Enbrel® (etanercept)
Erelzi (etanercept-szzs) - biosimilar

Policy Number: 5.01.501
Last Review: 08/2019
Origination: 09/2003
Next Review: 08/2020

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Enbrel® (etanercept) and biosimilars when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Enbrel® (etanercept) requires prior authorization through the pharmacy services area. Enbrel® is considered medically necessary in the treatment of the following conditions:

Rheumatoid arthritis
- In combination with methotrexate or alone 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*, in patients who have had inadequate response to one or more DMARDs (disease-modifying anti-rheumatic drugs (i.e., methotrexate, sulfasalazine)).
- Etanercept will be considered for coverage at a dosage of 25 mg injected subcutaneously twice weekly 72-96 hours apart or 50 mg injected subcutaneously once weekly as specified in the product information provided by the manufacturer.

Polyarticular juvenile idiopathic arthritis
- Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages 2 and older.

Psoriatic arthritis
- Reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis. Etanercept can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.
- Etanercept will be considered for coverage at a dosage of 25 mg injected subcutaneously twice weekly 72-96 hours apart or 50 mg injected subcutaneously once weekly as specified in the product information provided by the manufacturer.

Ankylosing spondylitis
- Reducing signs and symptoms in patients with active ankylosing spondylitis*; in patients who have not had an adequate response to conventional therapy; (i.e., nonsteroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, methotrexate);
- Etanercept will be considered for coverage at a dosage of 25 mg injected subcutaneously twice weekly 72-96 hours apart or 50 mg injected subcutaneously once weekly as specified in the product information provided by the manufacturer.
Plaque Psoriasis

- Treatment of patients 4 years and older (Enbrel) or 18 years and older (Erelzi) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy after a 12-week course of treatment of Humira has been tried.

- The recommended dose of etanercept for the treatment of psoriasis is 50mg injected subcutaneously twice weekly (administered 3-4 days apart) for 3 months followed by a reduction to a maintenance dose of 50mg per week.

Other Uses with Supportive Evidence:

Autoimmune Mucocutaneous Blistering Diseases (pemphigus vulgaris, mucous membrane pemphigoid [cicatricial pemphigoid]). Approve if the patient meets the following criteria (a and b):

a. The patient has tried two conventional therapies (e.g., systemic corticosteroids, azathioprine, cyclophosphamide, dapsone, MTX, cyclosporine, mycophenolate mofetil); AND

b. Enbrel is prescribed by or in consultation with a dermatologist.

For mucous membrane pemphigoid (cicatricial pemphigoid) conventional therapy is dapsone AND cyclophosphamide, azathioprine, or mycophenolate mofetil. Controlled trials are lacking. A small double-blind, randomized, placebo-controlled pilot study randomized adult patients in a 2:1 ratio to treatment with Enbrel (n = 6) or placebo. Four patients receiving Enbrel completed the study. The primary end point was a 50% reduction in lesion number was met by three patients, one patient in the Enbrel treatment group and two patients in the placebo group. However, in a case report (n = 3) patients with mucous membrane pemphigoid (MMP) were treated with Enbrel 25 mg twice weekly with successful management of MMP. There are other case reports documenting successful use of Enbrel, one case for management of recalcitrant cicatricial pemphigoid and one case in combination with azathioprine for recalcitrant pemphigus vulgaris as well as other reports noting successful treatment of patients with pemphigus vulgaris, all of whom have failed other immunosuppressants.

Behcet’s Disease. Approve if the patient meets the following criteria (a and b):

a. The patient has tried at least one conventional therapy (e.g., systemic corticosteroids, immunosuppressants [azathioprine, MTX, mycophenolate mofetil, tacrolimus, Leukeran® {chlorambucil}, cyclophosphamide, or cyclosporine], interferon alfa) or Humira or Remicade; AND

b. Enbrel is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.

