MEDICAL MUTUAL®

Drug Policy

Policy:	**200805**	**Initial Effective Date: 12/01/2008**
Code(s):	**HCPCS J1438 and J3590†**	**Annual Review Date: 05/18/2023**
SUBJECT:	**Enbrel® (etanercept for subcutaneous [SC] injection)** **Erelzi (etanercept-szzs)** **Eticovo (etanercept-ykro)**	**Last Revised Date: 05/18/2023**

☒Subject to Site of Care

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

Initial and renewal requests for the medication(s) listed in this policy are subject to site of care management. When billed under the medical benefit, administration of the medication will be restricted to a non-hospital facility-based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center) unless the member meets the site of care exception criteria. To view the exception criteria and a list of medications subject to site of care management please click here.

OVERVIEW

Etanercept products are tumor necrosis factor inhibitors (TNFis) approved for the following uses:[1]

- **Ankylosing spondylitis**, for reducing signs and symptoms in patients with active disease.
- **Juvenile idiopathic arthritis (JIA)**, for reducing the signs and symptoms of moderate or severe active polyarticular disease in patients ≥ 2 years of age.
- **Plaque psoriasis**, for treatment patients ≥ 4 years of age with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
- **Psoriatic arthritis**, ± methotrexate for reducing the signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function.
- **Rheumatoid arthritis**, ± methotrexate for 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 disease.

POLICY STATEMENT

This policy involves the use of etanercept. Prior authorization is recommended for medical benefit coverage of etanercept. Approval is recommended for those who meet the conditions of coverage in the **Criteria, Dosing, Initial/Extended Approval, Duration of Therapy**, and **Labs/Diagnostics** for the diagnosis provided. **Waste Management** applies for all covered conditions that are administered by a healthcare professional. **Conditions Not Recommended for Approval** are

listed following the recommended authorization criteria and Waste Management section. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with etanercept as well as the monitoring required for AEs and long-term efficacy, initial approval requires etanercept be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of etanercept is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. **Rheumatoid Arthritis (RA) in an Adult.** Approve if the patient meets the following criteria (a, b, and c):[12]
   - **a)** 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];[12] NOTE: Examples include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD; AND
   - **b)** Enbrel is prescribed by or in consultation with a rheumatologist; AND
   - **c)** Site of care medical necessity is met *.

   Dosing in RA. The recommended dosing per the FDA approved label is 50 mg once weekly administered subcutaneously with or without methotrexate.[1]

   Initial Approval/Extended Approval.
   - **a)** *Initial Approval*: 6 months (180 days).[3]
   - **b)** *Extended Approval*. 1 year (365 days). Applies 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 AND site of care medical necessity is met *.

   Dosing in AS. The recommended dosing per the FDA approved label is 50 mg once weekly administered subcutaneously.[1]

Initial Approval/Extended Approval.

a) *Initial Approval*: 6 months (180 days).[15]

b) *Extended Approval*: 1 year (365 days). Applies if the patient has had a response (e.g., decreased pain or stiffness, improved function, or activities of daily living), as determined by the provider. 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, b, and c):

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}, Orencia® {abatacept for intravenous (IV) infusion}, Remicade® {infliximab for IV infusion}, Kineret® {anakinra for SC injection}, Actemra® {tocilizumab for IV infusion}]);[16] NOTE: A previous trial of a biologic (e.g., an adalimumab product [e.g., Humira], an infliximab product [e.g., Remicade, Renflexis, Inflectra], Actemra [tocilizumab IV infusion], Kineret [anakinra SC injection], or Orencia [abatacept IV infusion, abatacept SC injection]) also counts as a trial of one agent for JIA; 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;[16] AND

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

c) Site of care medical necessity is met*.

