups, respectively (combination versus both MTX and Etanercept, $p < 0.01$). Twenty-nine percent of patients in the MTX alone treatment group had an improvement of HAQ of at least 1 unit versus 40% and 51% in the Etanercept alone and the Etanercept/MTX combination treatment groups, respectively.

Radiographic Response

In Study III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score. Radiographs of hands/wrists and forefeet were obtained at baseline, 6 months, 12 months, and 24 months and scored by readers who were unaware of treatment group. The results are shown in Table 9. A significant difference for change in erosion score was observed at 6 months and maintained at 12 months.

Table 9. Mean Radiographic Change Over 6 and 12 Months in Study III

		MTX	25 mg Etanercept	MTX/Etanercept (95% Confidence Interval*)	P Value
12 Months	Total Sharp Score	1.59	1.00	0.59 (-0.12, 1.30)	0.1
	Erosion Score	1.03	0.47	0.56 (0.11, 1.00)	0.002
	JSN Score	0.56	0.52	0.04 (-0.39, 0.46)	0.5
6 Months	Total Sharp Score	1.06	0.57	0.49 (0.06, 0.91)	0.001
	Erosion Score	0.68	0.30	0.38 (0.09, 0.66)	0.001
	JSN Score	0.38	0.27	0.11 (-0.14, 0.35)	0.6

* 95% confidence intervals for the differences in change scores between MTX and Etanercept.

Patients continued on the therapy to which they were randomized for the second year of Study III. Seventy-two percent of patients had x-rays obtained at 24 months. Compared to the patients in the MTX group, greater inhibition of progression in TSS and erosion score was seen in the 25 mg Etanercept group, and, in addition, less progression was noted in the JSN score.

In the open-label extension of Study III, 48% of the original patients treated with 25 mg Etanercept have been evaluated radiographically at 5 years. Patients had continued inhibition of structural damage, as measured by the TSS, and 55% of them had no progression of structural damage. Patients originally treated with MTX had further reduction in radiographic progression once they began treatment with Etanercept.

In Study IV, less radiographic progression (TSS) was observed with Etanercept in combination with MTX compared with Etanercept alone or MTX alone at month 12 (Table 10). In the MTX treatment group, 55% of patients experienced no radiographic progression (TSS change ≤ 0.0) at 12 months compared to 63% and 76% in the Etanercept alone and the Etanercept/MTX combination treatment groups, respectively.

Table 10. Mean Radiographic Change in Study IV at 12 Months (95% Confidence Interval)

	MTX (N = 212)*	Etanercept (N = 212)*	Etanercept/MTX (N = 218)*
Total Sharp Score (TSS)	2.80 (1.08, 4.51)	0.52 ^a (-0.10, 1.15)	-0.54 ^{b,c} (-1.00, -0.07)
Erosion Score (ES)	1.68 (0.61, 2.74)	0.21 ^a (-0.20, 0.61)	-0.30 ^b (-0.65, 0.04)
Joint Space Narrowing (JSN) Score	1.12 (0.34, 1.90)	0.32 (0.00, 0.63)	-0.23 ^{b,c} (-0.45, -0.02)

* Analyzed radiographic ITT population.

^a p < 0.05 for comparison of Etanercept versus MTX.

^b p < 0.05 for comparison of Etanercept/MTX versus MTX.

^c p < 0.05 for comparison of Etanercept/MTX versus Etanercept.

Once Weekly Dosing

The safety and efficacy of 50 mg Etanercept (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. Fifty-three patients received placebo, 214 patients received 50 mg Etanercept once weekly, and 153 patients received 25 mg Etanercept twice weekly. The safety and efficacy profiles of the two Etanercept treatment groups were similar.

14.2 Polyarticular Juvenile Idiopathic Arthritis (JIA)

The safety and efficacy of Etanercept were assessed in a 2-part study in 69 children with polyarticular JIA who had a variety of JIA onset types. Patients ages 2 to 17 years with moderately to severely active polyarticular JIA refractory to or intolerant of MTX were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (≤ 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) Etanercept SC twice weekly. In part 2, patients with a clinical response at day 90 were randomized to remain on Etanercept or receive placebo for 4 months and assessed for disease flare. Responses were measured using the JIA Definition of Improvement (DOI), defined as $\geq 30\%$ improvement in at least three of six and $\geq 30\%$ worsening in no more than one of the six JIA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and ESR. Disease flare was defined as a $\geq 30\%$ worsening in three of the six JIA core set criteria and $\geq 30\%$ improvement in not more than one of the six JIA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on Etanercept experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo ($p = 0.007$). From the start of part 2, the median time to flare was ≥ 116 days for patients who received Etanercept and 28 days for patients who received placebo. Each component of the JIA core set criteria worsened in the arm that received placebo and remained stable or improved in the arm that continued on Etanercept. The data suggested the possibility of a higher flare rate among those patients with a higher baseline ESR. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on Etanercept continued to improve from month 3 through month 7, while those who received placebo did not improve.

The majority of JIA patients who developed a disease flare in part 2 and reintroduced Etanercept treatment up to 4 months after discontinuation re-responded to Etanercept therapy in open-label studies. Most of the responding patients who continued Etanercept therapy without interruption have maintained responses for up to 48 months.

Studies have not been done in patients with polyarticular JIA to assess the effects of continued Etanercept therapy in patients who do not respond within 3 months of initiating Etanercept therapy, or to assess the combination of Etanercept with MTX.

14.3 Psoriatic Arthritis

The safety and efficacy of Etanercept were assessed in a randomized, double-blind, placebo-controlled study in 205 patients with PsA. Patients were between 18 and 70 years of age and had active PsA (≥ 3 swollen joints and ≥ 3 tender joints) in one or more of the following forms: (1) distal interphalangeal (DIP) involvement ($N = 104$); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis; $N = 173$); (3) arthritis mutilans ($N = 3$); (4) asymmetric psoriatic arthritis ($N = 81$); or (5) ankylosing spondylitis-like ($N = 7$). Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Patients on MTX therapy at enrollment (stable for ≥ 2 months) could continue at a stable dose of ≤ 25 mg/week MTX. Doses of 25 mg Etanercept or placebo were administered SC twice a week during the initial 6-month double-blind period of the study. Patients continued to receive blinded therapy in an up to 6-month maintenance period until all patients had completed the controlled period. Following this, patients received open-label 25 mg Etanercept twice a week in a 12-month extension period.

Compared to placebo, treatment with Etanercept resulted in significant improvements in measures of disease activity (Table 11).

Table 11. Components of Disease Activity in Psoriatic Arthritis

Parameter (median)	Placebo N = 104		Etanercept ^a N = 101	
	Baseline	6 Months	Baseline	6 Months
Number of tender joints ^b	17.0	13.0	18.0	5.0
Number of swollen joints ^c	12.5	9.5	13.0	5.0
Physician global assessment ^d	3.0	3.0	3.0	1.0
Patient global assessment ^d	3.0	3.0	3.0	1.0
Morning stiffness (minutes)	60	60	60	15
Pain ^d	3.0	3.0	3.0	1.0
Disability index ^e	1.0	0.9	1.1	0.3
CRP (mg/dL) ^f	1.1	1.1	1.6	0.2

^a $p < 0.001$ for all comparisons between Etanercept and placebo at 6 months.

^b Scale 0-78.

^c Scale 0-76.

^d Likert scale: 0 = best; 5 = worst.

^e Health Assessment Questionnaire: 0 = best; 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

^f Normal range: 0-0.79 mg/dL.

Among patients with PsA who received Etanercept, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline. At 6 months, the ACR 20/50/70 responses were achieved by 50%, 37%, and 9%, respectively, of patients receiving Etanercept, compared to 13%, 4%, and 1%, respectively, of patients receiving placebo. Similar responses were seen in patients with each of the subtypes of PsA, although few patients were enrolled with the arthritis mutilans and ankylosing spondylitis-like subtypes. The results of this study were similar to those seen in an earlier single-center, randomized, placebo-controlled study of 60 patients with PsA.

The skin lesions of psoriasis were also improved with Etanercept, relative to placebo, as measured by percentages of patients achieving improvements in the Psoriasis Area and Severity Index (PASI). Responses increased over time, and at 6 months, the proportions of patients achieving a 50% or 75% improvement in the PASI were 47% and 23%, respectively, in the Etanercept group (N = 66), compared to 18% and 3%, respectively, in the placebo group (N = 62). Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Radiographic Response

Radiographic changes were also assessed in the PsA study. Radiographs of hands and wrists were obtained at baseline and months 6, 12, and 24. A modified Total Sharp Score (TSS), which included distal interphalangeal joints (i.e., not identical to the modified TSS used for RA) was used by readers blinded to treatment group to assess the radiographs. Some radiographic features specific to PsA (e.g., pencil-and-cup deformity, joint space widening, gross osteolysis, and ankylosis) were included in the scoring system, but others (e.g., phalangeal tuft resorption, juxta-articular and shaft periostitis) were not.

Most patients showed little or no change in the modified TSS during this 24-month study (median change of 0 in both patients who initially received Etanercept or placebo). More placebo-treated patients experienced larger magnitudes of radiographic worsening (increased TSS) compared to Etanercept treatment during the controlled period of the study. At 12 months, in an exploratory analysis, 12% (12 of 104) of placebo patients compared to none of the 101 Etanercept-treated patients had increases of 3 points or more in TSS. Inhibition of radiographic progression was maintained in patients who continued on Etanercept during the second year. Of the patients with 1-year and 2-year x-rays, 3% (2 of 71) had increases of 3 points or more in TSS at 1 and 2 years.