In a 4-week placebo-controlled trial (n = 40), Enbrel was effective in controlling some of the mucocutaneous lesions in Behcet’s disease; patients with serious organ involvement (e.g., eye, central nervous system, major arterial disease) were excluded. Colchicine and thalidomide have been effective therapy for mucocutaneous symptoms. In other reports, Enbrel has been effective in resolution of severe mucocutaneous lesions. Remicade seems to be more effective than Enbrel in disease manifestations of Behcet’s disease other than mucocutaneous or joint involvement. EULAR recommendations for the management of Behcet’s disease include Remicade use in refractory eye involvement. Arthritis can be managed with colchicine, and TNF antagonists (Enbrel, Remicade) can be used in rare cases with resistant, longer lasting and disabling attacks. For mucocutaneous involvement, TNF antagonists may be used in resistant cases. Recommendations for the use of TNF blockers in ocular inflammatory disorders from the American Academy of Ophthalmology (AAO) [2014] note that Enbrel may be considered in Behcet’s disease in patients with uveitis.

Giant Cell Arteritis. Approve if the patient meets the following criteria (a, b, and c):

a. Patient is currently taking a systemic corticosteroid; AND
b. Patient is unable to discontinue systemic steroid therapy; AND  
c. Enbrel is prescribed by or in consultation with a rheumatologist, ophthalmologist, or neurologist.

In a double-blind trial patients with biopsy proven giant cell arteritis with AEs due to corticosteroids were randomized to Enbrel 25 mg twice weekly (n = 8) or placebo (n = 9) for 12 months. Corticosteroids were continued but were reduced if possible according to a predefined protocol. The primary outcome was the ability to withdraw the corticosteroid therapy and control disease activity at 12 months. After 12 months, 50% of Enbrel patients and 22.2% of placebo patients were able to control the disease without corticosteroid therapy (not statistically significant). But patients on Enbrel had a significantly lower dose of accumulated prednisone during the first year of treatment (P = 0.03). In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.

**Graft-Versus-Host Disease (GVHD).** Approve if the patient meets the following criteria (a and b):

a. The patient meets one of the following conditions (i or ii):
   i. Patient has tried one conventional treatment for GVHD (e.g., high-dose systemic corticosteroids, antithymocyte globulin, cyclosporine, thalidomide, tacrolimus, mycophenolate mofetil); OR
   ii. Patient is concurrently receiving at least one of these medications (e.g., high-dose systemic corticosteroids, antithymocyte globulin, cyclosporine, thalidomide, tacrolimus, mycophenolate mofetil) in combination with Enbrel; AND

b. Enbrel is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.

In a Phase II trial, Enbrel in combination with Zenapax® (daclizumab injection) was effective in treating some patients with steroid-refractory acute GVHD. In another open-label, Phase II study, Enbrel was effective for GVHD prevention in some patients with high risk hematopoietic cell transplant, though the effectiveness may depend on the conditioning regimen. In a prospective non randomized study, Enbrel was given twice weekly for 8 weeks in combination with methylprednisolone in patients with acute GVHD (n = 61). Patients treated with Enbrel plus steroids were significantly more likely to achieve a complete response 4 weeks later than those on steroids alone (69% vs. 33%; P < 0.001). By 12 weeks after starting Enbrel, 77% of patients treated with Enbrel/steroids had attained a complete response vs. 50% of patients on steroids alone. These improved outcomes were for recipients of both related and unrelated donor transplants. A Phase II, randomized, 4-arm trial was conducted to identify the most promising agents for initial therapy in acute GVHD. Day 28 complete response (CR) rate was 26% in patients receiving Enbrel with oral or IV corticosteroid; at 9 months overall survival was 47%.

In another report, Enbrel was effective in some patients with acute GVHD and in steroid refractory chronic GVHD. In a retrospective review, Enbrel in combination with antithymocyte globulin and tacrolimus with or without mycophenolate mofetil was effective in some patients with refractory acute GVHD. In a short-term trial, Enbrel was given for 8 weeks in 10 patients with steroid-dependent chronic GVHD after allogeneic bone marrow transplant. Seven of 8 patients who finished 8 weeks of therapy showed subjective and/or objective improvement. In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.

**Polymyalgia Rheumatica (PMR).** Approve if patient meets the following criteria (a, b, and c):

a. Patient is currently taking a systemic corticosteroid; AND  
b. Patient is unable to discontinue steroid therapy; AND  
c. Enbrel is prescribed by or in consultation with a rheumatologist.

