Enbrel® (entanercept) subcutaneous [SC] injection
Prior Approval Criteria
November 2016

**Definition:** Etanercept (Enbrel®, Amgen, Thousand Oaks, CA) is a dimeric soluble form of the extracellular ligand-binding human 75 kilodalton (p75) tumor necrosis factor (TNF) receptor that is fused to the Fc fragment of human immunoglobulin (IgG1). Tumor necrosis factor-alpha is a naturally occurring cytokine playing a central role in the immunoregulatory process. Etanercept inhibits binding of tumor necrosis factor-alpha and tumor necrosis factor-beta to cell surface tumor necrosis factor receptors, thereby reducing the inflammatory response.

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); AND
2. reducing the signs and symptoms of moderate or severe active polyarticular juvenile idiopathic arthritis (JIA) in patients aged ≥ 2 years; 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); AND
4. for reducing signs and symptoms in patients with active ankylosing spondylitis (AS); AND
5. for treatment of patients ≥ 4 years of age with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

For RA, Enbrel can be used in combination with methotrexate (MTX) or used alone. For PsA, Enbrel can be used in combination with MTX in patients who do not respond adequately to MTX alone.

**Boxed Warnings**
Enbrel has boxed warnings concerning risks of serious infection and the risk of malignancy. 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.

**Policy Statement**
Prior approval is required for coverage of Enbrel. Because of the specialized skills required for evaluation and diagnosis of patients treated with Enbrel as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Enbrel to be prescribed by or in consultation with a physician who specializes in the condition being treated. All Food and Drug Administration (FDA)-approved indications are approved for initial 3-month approval duration, then for 1 year approval duration for continuation of therapy and other uses with supportive evidence unless otherwise noted below. Enbrel is subject to the Inflammatory Conditions Care Value Step Therapy.

**Recommended Authorization Criteria**
Coverage of Enbrel is recommended in those who meet the following criteria:

**Food and Drug Administration (FDA)-Approved Indications**

1. **Rheumatoid Arthritis (RA).** Approve if the patient meets the following criteria (a and b):
   a) The patient meets one of the following conditions (i, ii, iii, or iv):
      i. Patient has tried one disease-modifying antirheumatic drug (DMARD) (brand or generic; oral or injectable) for at least 3 months, [this includes patients who have tried other biologic DMARDs for at least 3 months];
      OR
      ii. Patient is concurrently receiving MTX;
      OR
      iii. Patient has a contraindication or intolerance to MTX and leflunomide, as determined by the prescribing physician;
      iv. Patient has early RA (defined as disease duration of < 6 months) with at least one of the following features of poor prognosis: functional limitation (e.g., based on Health Assessment Questionnaire Disability Index [HAQ-DI] score); extraarticular disease such as rheumatoid nodules, RA vasculitis, or Felty’s syndrome; positive rheumatoid factor or anti-cyclic citrullinated protein (anti-CCP) antibodies; or bony erosions by radiograph;
   AND
   b) Enbrel is prescribed by or in consultation with a rheumatologist.

**Initial Approval/Extended Approval.**
   a) Initial Approval. Approve for 3 months.
   b) Extended Approval. Approve for an additional 12 months of therapy if the patient has responded (e.g., less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids), as determined by the prescribing physician. The patient may not have a full response, but there should be some response to Enbrel.

2. **Ankylosing Spondylitis (AS).** Approve if Enbrel is prescribed by or in consultation with a rheumatologist.

**Initial Approval/Extended Approval.**
   a) Initial Approval. Approve for 3 months.
   b) Extended Approval. Approve for 12 months if the patient has had a response (e.g., decreased pain or stiffness, improved function or activities of daily living), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Enbrel.