Physical Function Response

In the PsA study, physical function and disability were assessed using the HAQ Disability Index (HAQ-DI) and the SF-36 Health Survey. Patients treated with 25 mg Etanercept twice weekly showed greater improvement from baseline in the HAQ-DI score (mean decreases of 54% at both months 3 and 6) in comparison to placebo (mean decreases of 6% at both months 3 and 6) ($p < 0.001$). At months 3 and 6, patients treated with Etanercept showed

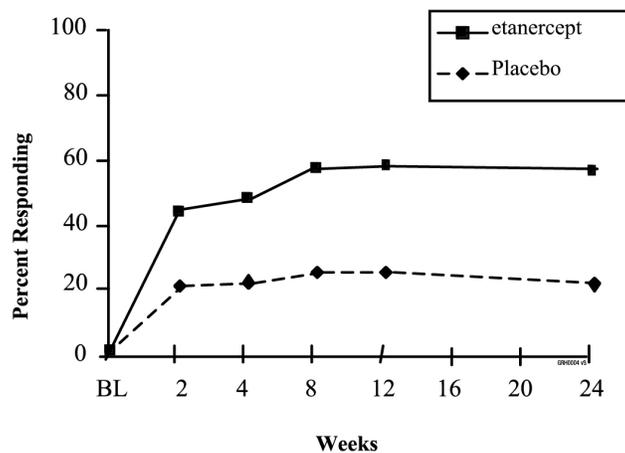
greater improvement from baseline in the SF-36 physical component summary score compared to patients treated with placebo, and no worsening in the SF-36 mental component summary score. Improvements in physical function and disability measures were maintained for up to 2 years through the open-label portion of the study.

14.4 Ankylosing Spondylitis

The safety and efficacy of Etanercept were assessed in a randomized, double-blind, placebo-controlled study in 277 patients with active AS. Patients were between 18 and 70 years of age and had AS as defined by the modified New York Criteria for Ankylosing Spondylitis. Patients were to have evidence of active disease based on values of ≥ 30 on a 0-100 unit Visual Analog Scale (VAS) for the average of morning stiffness duration and intensity, and two of the following three other parameters: a) patient global assessment, b) average of nocturnal and total back pain, and c) the average score on the Bath Ankylosing Spondylitis Functional Index (BASFI). Patients with complete ankylosis of the spine were excluded from study participation. Patients taking hydroxychloroquine, sulfasalazine, methotrexate, or prednisone (≤ 10 mg/day) could continue these drugs at stable doses for the duration of the study. Doses of 25 mg Etanercept or placebo were administered SC twice a week for 6 months.

The primary measure of efficacy was a 20% improvement in the Assessment in Ankylosing Spondylitis (ASAS) response criteria. Compared to placebo, treatment with Etanercept resulted in improvements in the ASAS and other measures of disease activity (Figure 2 and Table 12).

Figure 2. ASAS 20 Responses in Ankylosing Spondylitis



At 12 weeks, the ASAS 20/50/70 responses were achieved by 60%, 45%, and 29%, respectively, of patients receiving Etanercept, compared to 27%, 13%, and 7%, respectively, of patients receiving placebo ($p \leq 0.0001$, Etanercept versus placebo). Similar responses were seen at Week 24. Responses were similar between those patients receiving concomitant therapies at baseline and those who were not. The results of this study were similar to those seen in a single-center, randomized, placebo-controlled study of 40 patients and a multicenter, randomized, placebo-controlled study of 84 patients with AS.

Table 12. Components of Ankylosing Spondylitis Disease Activity

Median values at time points	Placebo N = 139		Etanercept ^a N = 138	
	Baseline	6 Months	Baseline	6 Months
ASAS response criteria				
Patient global assessment ^b	63	56	63	36
Back pain ^c	62	56	60	34
BASFI ^d	56	55	52	36
Inflammation ^e	64	57	61	33

Median values at time points	Placebo N = 139		Etanercept ^a N = 138	
	Baseline	6 Months	Baseline	6 Months
Acute phase reactants				
CRP (mg/dL) ^f	2.0	1.9	1.9	0.6
Spinal mobility (cm):				
Modified Schober's test	3.0	2.9	3.1	3.3
Chest expansion	3.2	3.0	3.3	3.9
Occiput-to-wall measurement	5.3	6.0	5.6	4.5

^a $p < 0.0015$ for all comparisons between Etanercept and placebo at 6 months. P values for continuous endpoints were based on percent change from baseline.

^b Measured on a Visual Analog Scale (VAS) with 0 = "none" and 100 = "severe".

^c Average of total nocturnal and back pain scores, measured on a VAS with 0 = "no pain" and 100 = "most severe pain".

^d Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions.

^e Inflammation represented by the average of the last 2 questions on the 6-question Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

^f C-reactive protein (CRP) normal range: 0-1.0 mg/dL.

14.5 Adult Plaque Psoriasis

The safety and efficacy of Etanercept were assessed in two randomized, double-blind, placebo-controlled studies in adults with chronic stable PsO involving $\geq 10\%$ of the body surface area, a minimum Psoriasis Area and Severity Index (PASI) score of 10 and who had received or were candidates for systemic antipsoriatic therapy or phototherapy. Patients with guttate, erythrodermic, or pustular psoriasis and patients with severe infections within 4 weeks of screening were excluded from study. No concomitant major antipsoriatic therapies were allowed during the study.

Study I evaluated 672 subjects who received placebo or Etanercept SC at doses of 25 mg once a week, 25 mg twice a week, or 50 mg twice a week for 3 months. After 3 months, subjects continued on blinded treatments for an additional 3 months during which time subjects originally randomized to placebo began treatment with blinded Etanercept at 25 mg twice weekly (designated as placebo/Etanercept in Table 13); subjects originally randomized to Etanercept continued on the originally randomized dose (designated as Etanercept/Etanercept groups in Table 13).

Study II evaluated 611 subjects who received placebo or Etanercept SC at doses of 25 mg or 50 mg twice a week for 3 months. After 3 months of randomized, blinded treatment, subjects in all three arms began receiving open-label Etanercept at 25 mg twice weekly for 9 additional months.

Response to treatment in both studies was assessed after 3 months of therapy and was defined as the proportion of subjects who achieved a reduction in PASI score of at least 75% from baseline. The PASI is a composite score that takes into consideration both the fraction of body surface area affected and the nature and severity of psoriatic changes within the affected regions (induration, erythema and scaling).

Other evaluated outcomes included the proportion of subjects who achieved a score of "clear" or "minimal" by the Static Physician Global Assessment (sPGA) and the proportion of subjects with a reduction of PASI of at least 50% from baseline. The sPGA is a 6-category scale ranging from "5 = severe" to "0 = none" indicating the physician's overall assessment of the PsO severity focusing on induration, erythema and scaling. Treatment success of "clear" or "minimal" consisted of none or minimal elevation in plaque, up to faint red coloration in erythema and none or minimal fine scale over $< 5\%$ of the plaque.

Subjects in all treatment groups and in both studies had a median baseline PASI score ranging from 15 to 17, and the percentage of subjects with baseline sPGA classifications ranged from 54% to 66% for moderate, 17% to 26% for marked and 1% to 5% for severe. Across all treatment groups, the percentage of subjects who previously received

systemic therapy for PsO ranged from 61% to 65% in Study I and 71% to 75% in Study II, and those who previously received phototherapy ranged from 44% to 50% in Study I and 72% to 73% in Study II.

More subjects randomized to Etanercept than placebo achieved at least a 75% reduction from baseline PASI score (PASI 75) with a dose response relationship across doses of 25 mg once a week, 25 mg twice a week and 50 mg twice a week (Tables 13 and 14). The individual components of the PASI (induration, erythema and scaling) contributed comparably to the overall treatment-associated improvement in PASI.

Table 13. Study I Outcomes at 3 and 6 Months

	Placebo/Etanercept		Etanercept/Etanercept	
	25 mg BIW (N = 168)	25 mg QW (N = 169)	25 mg BIW (N = 167)	50 mg BIW (N = 168)
3 Months				
PASI 75 n (%)	6 (4%)	23 (14%) ^a	53 (32%) ^b	79 (47%) ^b
Difference (95% CI)		10% (4, 16)	28% (21, 36)	43% (35, 52)
sPGA, “clear” or “minimal” n (%)	8 (5%)	36 (21%) ^b	53 (32%) ^b	79 (47%) ^b
Difference (95% CI)		17% (10, 24)	27% (19, 35)	42% (34, 50)
PASI 50 n (%)	24 (14%)	62 (37%) ^b	90 (54%) ^b	119 (71%) ^b
Difference (95% CI)		22% (13, 31)	40% (30, 49)	57% (48, 65)
6 Months				
PASI 75 n (%)	55 (33%)	36 (21%)	68 (41%)	90 (54%)

^a p = 0.001 compared with placebo.

^b p < 0.0001 compared with placebo.

Table 14. Study II Outcomes at 3 Months

	Placebo	Etanercept	
	(N = 204)	25 mg BIW (N = 204)	50 mg BIW (N = 203)
PASI 75 n (%)	6 (3%)	66 (32%) ^a	94 (46%) ^a
Difference (95% CI)		29% (23, 36)	43% (36, 51)
sPGA, “clear” or “minimal” n (%)	7 (3%)	75 (37%) ^a	109 (54%) ^a
Difference (95% CI)		34% (26, 41)	50% (43, 58)
PASI 50 n (%)	18 (9%)	124 (61%) ^a	147 (72%) ^a
Difference (95% CI)		52% (44, 60)	64% (56, 71)

^a p < 0.0001 compared with placebo.

Among PASI 75 achievers in both studies, the median time to PASI 50 and PASI 75 was approximately 1 month and approximately 2 months, respectively, after the start of therapy with either 25 or 50 mg twice a week.

In Study I, subjects who achieved PASI 75 at month 6 were entered into a study drug withdrawal and retreatment period. Following withdrawal of study drug, these subjects had a median duration of PASI 75 of between 1 and 2 months.

In Study I, among subjects who were PASI 75 responders at 3 months, retreatment with their original blinded Etanercept dose after discontinuation of up to 5 months resulted in a similar proportion of responders as in the initial double-blind portion of the study.

In Study II, most subjects initially randomized to 50 mg twice a week continued in the study after month 3 and had their Etanercept dose decreased to 25 mg twice a week. Of the 91 subjects who were PASI 75 responders at month 3, 70 (77%) maintained their PASI 75 response at month 6.