Enbrel has been used as a corticosteroid sparing agent in patients receiving prednisone for PMR. In a single center case series study, nine patients with newly diagnosed PMR and decompensated diabetes mellitus received Enbrel 25 mg twice weekly for 6 months. Prednisone had been started...
when PMR was diagnosed and after 30 days all patients had decompensated diabetes with fasting blood glucose > 450 mg/dL. After starting Enbrel, prednisone dose was reduced and tapered off. All of the patients went into remission and were still in remission after 12 months. In another study, six patients with relapsing PMR who could not reduce their dose of prednisone to less than 7.5 to 10 mg/day and who had severe corticosteroid related AEs were given Enbrel 25 mg twice weekly for 24 weeks.39 Patients were followed for 3 months after stopping Enbrel. All patients improved and were able to decrease their doses of prednisone without relapsing. Another randomized controlled trial found that the polymyalgia rheumatic activity score (PMR-AS) significantly decreased by 24% (95% confidence interval [CI]: 12, 33) at Day 14 in patients treated with Enbrel 25 mg biweekly and remained the same in patients treated with placebo (P = 0.011).40 In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.

**Pyoderma Gangrenosum.** Approve if the patient meets one of the following criteria (a and b):

a. The patient meets one of the following conditions (i or ii):
   i. Patient has tried one systemic corticosteroid; OR
   ii. Patient has tried one other immunosuppressant (e.g., mycophenolate mofetil, cyclosporine) for at least 2 months or was intolerant to one of these agents;41 AND

b. Enbrel is prescribed by or in consultation with a dermatologist.

Multiple topical and systemic therapies have been used to treat pyoderma gangrenosum. Oral prednisone is the most common initial immunosuppressant medication.42 Topical therapies (e.g., corticosteroids, immunomodulators) may be applied to the lesion. Other systemic therapies used for treatment of pyoderma gangrenosum include cyclosporine, MTX, azathioprine, cyclophosphamide, mycophenolate mofetil, Remicade, Enbrel, and Humira. In case series and case reports Enbrel has been effective treatment in pyoderma gangrenosum that was refractory to other therapies such as prednisone, cyclosporine, and Remicade.43-44 In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.

**Reactive Arthritis (Reiter’s Disease).** Approve if patient meets the following criteria (a and b):

a. Patient has had a 3-month trial of at least two different DMARDs (e.g., sulfasalazine, MTX, leflunomide), or was intolerant; AND

b. Enbrel is prescribed by or in consultation with a rheumatologist.

Typically, reactive arthritis presents as asymmetrical oligoarthritis; extraarticular manifestations may include enthesitis, tendinitis, bursitis, inflammatory back pain, eye disease, and skin changes.45 Although reactive arthritis presents similarly to ankylosing spondylitis (an approved indication), onset of reactive arthritis is preceded by an infection (e.g., gastrointestinal infection, *Chlamydia trachomatis*). Sulfasalazine is the most studied DMARD in reactive arthritis and has demonstrated efficacy in early onset and chronic disease. Favorable outcomes have also been documented with the use of TNF antagonists in patients with reactive arthritis. In one small open-label study in adults with reactive arthritis (n = 16), nine out of ten patients that completed 6 months of therapy with Enbrel improved clinically (decreased tender and swollen joint count and improvement in pain).46

**Scleritis or Sterile Corneal Ulceration.** Approve if the patient meets the following criteria (a and b):

a. The patient has tried one other therapy for these conditions (e.g., oral, topical [ophthalmic] or IV corticosteroids, MTX, oral NSAIDs, cyclosporine, or other immunosuppressants); AND

b. Enbrel is prescribed by or in consultation with an ophthalmologist.

Recommendations for the use of TNF blockers in ocular inflammatory disorders from the AAO (2014) note that Enbrel has a role in treating patients with scleritis who have failed other immunomodulatory therapies.30 In a retrospective review of 10 patients (13 eyes), Enbrel was used to treat sight-threatening scleritis or sterile corneal ulceration after conventional medications failed to decrease the requirement for corticosteroids or cytotoxic agents.47 Enbrel either alone or in
combination with other immunosuppressive agents controlled inflammation, arrested tissue ulceration, and in some patients allowed other therapies to be tapered or discontinued. In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.

