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Medication Policy Manual

Policy No: dru035

Topic: Enbrel[®], etanercept

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IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Etanercept (Enbrel[®]) binds to and inhibits the activity of tumor necrosis factor (TNF), a proinflammatory cytokine. Etanercept is administered as a subcutaneous injection.

Policy/Criteria

- I. Most contracts require prior authorization approval of etanercept for coverage. Etanercept may be considered medically necessary when the following criteria below (A through D) are met.

- A. **Psoriatic arthritis** when the diagnosis is established by a rheumatologist or a dermatologist.

OR

- B. **Ankylosing spondylitis** when the diagnosis is established by a rheumatologist.

OR

- C. **Rheumatoid arthritis (RA) or juvenile rheumatoid arthritis (JRA, Juvenile Idiopathic Arthritis) when:**

1. There is a diagnosis that has been established by a rheumatologist (or, for RA, by the criteria in Appendix 1).

AND

2. Methotrexate is ineffective after at least a 6 to 12 week treatment course based on documentation which includes one or more of the assessment components listed in Appendix 2 except if methotrexate is contraindicated or not tolerated based on clinical documentation.

OR

- D. **Chronic Plaque Psoriasis:** Initial authorization for etanercept may be considered medically necessary for patients when all of the following criteria (1 through 4) below are met:

1. Chart notes support a diagnosis of chronic plaque psoriasis involving at least 10% of the body surface area or causes significant functional disability.

AND

2. The prescribing physician is a dermatologist or rheumatologist.

AND

3. Treatment with phototherapy or photochemotherapy was ineffective, contraindicated, or not tolerated (see appendix 3).

AND

4. Treatment with at least one oral systemic agent for psoriasis was ineffective or not tolerated, unless all are contraindicated. Examples of systemic agents include, but are not limited to, cyclosporine, methotrexate, and acitretin.

II. Administration, Quantity Limitations, and Authorization Period

- A. Regence considers etanercept to be a self-administered medication.
- B. When prior authorization is approved, etanercept may be authorized in quantities as follows:
 1. **Rheumatologic conditions (rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis):** 50mg per week (given as a single 50mg weekly dose or 25mg twice weekly).*
 2. **Chronic Plaque Psoriasis**
 - a. Initial authorization may be given for doses up to 50mg twice per week for the first 3 months.*
 - b. Maintenance therapy does not exceed doses of 50mg per week.*
- C. *The use of etanercept at a dose greater than 50 mg per week is considered not medically necessary except when used in the initial 3 months of therapy for chronic plaque psoriasis.
- D. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

- III.** Etanercept is considered investigational when used for all other conditions, including, but not limited to:
- A.** The combined use of etanercept and a monoclonal antibody, tumor necrosis factor (TNF) or interleukin-1 (IL-1) inhibitor, such as adalimumab, infliximab or anakinra.
 - B.** Asthma
 - C.** Cancer Anorexia/Weight Loss Syndrome
 - D.** Cardiac Transplant Recipients
 - E.** Chronic Discogenic Low Back Pain
 - F.** Graft-Versus-Host Disease
 - G.** Hepatitis C Infection
 - H.** Metabolic Syndrome
 - I.** Non-plaque psoriasis
 - K.** Polymyalgia Rheumatica
 - L.** Polymyositis
 - M.** Reactive Arthritis
 - N.** Sarcoidosis
 - O.** Sjögren’s Syndrome
 - P.** Type 2 Diabetes
 - Q.** Wegener’s Granulomatosis

Position Statement

Treatment of rheumatic disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis) [1, 11, 39-43, 47, 49]

- There are many treatments for rheumatic disorders that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.