14.6 Pediatric Plaque Psoriasis

A 48-week, randomized, double-blind, placebo-controlled study enrolled 211 pediatric subjects 4 to 17 years of age, with moderate to severe plaque psoriasis (PsO) (as defined by a sPGA score ≥ 3 [moderate, marked, or severe], involving $\geq 10\%$ of the body surface area, and a PASI score ≥ 12) who were candidates for phototherapy or systemic therapy, or were inadequately controlled on topical therapy. Subjects in all treatment groups had a median baseline PASI score of 16.4, and the percentage of subjects with baseline sPGA classifications was 65% for moderate, 31% for marked, and 3% for severe. Across all treatment groups, the percentage of subjects who previously received systemic or phototherapy for PsO was 57%.

Subjects received Etanercept 0.8 mg/kg (up to a maximum of 50 mg per dose) or placebo once weekly for the first 12 weeks. After 12 weeks, subjects entered a 24-week open-label treatment period, in which all subjects received Etanercept at the same dose. This was followed by a 12-week withdrawal-retreatment period.

Response to treatment was assessed after 12 weeks of therapy and was defined as the proportion of subjects who achieved a reduction in PASI score of at least 75% from baseline. The PASI is a composite score that takes into consideration both the fraction of body surface area affected and the nature and severity of psoriatic changes within the affected regions (induration, erythema and scaling).

Other evaluated outcomes included the proportion of subjects who achieved a score of “clear” or “almost clear” by the sPGA and the proportion of subjects with a reduction in PASI score of at least 90% from baseline. The sPGA is a 6-category scale ranging from “5 = severe” to “0 = none” indicating the physician’s overall assessment of the PsO severity focusing on induration, erythema and scaling. Treatment success of “clear” or “almost clear” consisted of none or minimal elevation in plaque, up to faint red coloration in erythema and none or minimal fine scale over $< 5\%$ of the plaque.

Efficacy results are summarized in Table 15.

Table 15. Pediatric Plaque Psoriasis Outcomes at 12 Weeks

	Placebo (N = 105)	Etanercept 0.8 mg/kg Once Weekly (N = 106)
PASI 75, n (%)	12 (11%)	60 (57%)
PASI 90, n (%)	7 (7%)	29 (27%)
sPGA “clear” or “almost clear” n (%)	14 (13%)	55 (52%)

Maintenance of Response

To evaluate maintenance of response, subjects who achieved PASI 75 response at Week 36 were re-randomized to either Etanercept or placebo during a 12-week randomized withdrawal period. The maintenance of PASI 75 response was evaluated at Week 48. The proportion of subjects who maintained PASI 75 response at Week 48 was higher for subjects treated with Etanercept (65%) compared to those treated with placebo (49%).

15 REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Database (SEER) Program. SEER Incidence Crude Rates, 13 Registries, 1992-2002.
2. Bröms G, Granath F, Ekbom A, et al. Low Risk of Birth Defects for Infants Whose Mothers Are Treated With Anti-Tumor Necrosis Factor Agents During Pregnancy. *Clin Gastroenterol Hepatol*. 2016;14:234-241.e5

16 HOW SUPPLIED/STORAGE AND HANDLING

Etanercept injection is supplied as a clear and colorless sterile, preservative-free solution for subcutaneous administration in single-dose prefilled syringes, an Etanercept single-dose prefilled SureClick autoinjector with a

27-gauge, ½-inch needle, or a single-dose vial. The prefilled syringe and prefilled SureClick autoinjector are not made with natural rubber latex.

50 mg/mL single-dose prefilled syringe	Carton of 4	NDC 58406-483-24
50 mg/mL single-dose prefilled SureClick autoinjector	Carton of 4	NDC 58406-200-24
25 mg/0.5 mL single-dose prefilled syringe	Carton of 4	NDC 58406-377-24
25 mg/0.5 mL single-dose vial	Carton of 4	NDC 58406-257-24

Etanercept should be refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light or physical damage. Do not store Etanercept in extreme heat or cold. **DO NOT SHAKE. DO NOT FREEZE.**

For convenience, storage of individual single-dose prefilled syringes, prefilled SureClick autoinjectors or single-dose vials at room temperature at 68°F to 77°F (20°C to 25°C) for a maximum single period of 30 days is permissible, with protection from light and sources of heat. Once a single-dose prefilled syringe, prefilled SureClick autoinjector or single-dose vial has been stored at room temperature, it should not be placed back into the refrigerator. If not used within 30 days at room temperature, the single-dose prefilled syringe, prefilled SureClick autoinjector or single-dose vial should be discarded.

Do not use Etanercept beyond the expiration date stamped on the carton or label. Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise patients and/or caregivers to read the FDA-approved patient labeling (Medication Guide and Instructions for Use) before the patient starts using Etanercept, and each time the prescription is renewed, as there may be new information they need to know.

Patients or their caregivers should be provided the Etanercept “Medication Guide” and provided an opportunity to read it and ask questions prior to initiation of therapy. 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.

Patient Counseling

Patients should be advised of the potential benefits and risks of Etanercept. Physicians should instruct their patients to read the Medication Guide before starting Etanercept therapy and to reread each time the prescription is renewed.

Infections

Inform patients that Etanercept 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 Etanercept. Advise patients to report any symptoms suggestive of a pancytopenia, such as bruising, bleeding, persistent fever or pallor.

Allergic Reactions

Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions.

Administration of Etanercept

If a patient or caregiver is to administer Etanercept, the patient or caregiver should be instructed in injection techniques and how to measure and administer the correct dose [see “Instructions for Use”]. For weight-based dosing, instruct caregivers and patients on the proper techniques for preparing, storing, measuring, and administering Etanercept solution in a single-dose vial.

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.

When using the prefilled SureClick autoinjector to administer Etanercept, the patient or caregiver should be informed that the window turns yellow when the injection is complete. After removing the autoinjector, if the window has not turned yellow, or if it looks like the medicine is still injecting, this means the patient has not received a full dose. The patient or caregiver should be advised to call their healthcare provider immediately.

A puncture-resistant container for disposal of needles, syringes, prefilled SureClick autoinjectors and single-dose vials should be used.

Patients can be advised to call 1-888-436-2735 or visit www.etanercept.com for more information about Etanercept.

Etanercept

The logo for Amgen, consisting of the word "AMGEN" in a bold, black, sans-serif font.

Manufactured by:

Immunex Corporation
Thousand Oaks, CA 91320-1799
U.S. License Number 1132

Patent: <http://pat.amgen.com/enbrel/>

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Medication Guide

**Etanercept (ee – tan – er – sept)
injection, for subcutaneous use**

**Etanercept (ee – tan – er – sept)
for injection, for subcutaneous use**

This product is Enbrel® (etanercept).

Read the Medication Guide that comes with Etanercept before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or treatment. It is important to remain under your healthcare provider's care while using Etanercept.

Etanercept is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker that affects your immune system.

What is the most important information I should know about Etanercept?

Etanercept may cause serious side effects, including:

1. Risk of Infection
2. Risk of Cancer

1. Risk of infection

Etanercept can lower the ability of your immune system to fight infections. Some people have serious infections while taking Etanercept. These infections include tuberculosis (TB), and infections caused by viruses, fungi, or bacteria that spread throughout their body. Some people have died from these infections.

- Your healthcare provider should test you for TB before starting Etanercept.
- Your healthcare provider should monitor you closely for symptoms of TB during treatment with Etanercept even if you tested negative for TB.
- Your healthcare provider should check you for symptoms of any type of infection before, during, and after your treatment with Etanercept.

You should not start taking Etanercept if you have any kind of infection unless your healthcare provider says it is okay.

2. Risk of cancer

- There have been cases of unusual cancers, some resulting in death, in children and teenagers who started using TNF-blocking agents at less than 18 years of age.
- For children, teenagers, and adults taking TNF-blocker medicines, including Etanercept, the chances of getting lymphoma or other cancers may increase.
- People with rheumatoid arthritis, especially those with very active disease, may be more likely to get lymphoma.

Before starting Etanercept, be sure to talk to your healthcare provider:

Etanercept may not be right for you. Before starting Etanercept, tell your healthcare provider about all of your medical conditions, including:

Infections. Tell your healthcare provider if you:

- have an infection. See “**What is the most important information I should know about Etanercept?**”
- are being treated for an infection.
- think you have an infection.
- have symptoms of an infection such as fever, sweats or chills, cough or flu-like symptoms, shortness of breath, blood in your phlegm, weight loss, muscle aches, warm, red or painful areas on your skin, sores on your body, diarrhea or stomach pain, burning when you urinate or urinating more often than normal, and feel very tired.
- have any open cuts on your body.
- get a lot of infections or have infections that keep coming back.
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- were born in, lived in, or traveled to countries where there is a risk for getting TB. Ask your healthcare provider if you are not sure.
- live, have lived in, or traveled to certain parts of the country (such as the Ohio and Mississippi River valleys, or the Southwest) where there is a greater risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis). These infections may happen or become more severe if you use Etanercept. Ask your healthcare provider if you do not know if you live or have lived in an area where these infections are common.
- have or have had hepatitis B.

Also, before starting Etanercept, tell your healthcare provider:

- **About all the medicines you take including prescription and over-the-counter medicines, vitamins and herbal supplements including:**
 - **Orencia (abatacept) or Kineret (anakinra).** You have a higher chance for serious infections when taking Etanercept with Orencia or Kineret.

- **Cyclophosphamide (Cytoxan).** You may have a higher chance for getting certain cancers when taking Etanercept with cyclophosphamide.
- **Anti-diabetic medicines.** If you have diabetes and are taking medicine to control your diabetes, your healthcare provider may decide you need less anti-diabetic medicine while taking Etanercept.

Keep a list of all your medicines with you to show your healthcare provider and pharmacist each time you get a new medicine. Ask your healthcare provider if you are not sure if your medicine is one listed above.