**Still's Disease** (systemic-onset RA in adults, the disease may have begun in childhood). Approve if the patient meets the following criteria (a, b, and c):

a. Patient has tried one corticosteroid; AND
b. Patient has tried one conventional synthetic DMARD such as MTX given for at least 2 months or was intolerant to a conventional synthetic DMARD; AND
c. Enbrel is prescribed by or in consultation with a rheumatologist.

Still’s disease presents in adults with features similar to those of systemic onset JIA. In a 6-month open-label trial (n = 10), Enbrel therapy improved arthritis in 67% of patients with adult Still’s disease who had been previously treated unsuccessfully with at least one DMARD. In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.

**Undifferentiated Spondyloarthritis (Undifferentiated Arthritis).** Approve if Enbrel is prescribed by or in consultation with a rheumatologist.

Patients may present with signs and/or symptoms of inflammatory arthritis but do not meet diagnostic criteria for any specific type of arthritis. If a clinical work-up does not reveal another diagnosis and clinical presentation does not indicate a specific diagnosis, the patient is often diagnosed with a form of undifferentiated arthritis. Over time, a patient with undifferentiated arthritis may progress to meet the diagnostic criteria for another type of inflammatory arthritis. Treatment with Enbrel has produced regression of disease activity (assessed by the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]) in some patients. In another small study, patients on Enbrel for 6 months improved clinically.

**Uveitis (including other posterior uveitides and panuveitis syndromes).** Approve if the patient meets the following criteria (a and b):

a. The patient has tried one of the following therapies: periocular, intraocular, or systemic corticosteroids; immunosuppressives (e.g., MTX, mycophenolate mofetil, azathioprine, cyclophosphamide, or cyclosporine), Humira, or Remicade for this condition; AND
b. Enbrel is prescribed by or in consultation with an ophthalmologist.

In patients with uveitis, TNF levels are increased in the serum and aqueous humor. Enbrel has been effective in a small number of children with chronic active uveitis (either with JRA or idiopathic) refractory to other therapies. Recommendations for the use of TNF blockers in ocular inflammatory disorders from the AAO (2014) note that Enbrel has a role in treating patients with uveitis who have failed other immunomodulatory therapies. In general, TNF blockers can be used for treatment of other posterior uveitides and panuveitis syndromes including birdshot chorioretinitis, multifocal choroiditis with panuveitis, serpiginous choroiditis, and undifferentiated panuveitis. In a placebo-controlled trial in 12 children with uveitis associated with JIA, the success rate with Enbrel was about 50% which is a similar rate to that with standard care. Based on retrospective reviews, Remicade is more effective than Enbrel in the treatment of refractory uveitis in children and adults. In one small study in adults with chronic or recurrent uveitis controlled by MTX, Enbrel was no more effective than placebo in preventing relapses of uveitis in patients being tapered off MTX.

**Patient has been Established on Enbrel for ≥ 90 days.**

For conditions that do not have criteria for Patients Currently Receiving Enbrel but are indications or conditions addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications and Other Uses with Supportive Evidence), approve Enbrel, if the patient is
currently taking Enbrel for ≥ 90 days. (In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.)

When Policy Topic is not covered

Enbrel® (etanercept) is considered investigational when used for all other conditions, including, but not limited to:

1. **Concurrent Use with a Biologic DMARD or Targeted Synthetic DMARD.** Enbrel should not be administered in combination with another biologic agent for an inflammatory condition (e.g., TNF antagonists [Cimzia, Humira, Remicade, Simponi SC, or Simponi Aria], Actemra, Kineret, Orencia, Rituxan, or Stelara). Combination therapy with two biologic agents is not recommended due to a higher rate of AEs with combinations and lack of additive efficacy. Xeljanz should not be used in combination with biologic DMARDs such as Enbrel. Targeted synthetic DMARDs (e.g., Xeljanz, Otezla) do not have data supporting use in combination with biologic DMARDs. Do to similar safety concerns (i.e., increased risk of AEs) plus lack of evidence for additive efficacy, targeted synthetic DMARDs should not be used in combination with biologic DMARDs such as Enbrel. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Enbrel.