Dosing in JIA. The recommended dosing per the FDA approved label is < 63 kg, 0.8 mg/kg weekly or ≥ 63 kg, 50 mg weekly administered subcutaneously.[1]

Initial Approval/Extended Approval.

a) *Initial Approval*: 6 months (180 days).

b) *Extended Approval*: 1 year (365 days). Applies 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, b, c, and d):

a) The patient is greater than or equal to 4 years of age; AND

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

i. 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]);

NOTE: An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already has a 3-month trial or previous intolerance to at least one biologic (e.g., Cosentyx® [secukinumab SC injection], an adalimumab product [e.g., Humira], an infliximab product [e.g., Remicade, Renflexis, Inflectra], Siliq [brodalumab SC injection], Stelara® [ustekinumab SC injection], Taltz® [ixekizumab SC injection], or Tremfya [guselkumab SC injection]). These patients who have already tried a biologic for psoriasis are not required to "step back" and try a traditional systemic agent for psoriasis); OR

ii. 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

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

c) Enbrel is prescribed by or in consultation with a dermatologist; AND

d) Site of care medical necessity is met*.

Dosing in PsO. The recommended adult dosing per the FDA approved label is 50 mg twice weekly for 3 months initially, followed by 50 mg once weekly administered subcutaneously. Enbrel dosing for patients between 4 and 17 years of age is based on their weight (0.8mg/Kg/week SQ), with a weekly limit of 50mg. [1]

Initial Approval/Extended Approval.

a) *Initial Approval*: 3 months (90 days).

b) *Extended Approval*. 1 year (365 days). Applies 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 AND site of care medical necessity is met*.

Dosing in PsA. The recommended dosing per the FDA approved label is 50 mg once weekly administered subcutaneously with or without methotrexate.[1]

Initial Approval/Extended Approval.

a) *Initial Approval*: 6 months (180 days).

b) *Extended Approval*. 1 year (365 days). Applies 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 3 months if the patient meets the following criteria (a, b, and c):

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; NOTE: An exception to the requirement for a trial of one conventional therapy can be made if the patient has already had a trial of at least one biologic (e.g., an adalimumab product [e.g., Humira or infliximab product [e.g., Remicade, Renflexis, Inflectra]. These patients who have already tried a biologic for Behcet's disease are not required to "step back" and try a conventional therapy);
b) Enbrel is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist; AND
c) Site of care medical necessity is met*.

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.[21] Colchicine and thalidomide have been effective therapy for mucocutaneous symptoms. In other reports, Enbrel has been effective in resolution of severe mucocutaneous lesions.[22] 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.[23] 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.[24]

Dosing in Behcet's Disease. 25 mg twice weekly.

Initial Approval/Extended Approval.
a) *Initial Approval*: 3 months (90 days).
b) *Extended Approval*: 1 year (365 days). Applies if the patient has had a response per provider. The patient may not have a full response, but there should have been a recent or past response to Enbrel.

7. Still's Disease (systemic-onset RA in adults, the disease may have begun in childhood).[27-28] Approve if the patient meets the following criteria (a, b, c, and d):
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; AND
d) Site of care medical necessity is met*.

Still's disease presents in adults with features similar to those of systemic onset JIA.[29] 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.[27]

Dosing in Still's Disease. 25 mg twice weekly.

Initial Approval/Extended Approval.
- **a)** *Initial Approval*: 6 months (180 days).
- **b)** *Extended Approval*: 1 year (365 days). Applies if the patient has had a response per provider. The patient may not have a full response, but there should have been a recent or past response to Enbrel.

8. **Spondyloarthritis (SpA), Subtypes Other than Ankylosing Spondylitis or Psoriatic Arthritits** (e.g., undifferentiated arthritis, non-radiographic axial SpA, Reactive Arthritis [Reiter's disease]) [NOTE: For AS or PsA, refer to the respective criteria under FDA-approved indications]: Approve for if BOTH of the following conditions are met (a, b, and c):
   - **a)** The patient meets one of the following conditions (i or ii):
     - i. The patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet AND has tried at least ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) [e.g., methotrexate {MTX}, leflunomide, sulfasalazine] has been tried; OR
     - ii. The patient has axial spondyloarthritis; AND
   - **b)** Enbrel is prescribed by or in consultation with a rheumatologist; AND
   - **c)** Site of care medical necessity is met*.

   Dosing in Spondyloarthritis (SpA), Subtypes Other than Ankylosing Spondylitis or Psoriatic Arthritits. 50 mg once weekly

   Initial Approval/Extended Approval.
   - **a)** *Initial Approval*: 6 months (180 days).
   - **b)** *Extended Approval*. 1 year (365 days). Applies if the patient has had a response per provider. The patient may not have a full response, but there should have been a recent or past response to Enbrel.