Other important medical information you should tell your healthcare provider before starting Etanercept, includes if you:

- have or had a nervous system problem such as multiple sclerosis or Guillain-Barré syndrome.
- have or had heart failure.
- are scheduled to have surgery.
- have recently received or are scheduled to receive a vaccine.
 - All vaccines should be brought up-to-date before starting Etanercept.
 - People taking Etanercept should not receive live vaccines.
 - Ask your healthcare provider if you are not sure if you received a live vaccine.
- have been around someone with varicella zoster (chicken pox).
- are pregnant or plan to become pregnant. It is not known if Etanercept will harm your unborn baby. If you took Etanercept during pregnancy, talk to your healthcare provider prior to administration of live vaccines to your infant. If you are breastfeeding or plan to breastfeed, Etanercept can pass into breast milk. Talk to your healthcare provider about the best way to feed your baby while taking Etanercept.

See the section “**What are the possible side effects of Etanercept?**” below for more information.

What is Etanercept?

Etanercept is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker.

Etanercept is used to treat:

- **moderately to severely active rheumatoid arthritis (RA).** Etanercept can be used alone or with a medicine called methotrexate.
- **moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) in children 2 years of age or older.**
- **psoriatic arthritis (PsA) in adults.** Etanercept can be used alone or with methotrexate.
- **active juvenile psoriatic arthritis (JPsA) in children 2 years of age or older.**
- **ankylosing spondylitis (AS).**
- **chronic moderate to severe plaque psoriasis (PsO) in children 4 years of age or older and adults** who may benefit from taking injections or pills (systemic therapy) or phototherapy (ultraviolet light).

You may continue to use other medicines that help treat your condition while taking Etanercept, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as recommended by your healthcare provider.

Etanercept can help reduce joint damage and the signs and symptoms of the above-mentioned diseases. People with these diseases have too much of a protein called tumor necrosis factor (TNF), which is made by your immune system.

Etanercept can reduce the effect of TNF in the body and block the damage that too much TNF can cause, but it can also lower the ability of your immune system to fight infections. See “**What is the most important information I should know about Etanercept?**” and “**What are the possible side effects of Etanercept?**”

Who should not use Etanercept?

Do not use Etanercept if you:

- have an infection that has spread through your body (sepsis).

How should I use Etanercept?

- Etanercept is given as an injection under the skin (subcutaneous or SC).
- If your healthcare provider decides that you or a caregiver can give the injections of Etanercept at home, you or your caregiver should receive training on the right way to prepare and inject Etanercept. Do not try to inject Etanercept until you have been shown the right way by your healthcare provider or nurse.
- Etanercept is available in the forms listed below. Your healthcare provider will prescribe the type that is best for you.
 - Single-dose Prefilled Syringe
 - Single-dose Prefilled SureClick Autoinjector
 - Single-dose Vial
- See the detailed Instructions for Use with this Medication Guide for instructions about the right way to store, prepare, and give your Etanercept injections at home.

- Your healthcare provider will tell you how often you should use Etanercept. Do not miss any doses of Etanercept. If you forget to use Etanercept, inject your dose as soon as you remember. Then, take your next dose at your regular(ly) scheduled time. In case you are not sure when to inject Etanercept, call your healthcare provider or pharmacist. **Do not use Etanercept more often than as directed by your healthcare provider.**
- Your child's dose of Etanercept depends on his or her weight. Your child's healthcare provider will tell you which form of Etanercept to use and how much to give your child.

What are the possible side effects of Etanercept?

Etanercept can cause serious side effects, including:

- **See “What is the most important information I should know about Etanercept?”**
- **Infections.** Etanercept can make you more likely to get infections or make any infection that you have worse. Call your healthcare provider right away if you have any symptoms of an infection. See **“Before starting Etanercept, be sure to talk to your healthcare provider”** for a list of symptoms of infection.
- **Previous Hepatitis B infection.** If you have been previously infected with the hepatitis B virus (a virus that affects the liver), the virus can become active while you use Etanercept. Your healthcare provider may do a blood test before you start treatment with Etanercept and while you use Etanercept.
- **Nervous system problems.** Rarely, people who use TNF-blocker medicines have developed nervous system problems such as multiple sclerosis, seizures, or inflammation of the nerves of the eyes. Tell your healthcare provider right away if you get any of these symptoms: numbness or tingling in any part of your body, vision changes, weakness in your arms and legs, and dizziness.
- **Blood problems.** Low blood counts have been seen with other TNF-blocker medicines. Your body may not make enough of the blood cells that help fight infections or help stop bleeding. Symptoms include fever, bruising or bleeding very easily, or looking pale.
- **New heart failure or worsening of heart failure you already have.** New or worse heart failure can happen in people who use TNF-blocker medicines like Etanercept. If you have heart failure your condition should be watched closely while you take Etanercept. Call your healthcare provider right away if you get new or worsening symptoms of heart failure while taking Etanercept, such as shortness of breath or swelling of your lower legs or feet.
- **Psoriasis.** Some people using Etanercept developed new psoriasis or worsening of psoriasis they already had. Tell your healthcare provider if you develop red scaly patches or raised bumps that may be filled with pus. Your healthcare provider may decide to stop your treatment with Etanercept.
- **Allergic reactions.** Allergic reactions can happen to people who use TNF-blocker medicines. Call your healthcare provider right away if you have any symptoms of an allergic reaction. Symptoms of an allergic reaction include a severe rash, a swollen face, or trouble breathing.
- **Autoimmune reactions, including:**
 - **Lupus-like syndrome.** Symptoms include a rash on your face and arms that gets worse in the sun. Tell your healthcare provider if you have this symptom. Symptoms may go away when you stop using Etanercept.
 - **Autoimmune hepatitis.** Liver problems can happen in people who use TNF-blocker medicines, including Etanercept. These problems can lead to liver failure and death. Call your healthcare provider right away if you have any of these symptoms: feel very tired, skin or eyes look yellow, poor appetite or vomiting, pain on the right side of your stomach (abdomen).

Common side effects of Etanercept include:

- **Injection site reactions** such as redness, itching, pain, swelling, bleeding or bruising. These symptoms usually go away within 3 to 5 days. If you have pain, redness, or swelling around the injection site that does not go away or gets worse, call your healthcare provider.
- **Upper respiratory infections** (sinus infections).

These are not all the possible side effects with Etanercept. Tell your healthcare provider about any side effect that bothers you or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Etanercept?

- Store Etanercept in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Store Etanercept in the original carton to protect from light or damage.
- If needed, you may store the Etanercept prefilled syringe, prefilled SureClick autoinjector or single-dose vial at room temperature between 68°F to 77°F (20°C to 25°C) for up to 30 days.
 - When Etanercept has reached room temperature, do not put it back in the refrigerator.
 - Throw away Etanercept that has been stored at room temperature after 30 days.
- **Do not** store Etanercept in extreme heat or cold such as in your vehicle's glove box or trunk.
- **Do not shake.**
- **Do not freeze.**
- **Keep Etanercept and all medicines out of the reach of children.**

General information about the safe and effective use of Etanercept.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Etanercept for a condition for which it was not prescribed. Do not give Etanercept to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Etanercept. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Etanercept that is written for health professionals.

What are the ingredients in Etanercept?**Single-dose Prefilled Syringe, Single-dose Prefilled SureClick Autoinjector and Single-dose Vial:**

Active Ingredient: etanercept

Inactive Ingredients: L-arginine hydrochloride, sodium chloride, and sucrose



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For more information, call 1-888-436-2735 or visit www.etanercept.com.



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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: 01/2026

Instructions for Use
Etanercept (ee – tan – er – sept)
injection, for subcutaneous use
Single-dose Prefilled Syringe
This product is Enbrel® (etanercept).

How do I prepare and give an injection with Etanercept Single-dose Prefilled Syringe?

There are 2 types of Etanercept single-dose prefilled syringes:

- The 50 mg/mL single-dose prefilled syringe that contains one 50 mg dose of Etanercept.
- The 25 mg/0.5 mL single-dose prefilled syringe that contains one 25 mg dose of Etanercept.

Your healthcare provider will tell you which one to use.

A 50 mg dose can be given as one injection using a 50 mg/mL single-dose prefilled syringe or as two injections using 25 mg/0.5 mL single-dose prefilled syringes. Your healthcare provider will tell you whether the two injections with 25 mg/0.5 mL single-dose prefilled syringes should be given on the same day once a week or on two different days (3 or 4 days apart) in the same week.

Children must weigh at least 138 pounds to use the Etanercept 50 mg/mL single-dose prefilled syringe. Children who weigh less than 138 pounds should use a different form of Etanercept. The Etanercept 25 mg/0.5 mL single-dose prefilled syringe should not be used in pediatric patients weighing less than 68 pounds.

Important: The Etanercept prefilled syringe is not made with natural rubber latex.

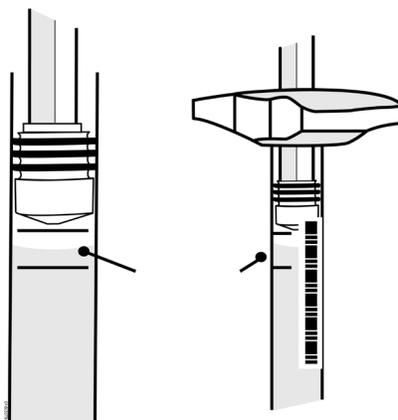
Storage of your Etanercept prefilled syringe

- Store the Etanercept prefilled syringe in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Store the Etanercept prefilled syringe in the original carton to protect from light or physical damage.
- If needed, you may store your Etanercept prefilled syringe at room temperature between 68°F to 77°F (20°C to 25°C) for up to 30 days.
 - Once the Etanercept prefilled syringe has reached room temperature, do not put it back in the refrigerator.
- Throw away any Etanercept prefilled syringe that has been stored at room temperature after 30 days.
- **Do not** store the Etanercept prefilled syringe in extreme heat or cold. For example, avoid storing Etanercept prefilled syringe in your vehicle's glove box or trunk.
- **Do not freeze.**
- **Do not shake.**
- **Keep the Etanercept prefilled syringe and all medicines out of the reach of children.**

If you have any questions about storage, contact your healthcare provider or call 1-888-436-2735 for further instructions.