2. **Crohn’s Disease.** In a double-blind, placebo-controlled trial Enbrel was not effective for the treatment of moderate to severe Crohn’s disease. However, arthritis (spondyloarthropathy, ankylosing spondylitis) may be associated with Crohn’s disease and Enbrel may be effective for the spondyloarthropathy in these patients.

3. **Dermatomyositis or Polymyositis.** Information is conflicting. In one retrospective review of eight patients with either dermatomyositis or polymyositis some patients responded (improved motor strength and decreased fatigue) to treatment with Enbrel. In this case series, Enbrel was added on to treatment with corticosteroids, intravenous immunoglobulin (IVIG), and DMARDs; there were no standardized outcome measures. In another case series in patients (n = 5) with dermatomyositis who had not responded to steroids and cytotoxic therapy (MTX, azathioprine, cyclosporine), the cytotoxic drugs were discontinued and Enbrel was given for at least 3 months. All patients had exacerbation of disease and Enbrel was stopped. In a 1-year, double-blind study, patients were randomized to receive Enbrel 50 mg weekly (n = 11) or placebo (n = 5). All patients who received placebo were judged as treatment failures whereas five patients in the Enbrel group were successfully weaned off of prednisone. More studies are needed demonstrating the efficacy of Enbrel and its long-term effects. In a 6-month, open-label study of Enbrel in patients with refractory juvenile dermatomyositis (n = 9), minimal improvement was noted in disease activity with some patients experiencing worsening disease.

4. **Hidradenitis Suppurativa.** A prospective, randomized, double-blind, placebo-controlled study assigned patients (n = 20) to treatment with Enbrel 50 mg twice weekly or placebo for 12 weeks. Following 12 weeks of treatment, all patients received open-label Enbrel for an additional 12 weeks. The study found no statistically significant difference between Enbrel 50 mg twice weekly and placebo among physician global assessment, patient global assessment, and the Dermatology Life Quality Index (DLQI) at Week 12 or Week 24. A systematic review (2013) extracted data from case reports and RCTs and recommended against the use of Enbrel for treatment of hidradenitis suppurativa.

5. **Immune-Mediated Cochleovestibular Disorders** (autoimmune sensorineural hearing loss, autoimmune inner ear disease, immune-mediated Meniere’s disease). In a retrospective case series, Enbrel was effective in improving or stabilizing hearing loss and improving tinnitus, vertigo, and aural fullness in patients who did not respond or had adverse effects with conventional therapy. In other short-term prospective studies, Enbrel was not effective. Well-controlled trials are needed.
6. **Sarcoidosis, Ocular.** Recommendations for the use of TNF blockers in ocular inflammatory disorders from the AAO (2014) note that Remicade or Humira may be considered as second-line immunomodulatory therapy for patients failing or intolerant of standard immunomodulatory agents. A discretionary recommendation (indicating trade-offs are less certain) is that Enbrel should not be used in the treatment of ocular sarcoidosis (moderate-quality evidence). In a double-blind study patients (n = 18) with chronic ocular sarcoidosis and ongoing inflammation were randomized to Enbrel or placebo for 6 months. Patients had received ≥ 6 months of therapy with MTX and were currently on corticosteroids. For most of the patients, therapy with Enbrel was not associated with significant improvement.

7. **Sarcoidosis, Pulmonary.** In a prospective, open-label trial in patients with Stage II or III progressive pulmonary sarcoidosis, treatment with Enbrel was frequently associated with early or late treatment failure. This trial was ended early because an excessive number of patients (n = 11/17) had disease progression on Enbrel. Recommendations for best practice in the management of pulmonary and systemic sarcoidosis mention Humira and Remicade as therapeutic options for management of disease.

8. **Sjögren’s syndrome.** In a small pilot study (n = 15), Enbrel was not effective in improving salivary and lachrymal gland function in Sjögren’s syndrome, but a few patients had reduced fatigue. In a 12-week randomized double-blind study in 28 patients, Enbrel was not more effective than placebo.

