

Horizon BCBSNJ
Medical Necessity Guideline

Section	Drugs
Policy Number	
Effective Date	6/25/04
Review Date	2/25/05, 1/2006, 4/27/06, 6/22/06, 11/12/07, 9/26/08

Subject:

BRAND NAME **Enbrel**
(Generic) **(etanercept)**

IMPORTANT NOTE:

*The purpose of this policy is to provide general information applicable to the administration of outpatient prescription drug benefits that Horizon Blue Cross Blue Shield of New Jersey and Horizon Healthcare of New Jersey, Inc. (collectively "Horizon BCBSNJ") insures or administers. **Outpatient prescription drugs are not covered under all Horizon benefit plans.** If the member's contract benefits differ from the pharmacy guideline, the contract prevails. Although a service, supply drug or procedure may be medically necessary, it may be subject to limitations and/or exclusions under a member's benefit plan. If a service, supply drug or procedure is not covered and the member proceeds to obtain the service, supply drug or procedure, the member may be responsible for the cost. Decisions regarding treatment and treatment plans are the responsibility of the physician. This policy is not intended to direct the course of clinical care a physician provides to a member, and it does not replace a physician's or pharmacist's independent professional clinical judgment or duty to exercise special knowledge and skill in the treatment of Horizon BCBSNJ members. Horizon BCBSNJ is not responsible for, does not provide, and does not hold itself out as a provider of medical care. The physician remains responsible for the quality and type of health care services provided to a Horizon BCBSNJ member.*

Horizon BCBSNJ pharmacy guidelines do not constitute medical advice, authorization, certification, approval, explanation of benefits, offer of coverage, contract or guarantee of payment.

BLACK BOX WARNINGS

Risk of infections:

Infections, including serious infection leading to hospitalization or death, have been observed in patients treated with etanercept. Infections have included bacterial sepsis and tuberculosis. Educate patients about the symptoms of infection and closely monitor them for signs and symptoms of infection during and after treatment with etanercept. Evaluate patients who develop an infection for appropriate antimicrobial treatment and, in patients who develop a serious infection, discontinue etanercept.

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been observed in patients receiving tumor necrosis factor (TNF)-blocking agents, including etanercept. Tuberculosis may be due to reactivation of latent tuberculosis infection or to new infection. 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. Evaluate patients for tuberculosis risk factors and test for latent tuberculosis infection prior to initiating etanercept and during treatment. Initiate treatment of latent tuberculosis infection prior to therapy with etanercept. Treatment of latent tuberculosis in patients with a reactive tuberculin test reduces the risk of tuberculosis reactivation in patients receiving TNF blockers. Some patients who tested negative for latent tuberculosis prior to receiving etanercept have developed active tuberculosis. Monitor patients receiving etanercept for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.

FDA-APPROVED INDICATIONS

Enbrel is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. Enbrel can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone or Enbrel could be used alone as monotherapy.

Enbrel is indicated for reducing signs and symptoms of moderately to severely active polyarticular-course juvenile rheumatoid arthritis (JRA) in patients who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs).

Enbrel is indicated for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis. Enbrel can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

Enbrel is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Enbrel is indicated for treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Medical Necessity Guideline:

The following questionnaire may be used to determine medical necessity of Enbrel prescriptions.

CRITERIA FOR APPROVAL		
1. Does the patient have one of the following diagnosis: -Active adult rheumatoid arthritis -Active polyarticular-course Juvenile Idiopathic Arthritis in patients 2-17 years of age -Active ankylosing spondylitis -Active psoriatic arthritis -Reactive arthritis -Inflammatory bowel disease arthritis -Wegener’s granulomatosis that is refractory to standard therapy (i.e., prednisone, cyclophosphamide, methotrexate, azathioprine, cyclosporine) [If the answer is no, then skip to question 3.]	Yes	No
2. Has the patient received at least 3 months of Enbrel therapy? [If the answer to this question is yes, then skip to question 9.] [If the answer to this question is no, then skip to question 10.]	Yes	No
3. Does the patient have a diagnosis of chronic moderate to severe plaque psoriasis? [If the answer to this question is no, then no further questions required.]	Yes	No
4. Has the patient received at least 3 months of Enbrel therapy? [If the answer to this question is yes, then skip to question 9.]	Yes	No
5. Will Enbrel be used for a patient pediatric between ages 4-17? [If the answer is no, then skip to question 7.]	Yes	No
6. Has the patient demonstrated all of the following: -documented failure to respond to topical therapy -documented failure to respond to phototherapy OR increased risk of melanoma -documented contraindication, intolerance, or failure to respond to systemic therapy (e.g., methotrexate, oral cyclosporine, oral retinoids)? [Skip to question 10.]	Yes	No
7. Is this request for two 50 mg injections per week? [If the answer to this question is no, then skip to question 10.]	Yes	No
8. Will the dose above be used for greater than 3 months of therapy? [Skip to question 10.]	Yes	No
9. Does the patient have improvement in symptoms or stabilization of disease after the start of therapy? [Skip to question 13.]	Yes	No
10. Does the patient have an active infection? [If the answer to this question is yes, then no further questions required.]	Yes	No
11. Has the patient been evaluated for latent tuberculosis infection? [If the answer to this question is no, then no further questions required.]	Yes	No