Step 1: Setting Up for an Injection

1. Select a clean, well-lit, flat work surface, such as a table.
2. Take the Etanercept carton containing the prefilled syringes out of the refrigerator and place it on your flat work surface. Remove one prefilled syringe and place it on your work surface. Carefully lift the prefilled syringe straight up out of the box. **Do not shake** the prefilled syringe of Etanercept. Place the carton containing any remaining prefilled syringes back into the refrigerator at 36°F to 46°F (2°C to 8°C).
3. Check the expiration date on the prefilled syringe. If the expiration date has passed, **do not** use the prefilled syringe and contact your pharmacist or call 1-888-436-2735 for assistance.
4. **Do not** use the prefilled syringe if the needle cover is missing or not securely attached. Call 1-888-436-2735.
5. For a more comfortable injection, leave the prefilled syringe at room temperature for about 15 to 30 minutes before injecting. **Do not** remove the needle cover while allowing it to reach room temperature. **Do not** warm Etanercept in any other way (for example, **do not** warm it in a microwave or in hot water).
6. Hold the prefilled syringe with the covered needle pointing down. If bubbles are seen in the syringe, very gently tap the prefilled syringe to allow any bubbles to rise to the top of the syringe. Turn the syringe so that the purple horizontal lines on the barrel are directly facing you. Check to see if the amount of liquid in the syringe falls between the purple lines. The top of the liquid may be curved. If the syringe does not have the right amount of liquid, **do not** use that syringe. Contact your pharmacist or call 1-888-436-2735 for assistance.



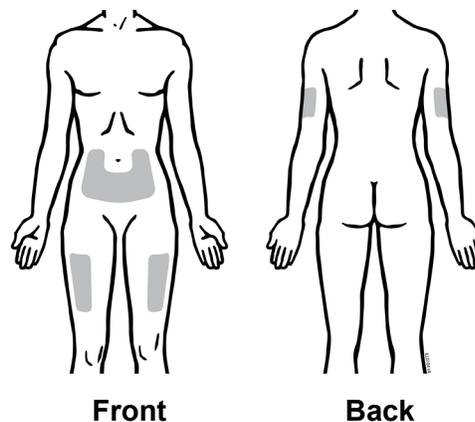
Fill Level Indicator

7. Assemble the additional supplies you will need for your injection. These include an alcohol swab, a cotton ball or gauze, and a sharps disposal container (see “**Step 4: Disposing of Supplies**”).
8. Wash your hands with soap and warm water.

9. Make sure the solution in the prefilled syringe is clear and colorless. You may notice small white particles in the solution. These particles are formed from Etanercept and this is acceptable. However, **do not inject the solution if it is cloudy or discolored, or contains large or colored particles**, call 1-888-436-2735.

Step 2: Choosing and Preparing an Injection Site

1. Recommended injection sites for Etanercept using a prefilled syringe include:
 - the front of the middle thigh
 - the stomach area (abdomen), except for the **2-inch** area right around the navel (belly button)
 - the outer area of the upper arm (only if someone else is giving you the injection)

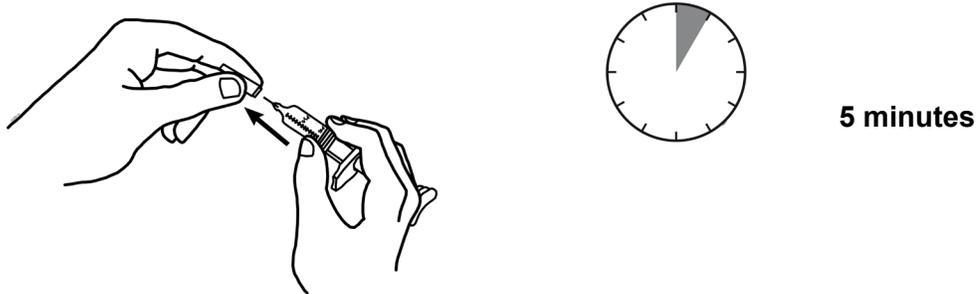


2. Rotate the site for each injection. **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.
3. If you have psoriasis, you should not inject directly into any raised, thick, red, or scaly skin patches or lesions.
4. To prepare the area of skin where Etanercept is to be injected, wipe the injection site with an alcohol swab. **Do not touch this area again before giving the injection.**

Step 3: Injecting Etanercept Using a Prefilled Syringe

Do not remove the needle cover from the prefilled syringe until you are ready to inject.

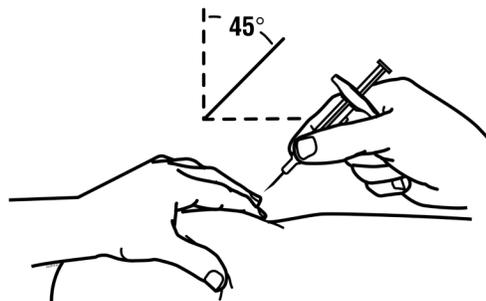
1. Pick up the prefilled syringe from your flat work surface. Hold the barrel of the prefilled syringe with one hand and pull the needle cover straight off, only when you are ready to inject. **Do not** leave the needle cover off for more than **5 minutes**. This can dry out the medicine.



To avoid damaging the needle, **do not** twist or bend the needle cover while you are removing it, and **do not** try to put the needle cover back onto the prefilled syringe.

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.

2. Holding the syringe with the needle pointing up, check the syringe for air bubbles. If there are bubbles, **gently** tap the syringe with your finger until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.
3. Holding the syringe in one hand like a pencil, use the other hand to gently pinch a fold of skin at the cleaned injection site and hold it firmly.
4. With a quick and “dart-like” motion, insert the needle at a 45-degree angle into the skin.



5. When the needle is completely inserted into the skin, let go of the skin that you are holding. With your free hand, hold the syringe near its base to stabilize it. Then push the plunger to inject all of the Etanercept solution at a slow, steady rate.

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 syringe should **never** be reused. **Never** recap a needle.

- Put the used prefilled syringes in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) prefilled syringes in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used syringes and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>
- **Do not** reuse the syringe.
- **Do not** recycle the syringe or sharps disposal container or throw them into household trash.

Important: Always keep the sharps disposal container out of the reach of children.

A healthcare provider familiar with Etanercept should answer all questions. Call 1-888-436-2735 or visit www.etanercept.com for more information about Etanercept.

This Instructions for Use have been approved by the U.S. Food and Drug Administration.

AMGEN

Manufactured by:

Immunex Corporation

Thousand Oaks, CA 91320-1799

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1XXXXXX – vX

Revised: 01/2026



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Instructions for Use
Etanercept (ee – tan – er – sept)
injection, for subcutaneous use
single-dose vial
This product is Enbrel® (etanercept).

Read this Instructions for Use before you start taking Etanercept and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition and treatment.

Step 1: Set up



1a. Strength and dose

Each single-dose vial contains 25 mg (0.5 mL).

Review your prescription carefully for dose and dosing schedule. Only inject Etanercept after you or your caregiver has received training by your healthcare provider. Your healthcare provider will tell you how often you should use Etanercept. **Do not use Etanercept more often than directed by your healthcare provider.** If you forget to use Etanercept, inject your dose right away. Inject your next dose at your regular scheduled time. If you do not know when to inject Etanercept, call your healthcare provider or pharmacist.

Keep Etanercept out of the reach of children.



1b. Store Etanercept single-dose vials

Store Etanercept in the refrigerator between 36°F to 46°F (2°C to 8°C). You may also store the Etanercept single-dose vials at room temperature between 68°F to 77°F (20°C to 25°C) for up to 30 days. Throw away Etanercept that has been stored at room temperature after 30 days.

Do not shake.

Do not freeze or store in extreme heat or cold.

Store Etanercept in the original carton to protect from light or damage.

If your dose is
0.5 mL, or LESS

Remove 1 single-dose vial



If your dose is MORE
than 0.5 mL

Remove 2 single-dose vials



1c. Remove correct number of vials

Remove the correct number of Etanercept single-dose vials from the original carton. Check your prescription to determine if your dose will require 1 or 2 single-dose vials. Your dose is determined in milliliters (mL).

Your child's dose of Etanercept depends on his or her weight. Your child's healthcare provider will tell you which form of Etanercept to use and how much to give your child.

Green vial cap

WAIT



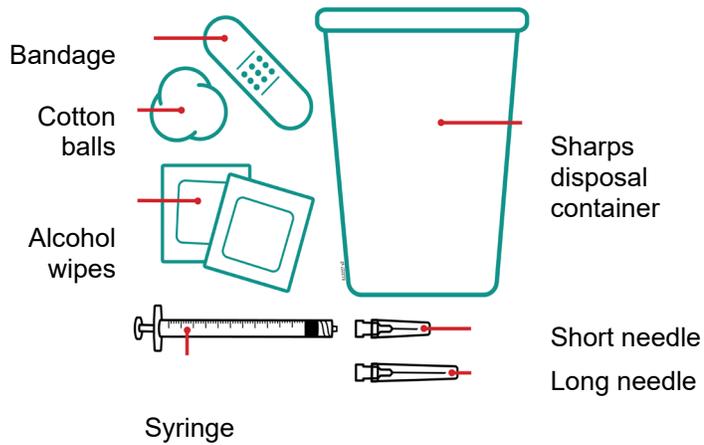
1d. Inspect the single-dose vial(s)

Leave the single-dose vial(s) at room temperature, with the green cap(s) on, for at least 30 minutes. Etanercept is clear and colorless. There may be small white particles in the solution. Check the expiration date. Keep out of direct sunlight.

Do not use Etanercept if:

- the expiration date has passed
- the green cap is not attached
- it has lumps, is discolored, or is cloudy.