9. **Systemic Sclerosis (Scleroderma).** Very limited published information is available. In a retrospective review from one scleroderma center, 18 patients with scleroderma who had active joint disease (synovitis or inflammatory signs) were treated with Enbrel 25 mg twice weekly or 50 mg once weekly. The duration of therapy ranged from 2 to 66 months (mean 30 months). Fifteen of 18 patients had a positive response to Enbrel with a significant decrease in signs of inflammation or synovitis and complete resolution of joint symptoms. Mean Health Assessment Questionnaire (HAQ) scores from baseline to latest available follow-up decreased from 1.08 ± 0.70 to 0.74 ± 0.56 (P = 0.13). Prospective, randomized, double-blind trials are needed to determine if Enbrel is effective in scleroderma-associated joint disease.

10. **Takayasu’s Arteritis.** In a retrospective single center study in patients with refractory Takayasu’s arteritis (n = 25), patients were treated with Remicade (n = 21) or Enbrel (n = 9). Five patients who were initially treated with Enbrel were switched to Remicade. Therapy with anti-TNF agents was associated with remission in many patients and dose reduction or discontinuation of prednisone and other immunosuppressant therapies. A randomized controlled trial is needed to better define the efficacy and safety of Enbrel. Most patients with Takayasu's arteritis have a relapsing/remitting course.

11. **Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS).** Limited data are available. In patients with TRAPS, episodes of fever are responsive to corticosteroids but some patients may require continuous steroids. TRAPS attacks vary in length, intensity, and free intervals in the same person, so treatment efficacy is very difficult to ascertain. Enbrel has been effective in some patients with TRAPS in improving disease activity and allowing decreased corticosteroid doses. However, response is variable and may not be sustained. Immunosuppressants are ineffective in reducing the frequency and intensity of the episodes of inflammation and/or preventing the development of amyloidosis in patients with TRAPS. Other TNF inhibitors (i.e., Remicade and Humira) may cause paradoxical inflammatory attacks.

12. **Wegener’s Granulomatosis.** Enbrel is not effective in the induction or maintenance of disease remissions in patients with Wegener’s. In a double-blind trial, 180 patients with active Wegener’s granulomatosis were randomized to Enbrel or placebo in combination with standard therapies (e.g., cyclophosphamide, MTX, corticosteroids) depending on disease severity. When remission was achieved, standard medications were tapered according to protocol guidelines. Patients were
enrolled over 28 months and the mean follow-up was 27 months. Of the 174 patients who were evaluable, 126 patients (72.4%) achieved sustained remissions, but only 86 patients overall (49.4%) maintained their disease remissions throughout the trial. There were no differences between Enbrel and the control group in the percent of patients achieving sustained remissions (69.7% vs. 75.3%, P = 0.39); in the percent of patients with sustained periods of low disease activity (86.5% vs. 90.6%); or time to achieve these outcomes. Disease flares were common in both groups. AEs were frequent and often severe. During the study, 56.2% of patients on Enbrel and 57.1% on placebo had at least one severe or life-threatening AE or died. Six of the Enbrel patients and none of the controls developed solid malignancies. Use of Enbrel in patients with Wegener’s granulomatosis who are receiving immunosuppressant drugs is not recommended.1

Considerations
Based on a study of 50 mg etanercept twice weekly in patients with RA that suggested higher incidence of adverse reactions but similar ACR response rates, doses higher than 50 mg per week are not recommended.

Boxed Warnings
Enbrel has boxed warnings concerning risks of serious infection and the risk of malignancy.1 Prior to initiating therapy with Enbrel, patients should be evaluated for active tuberculosis (TB) infection; periodically during therapy, patients should be assessed for latent TB infection. Patients should also be monitored for signs and symptoms of infection during and after treatment with Enbrel, and if a serious infection or sepsis develops, Enbrel should be discontinued. It is also recommended that patients treated with any TNF antagonist should be monitored for malignancies.

Although Enbrel® has been assigned a HCPCS infusion code, benefits will pay through pharmacy.

This Blue Cross and Blue Shield of Kansas City policy statement was developed using available resources such as, but not limited to: Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers

Description of Procedure or Service
Enbrel® (etanercept) is a dimeric fusion protein administered subcutaneously that binds to and inhibits tumor necrosis factor alpha and beta, a cytokine that plays an important role in a variety of inflammatory processes. It is approved by the FDA to treat rheumatoid arthritis, polyarticular-course juvenile rheumatoid arthritis, psoriatic arthritis, psoriasis and ankylosing spondylitis.