9. **Pyoderma Gangrenosum.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **a)** Initial Therapy. Approve for 4 months if the patient meets BOTH of the following criteria (i and ii):
     - i. The patient meets ONE of the following (a or b):
       - **a)** The patient has tried one systemic corticosteroid; OR
         Note: An example is prednisone.
       - **b)** The patient has tried one other immunosuppressant for at least 2 months or was intolerant to one of these agents;
         Note: Examples include mycophenolate mofetil and cyclospore; AND
     - ii. The agent is prescribed by or in consultation with a dermatologist.
   - **b)** Patients Currently Receiving an Etanercept Product. Approve for 1 year if the patient has responded to therapy, as determined by the prescriber.
     Note: There may not have been a full response, but there should a recent or past response to an etanercept product.

   Dosing in Pyoderma Gangrenosum. 25 mg twice weekly.

   Initial Approval/Extended Approval.

a) *Initial Approval*: 4 months (120 days).
b) *Extended Approval*: 1 year (365 days).

10. Graft-Versus-Host Disease (GVHD). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month if the patient meets the following (i AND ii):
- **i.** The patient meets the following condition:
  - **a)** The patient has tried one conventional treatment for graft-versus-host disease (GVHD) [e.g., high-dose systemic corticosteroids, antithymocyte globulin, cyclosporine, thalidomide, tacrolimus, mycophenolate mofetil]; OR

  Note: Examples of conventional treatments the patient may have tried or may be receiving include a high-dose corticosteroid (e.g., methylprednisolone), antithymocyte globulin, cyclosporine, Thalomid (thalidomide tablets), tacrolimus, and mycophenolate mofetil; AND
- **ii.** The agent is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.

B) Patients Currently Receiving an Etanercept Product. Approve for 3 months if the patient has responded to therapy, as determined by the prescriber.

Dosing in Graft-Versus-Host Disease (GVHD). 0.4 mg/kg per dose given subcutaneously twice per week.

Initial Approval/Extended Approval.
a) *Initial Approval*: 1 month (30 days).
Extended Approval: 3 months (90 days).

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.). Site of care medical necessity must be met*.

Duration of Therapy in Etanercept. Until disease progression or unacceptable toxicities.

Labs/Diagnostics. None.

Waste Management for All Indications.
Enbrel is available in 25 mg/0.5 ml or 50 ml/ml subcutaneous prefilled syringes.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Etanercept has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. **Concurrent Use with a Biologic DMARD or Targeted Synthetic DMARD:** Enbrel should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see APPENDIX for examples). Combination therapy is generally not recommended due to a higher rate of AEs with combinations and lack of data supportive of additional efficacy.[47] 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.[49] However, arthritis (spondyloarthropathy, ankylosing spondylitis) may be associated with Crohn's disease and Enbrel may be effective for the spondyloarthropathy in these patients.[50]

3. **Inflammatory Myopathies (Polymyositis, Dermatomyositis, Inclusion Body Myositis):** 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.[51] 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.[52] 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).[53] 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.[54] 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.[55]

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.[56] 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.[57]

5. **Polymyalgia Rheumatica (PMR):** ACR/EULAR guidelines for the management of PMR (2015) strongly recommend against the use of TNFis for treatment of PMR.[58] This recommendation is based on lack of evidence for benefit as well as considerable potential for potential harm. While Enbrel has been evaluated in small numbers of patients with PMR, efficacy has not been established.[59-61]

6. **Sarcoidosis, Ocular:** Recommendations for the use of TNFis in ocular inflammatory disorders from the AAO (2014) note that Remicade or Humira may be considered as second-line immunomodulary therapy for patients failing or intolerant of standard immunomodulatory agents.[21] 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.[62] 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.[63] 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.[64]

8. **Large Vessel Vasculitis (e.g., Giant Cell Arteritis, Takayasu's Arteritis):** Guidelines from EULAR for the management of large vessel vasculitis (e.g., giant cell arteritis, Takayasu's arteritis) do not mention the use of TNFis.[65] Additionally, a meta-analysis of RCTs did not find evidence supporting remission or reduction of corticosteroid dose with the use of TNFs in large vessel vasculitis.[66] 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.[67] 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 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).[68] 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.