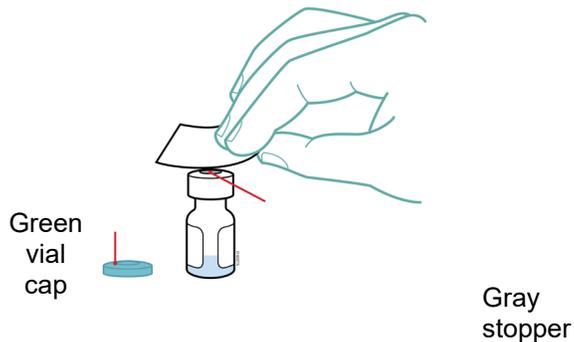
If there are any issues with your Etanercept single-dose vials, please call 1-888-436-2735.



1e. Gather all materials and wash hands
Wash your hands with soap and water.

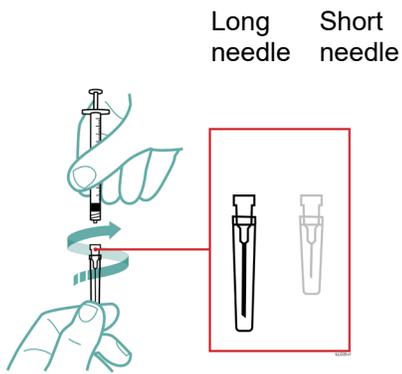
Place the following items on a clean well-lit, flat surface:

- 1 mL syringe
- Long needle: for withdrawal
- Short needle: for injection
- Alcohol wipes
- Cotton balls
- Bandage
- Sharps disposal container



1f. Pop off the green vial cap then wipe the gray stopper
Use an alcohol wipe to clean the gray stopper.

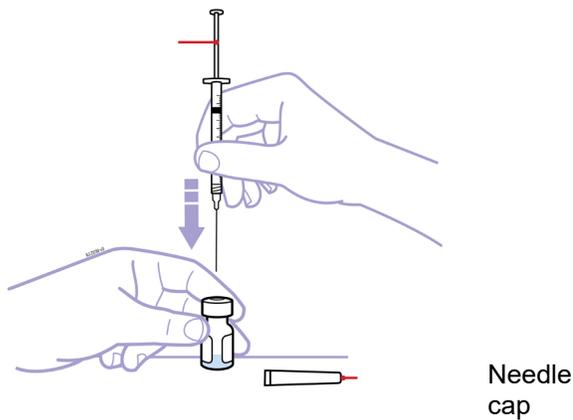
If you require a second single-dose vial, clean the gray stopper of the second single-dose vial with a new alcohol wipe.



1g. Attach the long needle to the syringe
Twist the long needle onto the syringe.

Step 2: Prepare dose

Plunger

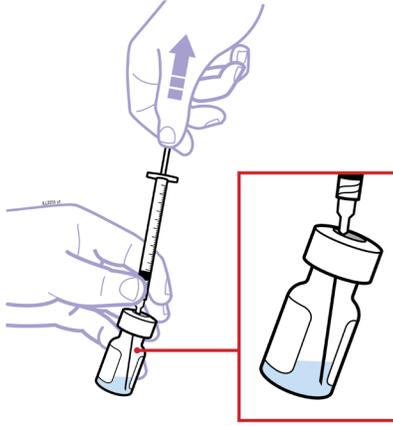


2a. Pull plunger back, insert needle, and push air into single-dose vial
Pull the needle cap straight off and away from your body. Save the needle cap for later.

Pull the syringe plunger back to 0.5 mL.

Hold the single-dose vial on a flat surface with 1 hand. Insert the long needle through the gray rubber stopper above the medicine in the single-dose vial.

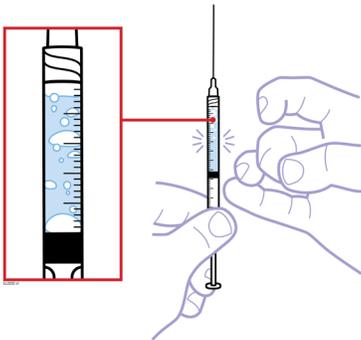
Slowly push 0.5 mL of air into the single-dose vial.



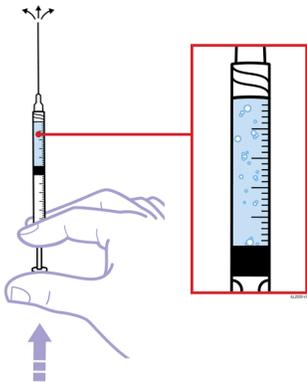
2b. Tilt the single-dose vial to withdraw **all** medicine
Slowly pull back the plunger to fill the syringe **with all the medicine from the single-dose vial**.

Remove needle from the single-dose vial.

The air in the syringe will be removed later.



2c. Gently tap the syringe with fingers to release bubbles
Gently tap the syringe with your fingers to release air pockets and bubbles until they rise to the top of the syringe.

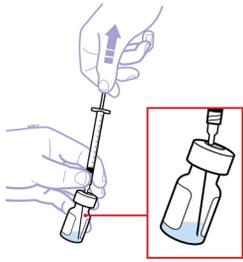


2d. Push out large air pockets and bubbles
After you have gently tapped the large air pockets and bubbles to the top of the syringe, push the plunger up to remove the air out of the syringe.

Small amounts of tiny air bubbles are ok.

If you need 1 single-dose vial, push the plunger to your **total prescribed dose** and continue to step 2g.

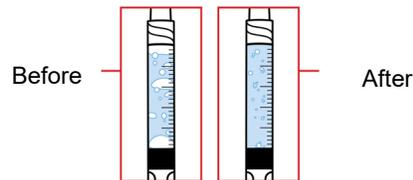
If you need more than 1 single-dose vial to get your **total prescribed dose**, follow these 2 steps:



2e. Insert the same needle in the second vial. Tilt vial to withdraw medicine. Slowly pull back the plunger to fill the syringe **with all medicine from the vial**.

Remove the needle from the single-dose vial.

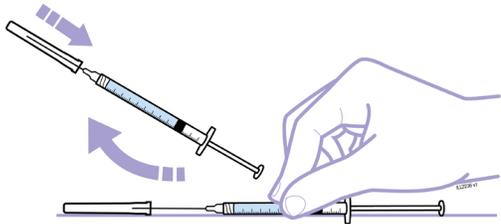
The air will be removed in the next step



2f. Gently tap the syringe to remove the air. Hold the needle pointing up and gently tap the syringe so air bubbles rise to the top.

Push the plunger to **your prescribed dose**.

Small amounts of tiny air bubbles are ok.

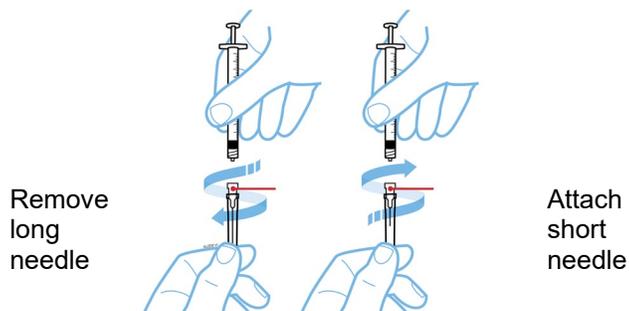


2g. Use 1-handed scoop method to recap. For your safety, place the needle cap on a flat surface.

Using 1 hand, slide the needle into the cap and scoop upwards to cap the needle, without using your other hand.

Then use your other hand to secure the cap and snap into place.

Step 3: Inject and throw away



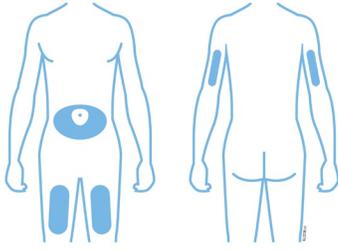
3a. Replace the long needle with the short needle

Twist the long needle off of the syringe.

Throw away the long needle in the sharps disposal container.

Twist the short needle onto the syringe.

Do not remove the needle cover until you are ready to inject.

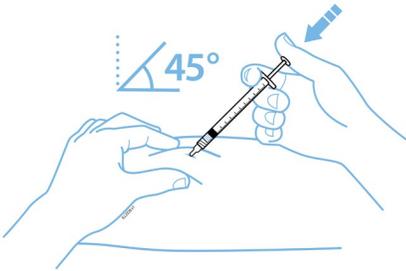


3b. Choose and clean the injection site

- thigh or stomach (avoid 2 inches around the navel)
- back of upper arm (only if someone else is giving the injection)

Choose a different site each time you give yourself an injection. Avoid injecting into tender, raised, red or scaly skin.

Clean the injection site with an alcohol wipe and let dry. **Do not** touch this area again before injecting.



3c. Pinch and inject Etanercept

Gently pinch skin. With a quick firm action, insert the needle into your skin at a 45-degree angle.

When the needle is completely inserted into the skin, slowly push the plunger all the way down.

When the syringe is empty, remove the needle and syringe from your skin. Do not recap the needle.

Do not rub the injection site. If you see drops of blood at the injection site, you can press a cotton ball over the injection site until bleeding has stopped. Apply an adhesive bandage, if needed.



3d. Throw away the used single-dose vials, needles and syringe

Single-dose vials do not contain preservatives and are for **1-time use only**. Unused medicine in the single-dose vials must be thrown away in a sharps disposal container.

Additional disposal information

Do not throw away the vials, needles, and syringe in your household trash.

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic
- can be closed with a tight-fitting, puncture-resistant lid without sharps being able to come out
- upright and stable during use
- leak-resistant
- properly labeled to warn of hazardous waste inside the container

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to throw away your sharps disposal container. There may be state or local laws about how you should throw away used vials, needles and syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>

- Do not throw away your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.
- Do not reuse the vials, syringe, or needles.
- Do not recycle the vials, syringe, needles, or sharps disposal container or throw them into household trash.

Important: Always keep the sharps disposal container out of the reach of children.

If you experience any difficulty using your Etanercept single-dose vials, please call 1-888-436-2735.