Rationale
Enbrel, a human soluble receptor fusion protein, inhibits the binding of tumor necrosis factor (TNF)α and β to cell surface TNF receptors.1 TNF is a proinflammatory cytokine that is involved in normal inflammatory and immune responses.

Enbrel is indicated for the following uses:
1. reducing the signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderate or severe active rheumatoid arthritis (RA)1-6; AND
2. reducing the signs and symptoms of moderate or severe active polyarticular juvenile idiopathic arthritis (JIA) in patients aged ≥ 2 years1,7; AND
3. reducing the signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (PsA)1,8; AND
4. for reducing signs and symptoms in patients with active ankylosing spondylitis (AS)1,9; AND
5. for treatment of adults with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.1,10-11
For RA, Enbrel can be used in combination with methotrexate (MTX) or used alone.¹ For PsA, Enbrel can be used in combination with MTX in patients who do not respond adequately to MTX alone.

**Other Therapies**
There are multiple other drugs available to treat inflammatory conditions, including other TNF blockers (e.g., Cimzia® [certolizumab pegol for subcutaneous {SC} injection], Enbrel® [etanercept for SC injection], Humira® [adalimumab for SC injection], Simponi® [golimumab for SC injection], Simponi Aria™ [golimumab for IV infusion], Actemra® [tocilizumab for IV infusion, tocilizumab for SC injection], Kineret® [anakinra for SC injection], Oricia® [abatacept for IV infusion, abatacept for SC injection], Rituxan® [rituximab for IV infusion], and Stelara® [ustekinumab for SC injection]). There are also targeted synthetic disease-modifying antirheumatic drugs (DMARDs) available (e.g., Xeljanz® [tocitinib tablets] and Otezla® [apremilast tablets]) which are indicated for certain inflammatory conditions. Conventional synthetic DMARDs (e.g., MTX, leflunomide, sulfasalazine) are also commonly utilized for management of certain inflammatory conditions

**Rheumatoid arthritis**
Enbrel is indicated for moderate or severe active RA in adults and can be used alone or in combination with MTX.¹ Most patients will have received initial therapy with MTX, another oral DMARD(s) (e.g., hydroxychloroquine, leflunomide, sulfasalazine, MTX), or combination DMARD therapy (including double or triple therapy).¹² However, current recommendations from ACR (2012) note that patients with important markers of poor prognosis may be started early on a biologic agent such as Enbrel, either alone or in combination with MTX. The guidelines generally recommend assessment at Month 3 with a general recommendation to switch biologic in patients with a loss or lack of benefit at this assessment. The criteria for patients with contraindications or intolerance to DMARDs are recommended based on the professional opinion of specialized physicians.

**Ankylosing spondylitis**
Enbrel is indicated for ankylosing spondylitis.¹ According to the Assessment of SpondyloArthritis International Society/European League Against Rheumatism (ASAS/EULAR) 2010 recommendations for AS, all patients should have an adequate trial of at least two nonsteroidal anti-inflammatory drugs (NSAIDs) for pain and stiffness, unless contraindicated.¹³⁻¹⁵ Recommendations for other therapies before receiving Enbrel or another TNF blocker vary according to the manifestations of the disease, level of current symptoms, clinical findings, etc. According to these recommendations, patients with pure axial manifestations do not have to try conventional synthetic DMARDs before Enbrel; patients with symptomatic peripheral arthritis should have an insufficient response to at least one local corticosteroid injection, if appropriate; patients with persistent peripheral arthritis should normally have a trial of a DMARD, preferably sulfasalazine; and patients with enthesitis should try appropriate local therapy (e.g., corticosteroid injection in selected cases).¹⁵ In the AS guidelines, it is recommended to assess a patient’s response to a TNF blocker after at least 12 weeks of therapy.