9. **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.[69] 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]

10. **Concurrent use with Otezla.** There is not evidence to suggest Otezla in combination with Enbrel is superior to monotherapy.

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

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

REFERENCES

1. Enbrel® injection [prescribing information]. Seattle, WA: Immunex Corporation; May 2018.
2. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med.* 1999;130:478-486.
3. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med.* 1999;340:253-259.
4. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med.* 2000;343:1586-1593.
5. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum.* 2002;46:1443-1450.
6. Klareskog L, van der Heijde D, de Jager JP, et al TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet.* 2004;363:675-681.
7. Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med.* 2000;342:763-769.
8. Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum.* 2004;50:2264-2272.
9. Davis JC Jr, Van Der Heijde D, Braun J, et al. Enbrel Ankylosing Spondylitis Study Group. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum.* 2003; 48: 3230-3236.
10. Leonardi CL, Powers JL, Matheson RT, et al for the Etanercept Psoriasis Study Group. Etanercept monotherapy in patients with psoriasis. *N Engl J Med.* 2003;349:2014-2022.
11. Papp KA, Tyring S, Lahfa M, et al; Etanercept Psoriasis Study Group. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol.* 2005;152:1304-1312.
12. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2012;64(5):625-639.
13. Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis.* 2011 Jun;70(6):896-904.
14. Zochling J, Braun J. Quality indicators, guidelines and outcome measures in ankylosing spondylitis. *Clin Exp Rheumatol.* 2007;25(6 Suppl 47):147-152.
15. van der Heijde D, Sieper J, Maksymowych WP, et al. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis.* 2011;70(6):905-908.

16. Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: Initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res (Hoboken).* 2011;63(4):465-482.
17. Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Rheum. 2013;65(10):2499-2512.
18. Hsu S, Papp KA, Lebwohl MG, et al. Consensus guidelines for the management of plaque psoriasis. *Arch Dermatol.* 2012;148(1):95-102.
19. Gossec L, Smolen JS, Gaujoux-Viala C, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis*. 2012;71(1):4-12.
20. Ritchlin CT, Kavanaugh A, Gladman DD, et al. Treatment recommendations for psoriatic arthritis. *Ann Rheum Dis.* 2009;68:1387-1394.
21. Melikoglu M, Fresko I, Mat C, et al. Short-term trial of etanercept in Behcet's disease: a double blind, placebo controlled study. *J Rheumatol.* 2005;32:98-105.
22. Sfikakis PP, Markomichelakis N, Alpsoy E, et al. Anti-TNF therapy in the management of Behcet's disease--review and basis for recommendations. *Rheumatology (Oxford).* 2007;46:736-741.
23. Hatemi G, Silman A, Bang, D, et al. EULAR recommendations for the management of Behcet disease. *Ann Rheum Dis.* 2008;67:1656-1662.
24. Levy-Clarke G, Jabs DA, Read RW, et al. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmology.* 2014;121(3):785-796.
25. Hannu T. Reactive arthritis. *Best Pract Res Clin Rheumatol*. 2011;25(3):347-357.
26. Flagg SD, Meador R, Hsia E, et al. Decreased pain and synovial inflammation after etanercept therapy in patients with reactive and undifferentiated arthritis: an open-label trial. *Arthritis Rheum.* 2005;53:613-617.
27. Husni ME, Maier AL, Mease PJ, et al. Etanercept in the treatment of adult patients with Still's disease. *Arthritis Rheum.* 2002;46:1171-1176.
28. Kontzias A, Efthimiou P. Adult-onset Still's disease: pathogenesis, clinical manifestations and therapeutic advances. *Drugs.* 2008;68:319-337.
29. Riera E, Olivé A, Narváez J, et al. Adult onset Still's disease: review of 41 cases. *Clin Exp Rheumatol.* 2011;29(2):331-336.
30. Machado P, Castrejon I, Katchamart W, et al. Multinational evidence-based recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis*. 2011;70(1):15-24.
31. Brandt J, Khariouzov A, Listing J, et al. Successful short term treatment of patients with severe undifferentiated spondylo-arthritis with the anti-tumor necrosis factor-alpha fusion receptor protein etanercept. *J Rheumatol.* 2004;31:531-538.
32. Reiff A. Long-term outcome of etanercept therapy in children with treatment-refractory uveitis [letter]. *Arthritis Rheum.* 2003;48:2079-2080.
33. Saurenmann RK, Levin AV, Rose JB, et al. Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. *Rheumatology (Oxford).* 2006;45:982-989.
34. Galor A, Perez VL, Hammel JP, Lowder CY. Differential effectiveness of etanercept and infliximab in the treatment of ocular inflammation. *Ophthalmology.* 2006;113:2317-2323.
35. Hale S, Lightman S. Anti-TNF therapies in the management of acute and chronic uveitis. *Cytokine.* 2006;33:231-237.
36. Smith JA, Thompson DJ, Whitcup SM, et al. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. *Arthritis Rheum.* 2005;53:18-23.
37. Foster CS, Tufail F, Waheed NK, et al. Efficacy of etanercept in preventing relapse of uveitis controlled by methotrexate. *Arch Ophthalmol.* 2003;121:437-440.