- Non-medical therapies, such as prescribed exercise therapy, physical therapy and weight loss, are important components in any treatment plan for patients suffering from a rheumatic disorder.
- When a systemic medication therapy is needed to manage one of the rheumatic disorders, oral therapies are usually the best value.
 - * Medications to control inflammation, such as nonsteroidal antiinflammatory medications (e.g., meloxicam, nabumetone, and naproxen) and glucocorticoids (oral and injected into the joint) are effective for the management of symptoms, particularly during the early stages of disease.
 - * Orally administered disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX), hydroxychloroquine, leflunomide, and sulfasalazine, are effective for decreasing symptoms and slowing disease progression, have a proven track record, and have been the standard of care for many years.
 - * Oral therapies have known potential risks. The management of these risks is well established.
- Methotrexate is considered effective in the treatment of RA and the standard reference DMARD to which newer DMARDs (etanercept, anakinra, adalimumab, and leflunomide) are compared for efficacy.
- When non-medical therapies and oral medications are inadequate, the biologic medications (e.g., adalimumab, etanercept, infliximab, or abatacept) may be appropriate. Certolizumab and rituximab have been studied in RA, but their role in therapy remains uncertain at this time.
- No studies have shown that any of biologic medications are more effective than another in the treatment of rheumatic disorders, with the exception that there is indirect evidence that anakinra may be less effective than other alternatives.
 - * The biologic DMARDs can decrease symptoms, help preserve joint functioning, and slow the progression of rheumatic disease.
 - * There have been no reliable, direct-comparative trials that have demonstrated a difference in clinical effect or safety of one agent over another.
 - * Individual responses and tolerability are unpredictable and may vary between patients.

- * Because responses vary, if one of the biologic DMARDs provides an inadequate response, another biologic medication may yet be effective.
- * In RA, the best response is seen when methotrexate is used concomitantly with any of the biologics. Infliximab has been shown to be effective only when used with methotrexate.

Efficacy of biologic agents in rheumatic conditions [1, 11, 34-39, 43, 49]

The benefit of medications can be indirectly compared by calculating their number needed to treat (NNT). The number needed to treat is a measure of the chances of a patient achieving a benefit (how many patients need to be treated before a benefit is achieved over a certain period of time). The lower the number needed to treat, the more likely the medication will have benefit.

Table 1 summarizes the chances that certain biologic rheumatologic medications will improve joint pain and stiffness in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis:

Table 1: Chances of improving joint pain and stiffness by at least 20% after six months of treatment with biologic medications (compared to no treatment). [1, 11, 34-39, 43, 49]

Biologic Medications (when used with methotrexate)	Rheumatoid Arthritis	Psoriatic Arthritis	Ankylosing Spondylitis
adalimumab (Humira) etanercept (Enbrel) infliximab (Remicade)	About 1 in 3 likely to benefit ^a NNT = 3 (Range 2-4)	About 1 in 3 likely to benefit ^a NNT = 3	About 1 in 4 likely to benefit ^a NNT = 4 (Range 3-4)
abatacept (Orencia)	About 1 in 4 likely to benefit ^a NNT = 4 (Range 3-4)	N/A	N/A
anakinra (Kineret)	About 1 in 7 likely to benefit ^a NNT = 7	N/A	N/A
certolizumab (Cimzia)	Uncertain ^b	N/A	N/A
rituximab (Rituxan)	Uncertain ^b	N/A	N/A

^a Benefit = at least 20% improvement in joint pain and stiffness after six months of treatment.

^b The trials for these medications had flaws that make estimating their efficacy uncertain. These flaws included large numbers of patients not completing the clinical trials, not all patients counted in the final results, and uncertainty about whether patients and caregivers were truly unaware of the assigned treatments.

- There is reliable evidence that etanercept, adalimumab, and abatacept (when given with methotrexate) are effective in the management of patients with juvenile idiopathic arthritis (JIA). The design of the clinical studies prevents calculation of “number-needed-to-treat” (NNT) for this use. [1, 41, 43]

Efficacy of etanercept in rheumatic conditions

- Long-term experience with etanercept has been published. Persistence with therapy was reported to range between 66% at 3 years and 41% at 6 years. ACR20 scores ranged from 78% at 3 years to 73% at 6 years. ^[16,17]
- Combining etanercept with another DMARD (methotrexate) resulted in statistically better patient responses as measured by ACR or DAS scores than with any agent alone. ^[18,19] Therapy with etanercept either alone or combined resulted in improved patient responses over sulfasalazine alone in patients who had had an inadequate response to sulfasalazine. ^[20]
- The recommended dose of etanercept for adult patients with RA, PsA, or AS is 50 mg weekly, given as a single subcutaneous (SC) injection or as 25 mg given twice weekly SC 72-96 hours apart. ^[1,32] The recommended dose for pediatric patients ages 4 to 17 with active polyarticular-course JRA is 0.8 mg/kg SC each week (up to a maximum of 50 mg per week).
- In a head-to-head trial comparing etanercept 25 mg twice weekly to 50 mg twice weekly in patients with active rheumatoid arthritis, the higher dose resulted in similar efficacy responses but had an increase in upper respiratory tract infections (26% vs. 4%, P=0.027, NNH=6) ^[21]