If you have any questions about your Etanercept dosing, please call your healthcare provider.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Revised: 01/2026 vX

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Front Panel

**Read these instructions before
using Etanercept
Single-Dose Vial
Instructions for Use**

INSTRUCTIONS FOR USE

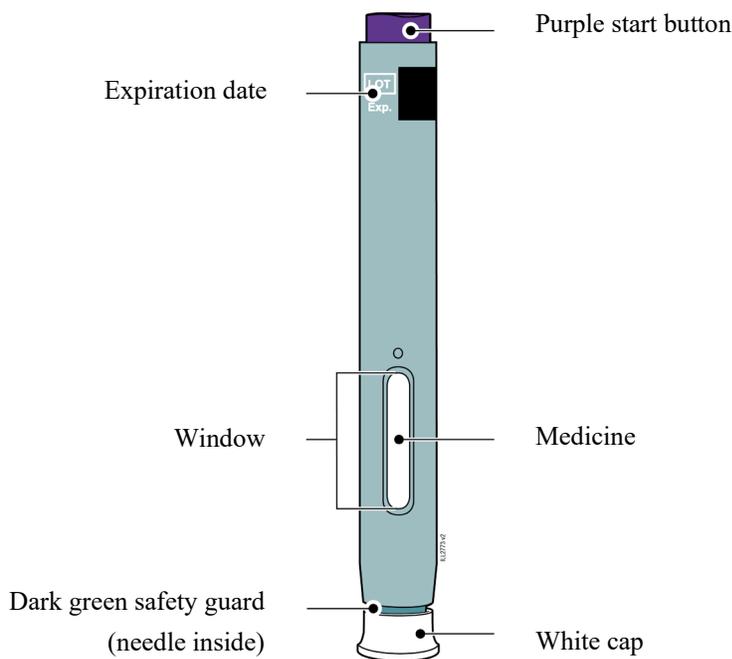
**Etanercept [ee – tan – er – sept]
injection, for subcutaneous use
50 mg/mL
single-dose prefilled SureClick® autoinjector
This product is Enbrel® (etanercept).**

This Instructions for Use contains information on how to inject Etanercept with a prefilled SureClick autoinjector.

If your healthcare provider decides that you or a caregiver may be able to give your injections of Etanercept at home, you should receive training on the right way to prepare and inject Etanercept. Do not try to inject yourself until you have been shown the right way to give the injections by your healthcare provider or nurse.

The medicine in the Etanercept autoinjector is for injection under the skin (subcutaneous injection). See the Etanercept Medication Guide for information about Etanercept.

Getting to know the prefilled autoinjector



50 mg/mL

Important Information You Need to Know Before Injecting Etanercept

- It is important that you do not try to give the injection until you have fully read and understood this Instructions for Use.
- Check the autoinjector label and prescription to make sure you have the correct medicine and dose.
- **Do not** use the autoinjector if the carton is damaged or the seal is broken.
- **Do not** use the autoinjector after the expiration date on the label.
- **Do not** shake the autoinjector.
- **Do not** remove the white cap from the autoinjector until you are ready to inject.
- **Do not** use the autoinjector if it has been frozen.

- **Do not** use the autoinjector if it has been dropped on a hard surface. Part of the autoinjector may be broken even if you cannot see the break. Use a new autoinjector, and call 1-888-436-2735.
- **Children must weigh at least 138 pounds to use the Etanercept prefilled SureClick autoinjector. Children who weigh less than 138 pounds should use a different form of Etanercept.**
- The autoinjector is not made with natural rubber latex.

Frequently asked questions:

For additional information and answers to frequently asked questions, visit www.etanercept.com.

Where to get help:

If you want more information or help using Etanercept:

- Contact your healthcare provider,
- Visit www.etanercept.com, or
- Call 1-888-436-2735.

Storing and Preparing to Inject Etanercept

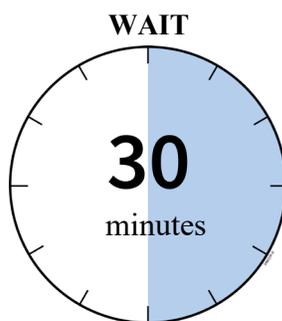


Refrigerate in carton until ready to use

1 Refrigerate the autoinjector carton until you are ready to use it.

- Keep the autoinjector in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep the autoinjector in the original carton to protect it from light or physical damage.
- **Do not** freeze the autoinjector.
- **Do not** store the autoinjector in extreme heat or cold. For example, avoid storing in your vehicle's glove box or trunk.

Important: Keep the autoinjector and all medicines out of the sight and reach of children.



2 Wait 30 minutes for the autoinjector to reach room temperature.

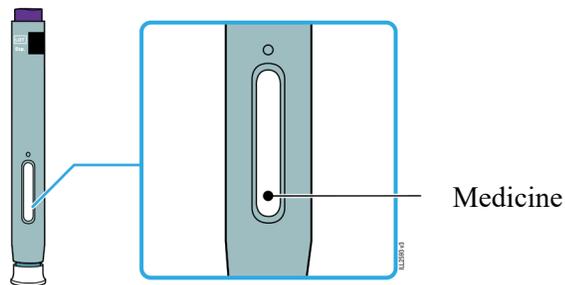
- Remove the autoinjector and put any unused autoinjectors back into the refrigerator.
- Let the autoinjector warm up naturally.
- **Do not** heat the autoinjector with hot water, a microwave, or direct sunlight.
- **Do not** shake the autoinjector at any time.
- Using the autoinjector at room temperature makes sure the full dose is delivered and allows for a more comfortable injection.



3 You may keep Etanercept at room temperature for up to 30 days, if needed.

- For example, when you are traveling, you may keep Etanercept at room temperature.
- Keep it at room temperature between 68°F to 77°F (20°C to 25°C).
- **Do not** put it back in the refrigerator.
- Record the date you removed it from the refrigerator and use it within **30** days.

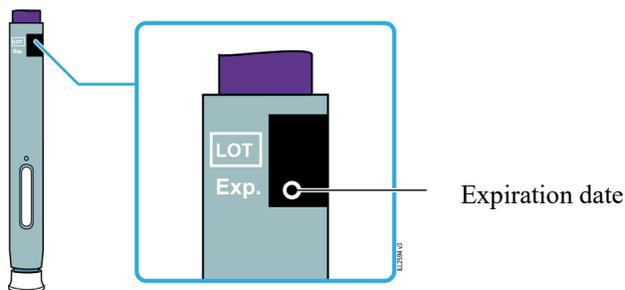
Important: Place the autoinjector in a sharps disposal container if it has reached room temperature and has not been used within **30** days.



4 Inspect the medicine. It should be clear and colorless to slightly yellow.

- It is okay to see air bubbles or small white particles in the medicine.
- **Do not** use the autoinjector if the medicine is cloudy, discolored, or contains large lumps, flakes or colored particles.

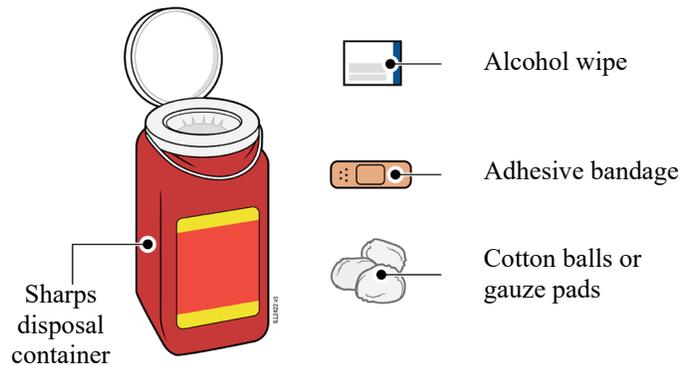
Important: If the medicine is cloudy, discolored, or contains large lumps, flakes or colored particles, or if the autoinjector is damaged or expired, call 1-888-436-2735.



5 Check the expiration date (Exp.) and inspect the autoinjector for damage.

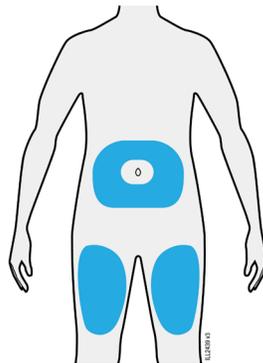
- **Do not** use the autoinjector if the expiration date has passed.
- **Do not** use the autoinjector if:
 - the white cap is missing or loose in carton,
 - it has cracks or broken parts, or
 - it has been dropped on a hard surface.

Getting Ready to Inject Etanercept



6 Gather and place the following items for your injection on a clean, flat, and well-lit surface:

- Etanercept autoinjector (room temperature),
- Sharps disposal container [see Completing the Injection and Disposal],
- Alcohol wipe,
- Adhesive bandage, and
- Cotton balls or gauze pads.



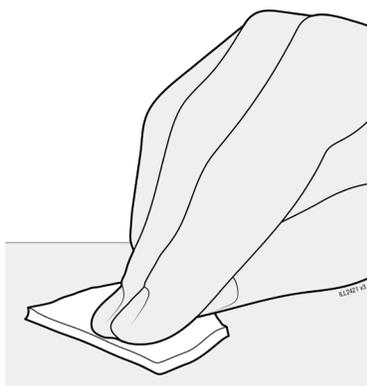
7 Select 1 of these injection sites.

- Select the thigh or stomach (except for 2 inches around the belly button).
- Someone else can inject in your thigh, stomach, or back of the upper arm.
- Change injection site each time, shifting the area of the injection to avoid skin irritation.

Important: Avoid areas with scars or stretch marks, or where the skin is tender, bruised, red, hard, raised, thick or scaly skin patch, or lesion.



8 Wash your hands thoroughly with soap and water.



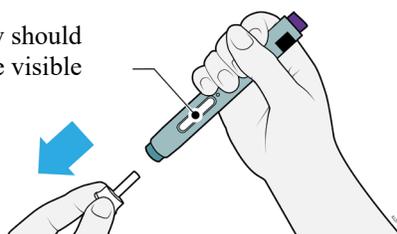
9 Clean the injection site with an alcohol wipe.

- Let the skin dry on its own.
 - **Do not** touch this area again before injecting.
-

Injecting Etanercept

Important: Only remove the white cap when you can inject right away (within 5 minutes) because the medicine can dry out. **Do not** recap.