38. Furst DE, Keystone EC, So AK, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. *Ann Rheum Dis*. 2013;72 Suppl 2:ii2-34.Berman B, Patel JK, Perez OA, et al. Evaluating the tolerability and efficacy of etanercept compared to triamcinolone acetonide for the intralesional treatment of keloids. *J Drugs Dermatol*. 2008;7:757-761.
39. Xeljanz® tablets [prescribing information]. New York, NY: Pfizer Inc; November 2012.
40. Sandborn WJ, Hanauer SB, Katz S, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Gastroenterology*. 2001;121:1088-1094.
41. Marzo-Ortega H, McGonagle D, O'Connor P, et al. Efficacy of etanercept for treatment of Crohn's related spondyloarthritis but not colitis. *Ann Rheum Dis*. 2003;62:74-76.
42. Efthimiou P, Schwartzman S, Kagen LJ. Possible role for tumour necrosis factor inhibitors in the treatment of resistant dermatomyositis and polymyositis: a retrospective study of eight patients. *Ann Rheum Dis.* 2006;65:1233-1236.
43. Iannone F, Scioscia C, Falappone PC, et al. Use of etanercept in the treatment of dermatomyositis: a case series. *J Rheumatol.* 2006;33:1802-1804.
44. Amato AA, Tawil R, Kissel J, et al. A randomized, pilot trial of etanercept in dermatomyositis. *Ann Neurol*. 2011;70(3):427-436.
45. Iorizzo LJ 3rd, Jorizzo JL. The treatment and prognosis of dermatomyositis: an updated review. *J Am Acad Dermatol.* 2008;59:99-112.
46. Rouster-Stevens KA, Ferguson L, Morgan G, et al. Pilot study of etanercept in patients with refractory juvenile dermatomyositis. *Arthritis Care Res (Hoboken).* 2014 May;66(5):783-787.
47. Adams DR, Yankura JA, Fogelberg AC, et al. Treatment of hidradenitis suppurativa with etanercept injection. *Arch Dermatol*. 2010;146(5):501-504.
48. van Rappard DC, Limpens J, Mekkes JR. The off-label treatment of severe hidradenitis suppurativa with TNF-α inhibitors: a systematic review. *J Dermatolog Treat*. 2013 Oct;24(5):392-404.
49. Rahman MU, Poe DS, Choi HK. Etanercept therapy for immune-mediated cochleovestibular disorders: preliminary results in a pilot study. *Otol Neurotol.* 2001;22:619-624.
50. Matteson EL, Choi HK, Poe DS, et al. Etanercept therapy for immune-mediated cochleovestibular disorders: a multi-center, open-label, pilot study. *Arthritis Rheum.* 2005;53:337-342.
51. Cohen S, Shoup A, Weisman MH, et al. Etanercept treatment for autoimmune inner ear disease: results of a pilot placebo-controlled study. *Otol Neurotol.* 2005;26:903-907.
52. Baughman RP, Lower EE, Bradley DA, et al. Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. *Chest.* 2005;128:1062-1047.
53. Utz JP, Limper AH, Kalra S, et al. Etanercept for the treatment of state II and III progressive pulmonary sarcoidosis. *Chest.* 2003;124:177-185.
54. Amin EN, Closser DR, Crouser ED. Current best practice in the management of pulmonary and systemic sarcoidosis. *Ther Adv Respir Dis*. 2014;8(4):111-132.
55. Zandbelt MM, de Wilde P, van Damme P, et al. Etanercept in the treatment of patients with primary Sjogren's syndrome: a pilot study. *J Rheumatol*. 2004;31:96-101.
56. Sankar V, Brennan MT, Kok MR, et al. Etanercept in Sjogren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. *Arthritis Rheum.* 2004;50:2240-2245.
57. Lam GK, Hummers LK, Woods A, et al. Efficacy and safety of etanercept in the treatment of scleroderma-associated joint disease. *J Rheumatol.* 2007;34:1636-1637.
58. Molloy ES, Langford CA, Clark TM, et al. Anti-tumour necrosis factor therapy in patients with refractory Takayasu arteritis: long-term follow-up. *Ann Rheum Dis.* 2008;67:1567-1569.
59. Jacobelli S, André M, Alexandra JF, Dodé C, Papo T. Failure of anti-TNF therapy in TNF Receptor 1-Associated Periodic Syndrome (TRAPS). *Rheumatology (Oxford).* 2007;46:1211-1212.
60. Drewe E, McDermott EM, Powell PT, et al. Prospective study of anti-tumour necrosis factor receptor superfamily 1B fusion protein, and case study of anti-tumour necrosis factor receptor superfamily 1A fusion protein, in tumour necrosis factor receptor associated