Treatment of plaque psoriasis ^[1, 39, 43-46,]

- There are many treatments for psoriasis that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.
 - * Light therapy, including UVB and PUVA is very effective and safe. UVB therapy can be used at home, as well as at the doctor's office. PUVA can result in long term remissions.
 - * When systemic therapy is needed to manage psoriasis, oral therapies are the best value.
 - Oral therapies, including methotrexate and cyclosporine, have a proven track record and have been the standard of care for many years.
 - Oral medications are effective for most patients, and cyclosporine is known to work rapidly.
 - Oral therapies have known potential risks. The management of these risks is well established.

- When oral medications and phototherapy are inadequate, the biologic medications (e.g., adalimumab, etanercept, infliximab, efalizumab, alefacept) may be appropriate. Each of these biologics been shown to be effective for psoriasis.
- There are no studies that have shown any one TNF- α inhibitor (including etanercept, adalimumab, and infliximab) to be more effective than any other.
- Alefacept and efalizumab are also effective in some patients, but there is indirect evidence that they may be less effective than other alternatives.
- Individual responses and tolerability are unpredictable and may vary between patients.
- Because responses vary, if one of the biologic DMARDs provides an inadequate response, another biologic medication may yet be effective.

Efficacy of biologic agents in plaque psoriasis [1, 39, 43-46,]

The benefit of medications can be indirectly compared by calculating their number needed to treat (NNT). The number needed to treat is a measure of the chances of a patient achieving a benefit (how many patients need to be treated before a benefit is achieved over a certain period of time). The lower the number needed to treat, the more likely the medication will have benefit.

Table 2 summarizes the chances that certain biologic medications will improve size and thickness of skin lesions, redness, and itching in moderate to severe plaque psoriasis:

Table 2: Chances of improving skin lesions, redness, and itching by 75% after 12 to 16 weeks of treatment with biologic medications (compared to no treatment). [1, 39, 43-46.]

Medications	Benefit In Moderate To Severe Plaque Psoriasis
etanercept (Enbrel), adalimumab (Humira), infliximab (Remicade)	About 1 in 3 likely to benefit ^a NNT = 3 (Range 2-4)
alefacept (Amevive)	About 1 in 9 likely to benefit ^a NNT = 9 (Range 2 – 4)
efalizumab (Raptiva)	About 1 in 5 likely to benefit ^a NNT = 5 (Range 3 – 6)

^a Benefit = at least 75% improvement in size and thickness of skin lesions, redness, and itching after 12 to 16 weeks of treatment.

Efficacy of etanercept in plaque psoriasis

- Etanercept was shown to be safe and efficacious in two double-blind, randomized controlled trials.
- There are no data available establishing that continued therapy with etanercept at a dose of 50 mg twice weekly (beyond 3 months of initial therapy) offers a significant advantage over continued therapy with 50 mg of etanercept weekly. [29]
- In one 24-week double-blind study, 672 patients with plaque psoriasis were randomized to received etanercept 25 mg once weekly (low dose), 25 mg twice weekly (medium dose) or 50 mg twice weekly (high dose) for 24 weeks. [12] High-dose etanercept appeared to be more effective initially, but the incremental benefit was not sustained.
 - * At the initial, 12-week efficacy assessment, there was a statistically significant difference in the proportion of patients achieving a PASI 75 response when patients receiving an initial dose of 25 mg twice weekly were compared to patients receiving an initial dose of 50 mg twice weekly (34% versus 49%, respectively; p<0.005). [12]