**Polyarticular juvenile idiopathic arthritis**
Enbrel is indicated for moderately to severely active polyarticular JIA in patients 2 years of age and older.¹ The 2011 ACR recommendations for the treatment of JIA propose initial DMARD treatment with MTX in most patients; however, sulfasalazine is recommended for patients with enthesitis-related arthritis and may also be used in certain patients with sacroiliac arthritis.¹⁶ Leflunomide may be an appropriate initial DMARD in certain patients with high disease activity and/or a poor prognosis. Kineret may be used in systemic arthritis and Actemra may be used in systemic and polyarticular juvenile arthritis arthritis.¹⁸ TNF antagonists such as Enbrel may also be used as second- or third-line treatment for systemic JIA. Guidelines for JIA generally recommend that TNF blockers be given for a minimum of 3 months for SJIA. The criteria for patients starting on Humira concurrently with a conventional synthetic DMARD or for patients with an absolute contraindication MTX, sulfasalazine, or leflunomide are recommended based on the professional opinion of specialized physicians.
**Plaque Psoriasis**

Enbrel is indicated for plaque psoriasis. Guidelines for treatment of plaque psoriasis recommend topical therapy for limited disease. However, for patients with chronic plaque psoriasis that does not respond to topical therapies or patients with more extensive disease, systemic therapy may be used. The traditional systemic agents for plaque psoriasis are MTX, Soriatane, and cyclosporine. An injectable biologic agent such as Enbrel is an option for patients who are candidates for phototherapy or systemic therapy, especially those who are intolerant of or unresponsive to traditional systemic agents. In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.

**Psoriatic arthritis**

Enbrel is indicated for PsA and can be used in combination with MTX in patients who do not respond adequately to MTX alone. In clinical trials, Enbrel was effective in patients with active PsA despite therapy with a NSAID. There are few well-controlled, prospective studies with adequate duration that have evaluated the efficacy of the oral DMARDs. According to 2012 The European League Against Rheumatism (EULAR) recommendations for treatment of PsA, NSAIDs are recommended as first-line treatment. Recommendations for other therapies before receiving a TNF blocker vary according to the manifestations of the disease, prognostic factors, and efficacy/toxicity of previous therapies. The TNF inhibitors (e.g., Enbrel, Humira, Remicade, or Simponi SC) are equally effective for treatment of PsA, inhibition of radiographic progression, and improving physical function in patients with PsA. The conventional synthetic DMARDs have not been shown to prevent the progression of radiographic (structural) damage or to have significant impact on axial disease, dactylitis, or enthesitis in PsA. This is in contrast with the newer biologic DMARDs which have shown efficacy in well-controlled trials in reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with PsA.

**References**


Other References Utilized

**Billing Coding/Physician Documentation Information**

| NA | Enbrel® (etanercept) is a pharmacy benefit. |

**Additional Policy Key Words**

5.01.501

**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/01/2003</td>
<td>New policy titled Enbrel (etanercept)</td>
</tr>
<tr>
<td>9/01/2004</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>9/01/2005</td>
<td>Policy updated to include indication and criteria for psoriasis.</td>
</tr>
<tr>
<td>1/01/2006</td>
<td>Policy statement revised to specify criteria for ankylosing spondylitis manifested as axial disease, peripheral arthritis, or enthesitis.</td>
</tr>
<tr>
<td>9/01/2006</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>9/01/2007</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>9/01/2008</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>9/01/2009</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>5/01/2010</td>
<td>Revised policy to reflect BCBSA criteria for RA, AS, Ps, and PsA as defined in policy 5.01.15.</td>
</tr>
<tr>
<td>Date</td>
<td>Changes</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>9/01/2010</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>9/01/2011</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>9/01/2013</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>9/01/2014</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>9/01/2015</td>
<td>Added Other Uses with Supportive Evidence; updated references</td>
</tr>
<tr>
<td>9/2016</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>11/2016</td>
<td>Added biosimilar to the title and policy, until other evidence is available</td>
</tr>
<tr>
<td>03/2017</td>
<td>Updated Psoriasis indication to include prerequisites</td>
</tr>
<tr>
<td>08/2017</td>
<td>Reviewed – no changes to policy statement</td>
</tr>
<tr>
<td>08/2018</td>
<td>Reviewed – no changes made</td>
</tr>
<tr>
<td>08/2019</td>
<td>Reviewed – no changes made</td>
</tr>
</tbody>
</table>

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.