periodic syndrome (TRAPS): clinical and laboratory findings in a series of seven patients. *Rheumatology (Oxford).* 2003;42:235-239.
61. Drewe E, Huggins ML, Morgan AG, et al. Treatment of renal amyloidosis with etanercept in tumour necrosis factor receptor-associated periodic syndrome. *Rheumatology (Oxford).* 2004;43:1405-1408.
62. Stojanov S, Dejaco C, Lohse P, et al. Clinical and functional characterisation of a novel TNFRSF1A c.605T>A/V173D cleavage site mutation associated with tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS), cardiovascular complications and excellent response to etanercept treatment. *Ann Rheum Dis.* 2008;67:1292-1298.
63. Drewe E, Powell RJ, McDermott EM. Comment on: Failure of anti-TNF therapy in TNF receptor 1-associated periodic syndrome (TRAPS). *Rheumatology (Oxford).* 2007;46:1865-1866.
64. Bulua AC, Mogul DB, Aksentijevich I, et al. Efficacy of etanercept in the tumor necrosis factor receptor-associated periodic syndrome: a prospective, open-label, dose-escalation study. *Arthritis Rheum.* 2012;64(3):908-913.
65. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med.* 2005;352:351-361.

FOR MEDICAL BENEFIT COVERAGE REQUESTS:

Prior approval is required for HCPCS Codes J1438 and J3590†.

†When *unclassified biologics* (J3590) is determined to be Enbrel.

Edits and Denials:

Prior Approval: Prior approval is required for etanercept **(HCPCS Codes J1438 and J3590)**. Requests for prior approval will be authorized by a nurse reviewer if submitted documentation meets criteria outlined within the Corporate Medical Policy.

Requests for prior approval will be forwarded to a qualified physician reviewer if submitted documentation does not meet criteria outlined within the Corporate Medical Policy.

TOPPS: Claims received with **HCPCS Code J1438** will edit with **Remark Code M3M or M4M** and will be adjudicated in accordance with the Corporate Medical Policy.

Claims received with **HCPCS Code J3590** will pend with **Remark Code PRR** and will be adjudicated in accordance with the Corporate Medical Policy.

Liability: A participating provider will be required to write off charges denied as not medically necessary.

HCPCS Code(s):	
J1438	Injection, etanercept, 25 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)
J3590	Unclassified biologics

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, RA, PsA, UC
Sotyktu™ (deucravacitinib tablets)	Inhibition of TYK2	PsO
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC

Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.