- * At 24 weeks, there was at least a 75% improvement in the psoriasis area and severity index (PASI 75 response) in 25% of patients in the low-dose group, 44% of patients in the medium dose-group, and 59% of the patients in the high-dose group, compared with 4% in the placebo group.^[12] There was no statistical difference between groups receiving 25 mg twice weekly and 50 mg twice weekly at 24 weeks.
- Another blinded, randomized, controlled trial evaluated 618 patients with moderate-to-severe plaque psoriasis who were randomized to 12 weeks of placebo or etanercept 50 mg twice weekly.^[23]
 - * At week 12, 47% of the patients receiving etanercept achieved a PASI 75 score, as compared to 5% of the patients receiving placebo (P<0.0001).
 - * After week 12, patients were allowed to continue etanercept 50 mg SC twice weekly, or begin etanercept 50 mg SC twice weekly (placebo patients) in an open-label extension trial for up to 96 weeks. No significant safety signals were detected (see the Safety section). PASI 75 scores at 96 weeks were approximately 51% in both groups, which is consistent with other studies of etanercept in plaque psoriasis.^[29]
- Patients with plaque psoriasis (n=409) who responded to etanercept after a 24-week blinded, randomized controlled trial were re-randomized to receive their previous dose (25 mg or 50 mg twice weekly) or placebo for a single 12-week retreatment after disease relapse. Response rates seen after re-treatment were similar to those seen during the original treatment. There was no significant difference between the higher and lower doses.

Use of etanercept in other conditions

ASTHMA

- Thirty-nine patients with severe corticosteroid refractory asthma demonstrated a small but statistically significant improvement in Asthma Control (ACQ) Questionnaire scores after 12 weeks of etanercept, compared to placebo. Larger randomized, placebo controlled trials are required to clarify the role of TNF- α blockers in subjects with severe refractory asthma.^[48]

CANCER ANOREXIA/WEIGHT LOSS SYNDROME

- Etanercept administered at a dose of 25 mg SC twice-weekly did not appear to palliate the cancer anorexia/weight loss syndrome in 63 patients with advanced disease.^[25]

CARDIAC TRANSPLANT RECIPIENTS

- Etanercept administered at a dose of 25 mg SC twice weekly did not appear to have a statistically significant effect on the change in left ventricular mass from baseline to 6 months (vs. placebo) in 49 randomized cardiac transplant recipients. ^[27]

CHRONIC DISCOGENIC LOW BACK PAIN

- Etanercept administered as intra-disc injections in an escalating dose protocol did not appear to result in statistically significant improvement in pain or disability scores in 36 patients with low back pain. ^[28]

GRAFT-VERSUS-HOST DISEASE

- No randomized controlled trials have been published evaluating the use of etanercept in patients with graft-versus-host disease.

HEPATITIS C INFECTION

- Fifty patients with chronic hepatitis C virus (HCV) infection were randomly assigned to receive interferon alfa-2b and ribavirin with either etanercept or placebo for 24 weeks. At 24 weeks, HCV RNA was absent in 63% (12/19) of etanercept patients compared to 32% (8/25) of placebo patients (P=0.04). The results of this trial are confounded by the small number of patients and the lack of a true ITT analysis. Larger, better designed trials are needed to fully evaluate etanercept for this indication. ^[26]

METABOLIC SYNDROME

- No randomized controlled trials have been published evaluating the use of etanercept in patients with metabolic syndrome using clinically relevant endpoints, such as mortality, progression to development of diabetes, or progression to other diabetic complications.

NON-PLAQUE PSORIASIS

- Patients with guttate, erythrodermic, or pustular psoriasis at the time of screening were excluded from the clinical trials and use of etanercept in these conditions is considered investigational. ^[12]

POLYMYALGIA RHEUMATICA

- No randomized controlled trials have been published evaluating the use of etanercept in patients with Polymyalgia Rheumatica

POLYMYOSITIS

- No randomized controlled trials have been published evaluating the use of etanercept in patients with polymyositis.

REACTIVE ARTHRITIS

- No randomized controlled trials have been published evaluating the use of etanercept in patients with reactive arthritis.

SARCOIDOSIS

- In a small randomized, double-blind, placebo-controlled trial, 18 patients with chronic ocular sarcoidosis were randomized to receive etanercept 25 mg SC twice weekly or placebo for 6 months. There was no apparent reduction in corticosteroid use or improvement in ophthalmology global assessment between the treatment and control groups.^[37]

SJÖGREN'S SYNDROME

- Twenty-eight subjects with Sjögren's Syndrome were randomized to receive etanercept 25 mg twice weekly or placebo for 12 weeks in a randomized, controlled fashion. At the end of the study period, there were no significant differences in the subjective measures of disease severity.^[24]

TYPE 2 DIABETES

- No randomized controlled trials have been published evaluating the use of etanercept in patients with type 2 diabetes.