12. Will the patient be receiving an IL-1 inhibitor or another Tumor Necrosis Factor (TNF) blocking agent other than Enbrel (e.g., Humira, Remicade)? Yes No
 [If the answer to this question is yes, then no further questions required.]
13. Is the request for a maintenance dose of MORE THAN the dispensing limit of Enbrel 25 mg (2 injections per week) or Enbrel 50 mg (1 injection per week)? Yes No

Guidelines for Approval

Duration of Approval -6 months				Duration of Approval – 12 months			
Set 1		Set 2		Set 3-		Set 4	
Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)
1	2	3	1	3	1	1	13
11	10	5	4	4	13	2	
	12	6	10	9		9	
	13	11	12				
			13				
Plaque Psoriasis for Adults For initial only: Two 50mg Injections per week for 3 months, then one 50 mg injection per week for 3 months							
Set 5		Set 6					
Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)				
3	1	3	1				
7	4	11	4				
11	5		5				
	8		7				
	10		10				
	12		12				
	13		13				

DRUG LIMITATION CRITERIA

Enbrel 25 mg is limited to 6 kits (24 injections) per 84 days.
 Enbrel 50 mg is limited to 3 kits (12 injections) per 84 days.

Duration of 75 days is used for a 84-day fill to allow for refill processing.

Horizon BCBSNJ Pharmacy Guideline Development Process: This Horizon BCBSNJ Pharmacy Guideline (the “Pharmacy Guideline”) has been developed by Horizon BCBSNJ’s Pharmacy Drug Policy Subcommittee, Clinical Issues Subcommittee, and Quality Improvement Committee which include practicing physicians and pharmacists. This guideline is consistent with generally accepted standards of medical and pharmacy practice, and reflects Horizon BCBSNJ’s view of the subject health care services, supplies drugs or procedures, and in what circumstances they are deemed to be medically necessary or experimental/ investigational in nature. This Pharmacy Guideline also considers whether and to what degree the subject health care services, supplies or procedures are clinically appropriate, in terms of type, frequency, extent, site and duration and if they are considered effective for the illnesses, injuries or diseases discussed. Where relevant, this Pharmacy Guideline considers whether the subject prescription drugs are being requested primarily for the convenience of the covered person or the health care provider. It may also consider whether the prescription drugs are more costly than alternative prescription drugs that are at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the relevant illness, injury or disease. In reaching its conclusion regarding what it considers to be the generally accepted standards of medical and pharmacy practice, Horizon BCBSNJ reviews and considers the following: all credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, physician and health care provider specialty society recommendations, the views of physicians and health care providers practicing in relevant clinical areas (including, but not limited to, the prevailing opinion within the appropriate specialty), the findings and directives of the Food and Drug Administration and any other relevant factor as determined by applicable State and Federal laws and regulations.

RATIONALE

The intent of the criteria is to ensure that patients follow selection elements established by Horizon BCBS New Jersey's medical policies.

ADDITIONAL INFORMATION

Etanercept binds specifically to tumor necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes for rheumatoid arthritis, polyarticular-course juvenile rheumatoid arthritis, and ankylosing spondylitis and the resulting joint pathology. Elevated levels of TNF are found in involved tissues and fluids of patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

Dosage and Administration:

Adult Patients

The recommended dose of Enbrel for adult patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis is 25 mg given twice weekly as a subcutaneous injection 72-96 hours apart. Methotrexate, glucocorticoids, salicylates, nonsteroidal inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with Enbrel. Based on a study of 50 mg Enbrel twice weekly in patients with rheumatoid arthritis that suggested a higher incidence of adverse reactions but similar ACR response rates, doses higher than 25mg twice weekly are not recommended.