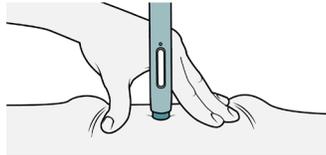
Window should
be visible



10 Grasp the autoinjector so you can see the window. Pull the white cap straight off. You may need to pull hard.

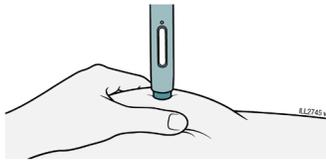
- **Do not** twist, bend, or wiggle the white cap to pull it off.
 - **Never** put the white cap back on. It may damage the needle.
 - **Do not** put your finger inside the dark green safety guard.
 - It is normal to see a drop of medicine come out of the needle or dark green safety guard.
-

STRETCH



OR

PINCH

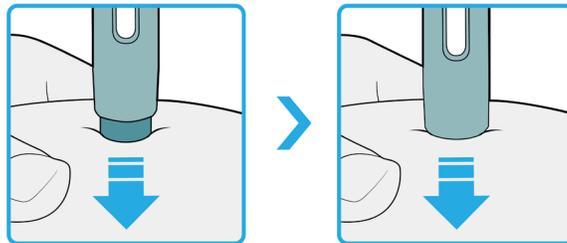


11

Stretch or pinch the skin to create a firm surface at the injection site until the injection is finished. Place the dark green safety guard straight against the skin.

- Make sure you can see the window.
- Make sure the autoinjector is positioned straight on the injection site (at a 90-degree angle).

**PUSH
and hold against skin**

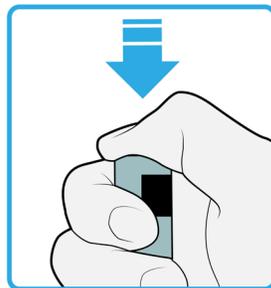


12

Firmly push the autoinjector down until the dark green safety guard stops moving. Hold the autoinjector down, do not lift.

- The dark green safety guard pushes in and unlocks the purple start button.

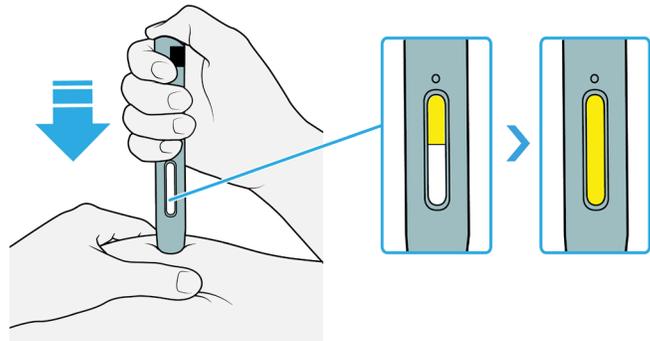
**PRESS
purple start button**



13 Keep pushing the autoinjector down and press the purple start button to start the injection.

- You may hear or feel a click.
- The window starts to turn yellow.
- It is okay to let go of the purple start button.

WATCH
window will turn fully yellow

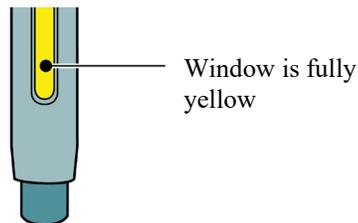


14 Keep pushing the autoinjector down. Wait for the window to turn fully yellow.

- The injection may take up to **15** seconds to complete.
- You may hear or feel a click.
- After the window turns fully yellow, lift the autoinjector away from the skin.
- The dark green safety guard locks around the needle.

Completing the Injection and Disposal

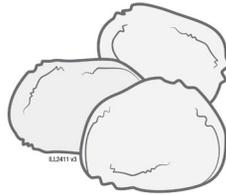
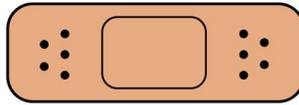
CONFIRM



15 Confirm a full dose of medicine was injected.

- **Do not** touch the dark green safety guard.
- A small drop of liquid on the injection site is okay.

Important: If the window has not turned fully yellow or if it looks like the medicine is still coming out, a full dose was not injected. Call your healthcare provider right away.



16 Check the injection site.

- **Do not** rub the injection site.
- If there is blood, press a cotton ball or gauze pad on your injection site.
- Apply an adhesive bandage if necessary.



17 Place the used autoinjector and white cap in an FDA-cleared sharps disposal.

Important: Do not throw away the autoinjector in your household trash.

- **Do not** reuse the autoinjector.
- **Do not** touch the dark green safety guard.

Additional information about your sharps disposal container

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

Disposing of sharps disposal containers:

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container.

There may be state or local laws about how you should throw away used needles and syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at:

<http://www.fda.gov/safesharpsdisposal>

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this.

Do not recycle your used sharps disposal container.

Keep the autoinjector and sharps disposal container out of the sight and reach of children.

For more information or help call 1-888-436-2735.

Etanercept

The logo for Amgen, consisting of the word "AMGEN" in a bold, black, sans-serif font. The letters are closely spaced and have a slightly irregular, blocky appearance.

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This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 01/2026 vXX

REFERENCE GUIDE

Side
1

Reference Guide

Etanercept [ee - tan - er - sept]
injection, for subcutaneous use
50 mg/mL

This product is Enbrel® (etanercept).

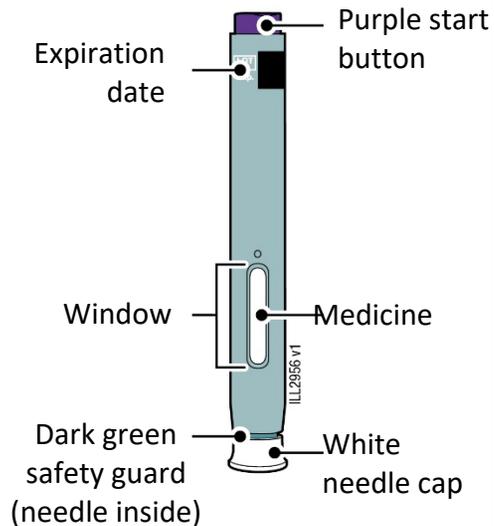
**Read Instructions for Use
in carton before injecting**

Questions?

Call 1-888-436-2735

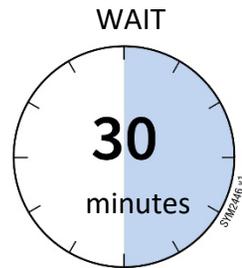


1. Guide to parts

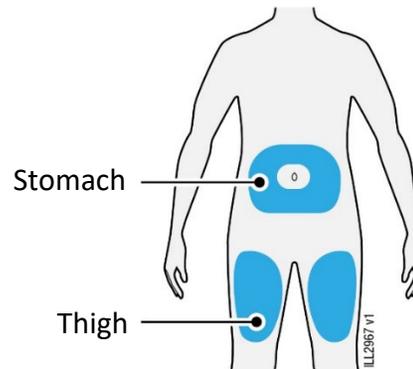


2. Wait 30 minutes

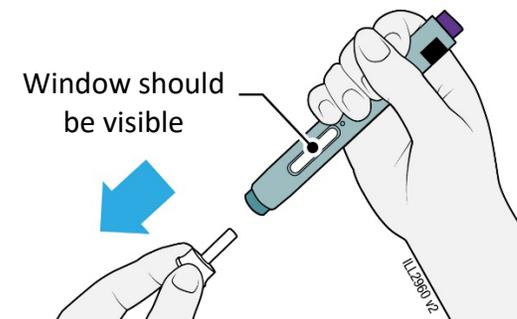
for the autoinjector to reach room temperature before giving your injection.



3. Prepare and clean your injection site.



4. Pull the white cap straight off when you are ready to inject within 5 minutes – the medicine can dry out.



Turn over to continue

Side
2

Reference Guide

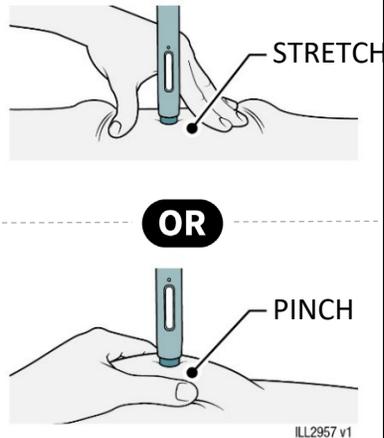
Etanercept [ee – tan – er – sept] injection, for subcutaneous use 50 mg/mL
This product is Enbrel® (etanercept).



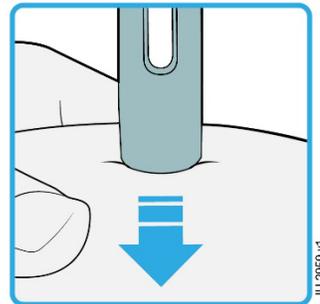
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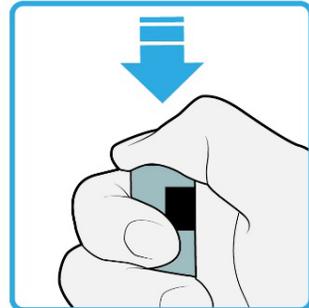
5. Stretch or pinch the skin to create a firm surface at the injection site until the injection is finished.



6. PUSH and HOLD down against the skin. Do not lift.

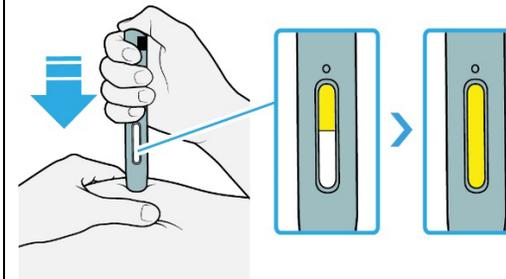


7. PRESS purple start button.



8. Keep pushing down for up to 15 seconds.

Wait for the window to turn fully yellow, then your injection is done.



Revised: 01/2026 vX