WEGENER'S GRANULOMATOSIS

- A randomized, placebo-controlled trial in 180 patients with Wegener's granulomatosis failed to show a statistically significant improvement in the maintenance of remission in patients treated with etanercept compared to placebo. The trial did reveal statistically significant increases in the risk of solid tumors among patients receiving etanercept. (P=0.01)^[38]

Safety of etanercept

- Etanercept carries a bolded warning stating that in post-marketing experience, serious infections and sepsis have been reported with the use of etanercept.^[1] Additionally, the warning states that rare cases of tuberculosis have been observed in patients treated with TNF-antagonists, including etanercept.
- The rate of serious infections was found to be higher in patients receiving a combination of etanercept and anakinra (7%) as compared to that in patients receiving either agent alone (0%).^[1] Additionally, the combination was not found to result in improved efficacy based on ACR response rates.
- The safety of etanercept 50 mg twice weekly administered in an open-label fashion for up to 96 weeks in patients with moderate to severe plaque psoriasis was reported.^[29]
 - * The most frequently observed non-infectious events included headache, injection-site hemorrhage, arthralgia, and back pain.
 - * Rates of infection and serious infections were similar between placebo and etanercept exposures.
 - * Longer-term studies are needed to detect potential increases in rare events, such as increase incidence of cancer or rare infectious disease.
- Longer-term safety data has been published. In general, rates of serious adverse reactions in patients treated up to 7 years in open-label, extension studies was similar to those seen in the shorter-term, randomized controlled trials. Frequent adverse events included upper respiratory infections, flu syndrome, rash and injection-site reactions.^[16,17]
- A meta-analysis was performed to assess the safety and efficacy of etanercept in elderly subjects with rheumatoid arthritis. A total of 1,353 subjects from 4 randomized controlled clinical trials were included in the analysis. In general, elderly patients tended to have more serious adverse-events than younger patients, but the rate in etanercept-treated elderly patients was similar to placebo-treated and methotrexate-treated elderly patients.^[13]
- Caution should be exercised before considering the use of etanercept in patients with pre-existing or recent onset of central nervous system demyelinating disorders.^[1]

Appendix 1: American College of Rheumatology (ACR) Classification Criteria for Establishing the Diagnosis of Rheumatoid Arthritis (RA) ^[16]

Diagnosis of RA requires the presence of at least 4 of 7 criteria below:

1.	Morning stiffness in and around joints lasting more than 1 hour.
2.	Arthritis in at least 1 area in a wrist or proximal interphalangeal (PIP) joint (hands or fingers) for > 6 weeks.
3.	Simultaneous swelling or fluid accumulation in 3 or more joints for > 6 weeks.
4.	Symmetric (bilateral joint) involvement for > 6 weeks.
5.	Presence of rheumatoid nodules.
6.	Positive serum rheumatoid factor.
7.	Radiographic changes typical of RA (erosion or unequivocal bony decalcification in or adjacent to the involved joint) on hand and wrist present.

Appendix 2: American College of Rheumatology (ACR) Assessment Components for Improvement in Rheumatoid Arthritis (RA) ^[17]

-	Tender joint count.
-	Swollen joint count.
-	Patient's assessment of pain.
-	Patient's global assessment of disease activity.
-	Physician's global assessment of disease activity.
-	Patient's assessment of physical function.

Appendix 3: Absolute and Relative Contraindications for Phototherapy or Photochemotherapy

Situations where phototherapy may be absolutely or relatively contraindicated include:

- Type 1 or type 2 skin
- History of photosensitivity
- Treatment of facial lesions
- Presence of premalignant lesions
- History of melanoma or squamous-cell carcinoma
- Physical inability to stand for the required exposure time

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Cross References
Humira [®] , adalimumab dru081
Kineret [®] , anakinra dru049
Orencia [®] , abatacept dru129
Remicade [®] , infliximab dru036
Amevive [®] , alefacept dru088
Raptiva [®] , efalizumab dru104
Cimzia [®] , certolizumab dru160

Codes	Number	Description
		Retail drug
HCPCS	J1438	Etanercept 25 mg and 50 mg (this code is used only when drug is given under direct supervision of a physician, not for use when drug is self-administered).