JRA Patients

The recommended dose of Enbrel for pediatric patients ages 4 to 17 years with active polyarticular-course JRA is 0.4mg/kg given twice weekly (up to a maximum of 25 mg per dose) as a subcutaneous injection 72-96 hours apart. Glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with Enbrel. Concurrent use with methotrexate and higher doses of Enbrel have not been studied in pediatric patients.

Enbrel is supplied in a carton containing four dose trays. Each dose tray contains one 25 mg vial of etanercept.

CONTRAINDICATIONS/WARNINGS/PRECAUTIONS

Warnings:

INFECTIONS

In Post-marketing reports, serious infections and sepsis, including fatalities, have been reported with the use of Enbrel. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections. Rare cases of tuberculosis (TB) have been observed in patients treated with TNF antagonists, including Enbrel. Patients who develop a new infection while undergoing treatment with Enbrel should be monitored closely. Administration of Enbrel should be discontinued if a patient develops a serious infection or sepsis. Treatment with Enbrel should not be initiated in patients with active infections including chronic or localized infections. Physicians should exercise caution when considering the use of Enbrel in patients with a history of recurring infections or with underlying conditions which may predispose patients to infections, such as advanced or poorly controlled diabetes. In a 24-week study of concurrent Enbrel and anakinra therapy, the rate of serious infections in the combination arm (7%) was higher than with Enbrel alone (0%). The combination of Enbrel and anakinra did not result in higher ACR response rates compared to Enbrel alone.

Neurological Events

Treatment with Enbrel and other agents that inhibit TNF have been associated with rare cases of new onset or exacerbation of central nervous system demyelinating disorders, some presenting with mental status changes and some associated with permanent disability. Cases of transverse myelitis, optic neuritis, multiple sclerosis, and new onset or exacerbation of seizure disorders have been observed in association with Enbrel therapy. The causal relationship to Enbrel therapy remains unclear. While no clinical trials have been performed evaluating Enbrel therapy in patients with multiple sclerosis, other TNF antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity. Prescribers should exercise caution in considering the use of Enbrel in patients with pre-existing or recent-onset central nervous system demyelinating disorders.

Hematologic Events

Rare reports of pancytopenia, including aplastic anemia, some with a fatal outcome, have been reported in patients treated with Enbrel. The causal relationship to Enbrel therapy remains unclear. Although no high-risk group has been identified, caution should be exercised in patients being treated with Enbrel 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 Enbrel. Discontinuation of Enbrel therapy should be considered in patients with confirmed significant hematologic abnormalities. Two percent of patients treated concurrently with Enbrel and anakinra developed neutropenia. While neutropenic, one patient developed cellulitis which recovered with antibiotic therapy.

Precautions:

Allergic Reactions

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

Patients with Heart Failure

There have been post-marketing reports of worsening of congestive heart failure (CHF) with and without identifiable precipitating factors, in patients taking Enbrel. There have also been rare reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. Physicians should exercise caution when using Enbrel in patients who have heart failure, and monitor patients carefully.

Immunosuppression

Anti-TNF therapies, including Enbrel, affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. The impact of treatment with Enbrel on the development and course of malignancies, as well as active and /or chronic infections, is not fully understood. The safety and efficacy of Enbrel in patients with immunosuppression or chronic infections have not been evaluated.

Immunizations

Most psoriatic arthritis patients receiving Enbrel were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had two-fold rise in titers compared to patients not receiving Enbrel. The clinical significance of this is unknown. Patients receiving Enbrel may receive concurrent vaccinations, EXCEPT for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving Enbrel.

It is recommended that JRA patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating Enbrel therapy. Patients with a significant exposure to varicella virus should temporarily discontinue Enbrel therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

Autoimmunity

Treatment with Enbrel may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome which may resolve following withdrawal of Enbrel. If a patient develops symptoms and findings suggestive of a lupus-like syndrome following treatment with Enbrel, treatment should be discontinued and the patient should be carefully evaluated.

Pediatric Use

Enbrel has not been studied in children < 4 years of age.

REFERENCES

1. Enbrel (etanercept) Product Information. Immunex Corporation. July 2003.
2. Enbrel in Early Rheumatoid Arthritis – Executive Summary. Immunex Corporation. June 2000.
3. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of Rheumatoid Arthritis – 2002 Update. *Arthritis & Rheumatism* 2002;46:328-346
4. Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. *Lancet* 2000; 356(9227): 385-390.
5. Centers for Disease Control and Prevention. 2000. Targeted tuberculin testing and treatment of latent tuberculosis infection. *American Thoracic Society. M.M.W.R.* 2000;49(RR-6):1-51

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