3. **Juvenile Idiopathic Arthritis (JIA) [or Juvenile Rheumatoid Arthritis (JRA)] (regardless of type of onset) [Note: This includes patients with juvenile spondyloarthropathy/active sacroiliac arthritis].** Approve if the patient meets the following criteria (a and b):
   a) The patient meets one of the following conditions (i, ii, iii, or iv):
      i. Patient has tried one other agent for this condition (e.g., MTX, sulfasalazine, or leflunomide, an NSAID, or a biologic DMARD [e.g., Humira® {adalimumab for subcutaneous (SC) injection}, Ocrevus® {abatacept for intravenous (IV) infusion], Remicade® {infliximab for IV infusion}, Kineret® {anakinra for SC injection}, Actemra® {tocilizumab for IV infusion}]));
      OR
ii. Patient will be starting on Enbrel concurrently with MTX, sulfasalazine, or leflunomide; OR

iii. Patient has an absolute contraindication to MTX (e.g., pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias), sulfasalazine, or leflunomide; OR

iv. Patient has aggressive disease, as determined by the prescribing physician; AND

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

**Initial Approval/Extended Approval.**

a) *Initial Approval.* Approve for 3 months.

b) *Extended Approval.* Approve for 12 months if the patient has had a response (e.g., has improvement in limitation of motion; less joint pain or tenderness; decreased duration of morning stiffness or fatigue; improved function or activities of daily living, reduced dosage of corticosteroids), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Enbrel.

4. **Plaque Psoriasis (PsO).** Approve if the patient meets the following criteria (a and b):

a) The patient meets one of the following conditions (i, ii, or iii):

1. The patient has tried at least one of the following agents for at least 3 months for plaque psoriasis: an oral therapy for psoriasis (e.g., MTX, cyclosporine, Soriatane® [acitretin tablets]); oral methoxsalen plus ultraviolet A light (PUVA); or a biologic agent (e.g., Humira, Remicade, or Stelara™ [ustekinumab for SC injection]); OR

2. The patient experienced an intolerance to a trial of at least one oral or biologic therapy for plaque psoriasis (e.g., MTX, cyclosporine, Soriatane, Humira, Remicade, or Stelara); OR

3. The patient has a contraindication to one oral agent for psoriasis such as MTX, as determined by the prescribing physician; AND

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

**Initial Approval/Extended Approval.**

a) *Initial Approval.* Approve for 3 months.

b) *Extended Approval.* Approve for 12 months if the patient has had a response, as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Enbrel.

5. **Psoriatic Arthritis (PsA).** Approve if Enbrel is prescribed by or in consultation with a rheumatologist or a dermatologist.

**Initial Approval/Extended Approval.**

a) *Initial Approval.* Approve for 3 months.

b) *Extended Approval.* Approve for 12 months if the patient has had a response, (e.g., less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants [for example, C-reactive protein {CRP}]), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Enbrel.

**Other Uses with Supportive Evidence**
6. **Behcet’s Disease.** Approve for 12 months 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.

7. **Reactive Arthritis (Reiter’s Disease).** Approve for 12 months 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.

8. **Still’s Disease** (systemic-onset RA in adults, the disease may have begun in childhood). Approve for 12 months if the patient meets the following criteria (a, b, and c):
   a) Patient has tried one corticosteroid; AND
   b) Patient has tried one non-biologic DMARD such as MTX given for at least 2 months or was intolerant to a non-biologic DMARD; AND
   c) Enbrel is prescribed by or in consultation with a rheumatologist.

9. **Undifferentiated Spondyloarthritis (Undifferentiated Arthritis).** Approve for 12 months if Enbrel is prescribed by or in consultation with a rheumatologist.

10. **Uveitis (including other posterior uveitides and panuveitis syndromes).** Approve for 12 months 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.

11. **Patient has been Established on Enbrel.** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications and Other Uses with Supportive Evidence) if the patient has been taking Enbrel for ≥ 90 days. (In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.)

**Exclusions**
Coverage of Enbrel is recommended in circumstances that are listed in the Recommended Authorization Criteria (FDA-Approved Indications and Other Uses with Supportive Evidence). The following provides rationale for specific Exclusions. This is not an exhaustive list of Exclusions.

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 (n = 5) in patients 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 on the efficacy of Enbrel and its long-term effects.

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 of 25 patients with refractory Takayasu’s arteritis, 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 these anti-TNF agents was associated with remission in many patients and dose reduction or discontinuation of prednisone and other immunosuppressive 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. **Wegener’s Granulomatosis.** Enbrel is not effective in the induction or maintenance of disease remissions in these patients. In a double-blind trial, 180 patients with active Wegener’s granulomatosis were randomized to Enbrel or placebo in combination with standard therapies (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. Adverse events 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 adverse event 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 immunosuppressive drugs is not recommended.

12. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.


**Other References Utilized**