Drug Policy

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<th>Policy:</th>
<th>200805</th>
<th>Initial Effective Date: 12/01/2008</th>
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<tr>
<td>Code(s):</td>
<td>HCPCS J1438 and J3590†</td>
<td>Annual Review Date: 11/21/2019</td>
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<tr>
<td>SUBJECT:</td>
<td>Enbrel® (etanercept for subcutaneous [SC] injection)</td>
<td>Last Revised Date: 11/21/2019</td>
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<td>Erelzi (etanercept-szzs)</td>
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Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

OVERVIEW
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)¹⁶; AND
2. reducing the signs and symptoms of moderate or severe active polyarticular juvenile idiopathic arthritis (PJIA) in patients aged ≥ 2 years¹⁷; 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)¹⁸; AND
4. for reducing signs and symptoms in patients with active ankylosing spondylitis (AS)¹⁹; 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.¹⁰⁻¹¹

For RA and PsA, Enbrel can be used in combination with methotrexate (MTX) or used alone.¹

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


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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. **Etanercept is subject to the Inflammatory Conditions Care Value Program under pharmacy benefits.**

**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.**
   
   I. **Initial Therapy:** Approve for 90 days if the patient meets the following criteria (a, b, and c).\(^{12}\)
      
      a) The patient meets one of the following conditions (i, ii, iv, or v):
      
      i. The patient has tried one disease-modifying antirheumatic drug (DMARD) (brand or generic; oral or injectable) for at least 3 months; OR
      
      ii. The patient has had a 3-month trial of at least ONE biologic [See APPENDIX A for examples]; OR
      
      iii. Patient is concurrently receiving MTX;\(^{1}\) OR
      
      iv. Patient has a contraindication or intolerance to MTX and leflunomide, as determined by the prescribing physician; OR
      
      v. 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;\(^{12}\) AND
      
      b) Etanercept is prescribed by or in consultation with a rheumatologist; AND
      
      c) Site of care medical necessity is met *.

   
   II. **Continuation of Therapy:** 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 Etanercept. Site of care medical necessity is met*.

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).\(^{12}\) Guidelines from the American College of Rheumatology (ACR) [2015] have TNF inhibitors and non-TNF biologics, administered with or without MTX, equally positioned as a recommended therapy following a trial of a conventional synthetic
DMARD (e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine). 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.

**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.**
\[\text{a) Initial Approval. Approve for 3 months.}^3\]
\[\text{b) Extended Approval. 1 year.}\]

2. **Ankylosing Spondylitis (AS).**
   
   I. **Initial Therapy:** Approve for 3 months if Etanercept is prescribed by or in consultation with a rheumatologist AND site of care medical necessity is met *. 
   
   II. **Continuation of therapy:** 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 Etanercept and site of care medical necessity is met *. 

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.\(^13\)-\(^15\) Guidelines for ankylosing spondylitis and nonradiographic axial spondylitis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019). TNFis are recommended for the initial biologic. In those who are secondary nonresponders to a TNFi, a second TNFi is recommended over switching out of the class.\(^67\) In the AS guidelines, it is recommended to assess a patient’s response to a TNF blocker after at least 12 weeks of therapy.

**Dosing in AS.** The recommended dosing per the FDA approved label is 50 mg once weekly administered subcutaneously.\(^1\)

**Initial Approval/Extended Approval.**
\[\text{a) Initial Approval. Approve for 3 months.}^15\]
\[\text{b) Extended Approval. 1 year}\]

3. **Juvenile Idiopathic Arthritis (PJIA) [or Juvenile Rheumatoid Arthritis (JRA)] (regardless of type of onset)** [Note: This includes patients with juvenile spondyloarthritis/active sacroiliac arthritis].

   I. **Initial Therapy:** Approve for 90 days 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. The patient meets one of the following: (1 or 2):
1. Patient has tried one other agent for this condition (e.g., MTX, sulfasalazine, or leflunomide, an NSAID; OR

2. The patient has tried a biologic DMARD [See Appendix A for examples]; OR

ii. Patient will be starting on Etanercept 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) Etanercept is prescribed by or in consultation with a rheumatologist; AND

c) Site of care medical necessity is met*.

II. Continuation of Therapy: 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 Etanercept. Site of care medical necessity is met*.

Enbrel is indicated for moderately to severely active polyarticular JIA in patients 2 years of age and older.¹ In polyarticular disease, the 2019 ACR recommendations propose initial DMARD treatment with a conventional synthetic DMARD such as MTX in most patients prior to a TNFi.⁶⁷ In those who are secondary nonresponders to a TNFi, a second TNFi may be tried; however, a non-TNF biologic is recommended for primary nonresponders. TNFis may also be used as second- or third-line treatment for systemic JIA. The criteria for patients starting on Etanercept concurrently with a traditional DMARD or for patients with an absolute contraindication MTX, sulfasalazine, or leflunomide are recommended based on the professional opinion of specialized physicians.

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 (50mg is the maximum dose) administered subcutaneously.¹ [For both Erelzi (etanercept-szxs) and Eticovo (etanercept-ykro) do not have dosage forms that allow dosing for weights less than 63kg. Alternative dosage forms should be utilized for patients less than 63kg]

Initial Approval/Extended Approval.

Initial Approval. Approve for 3 months.

Extended Approval. 1 year

4. Plaque Psoriasis (PsO).

I. Initial Therapy: 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 meets on of the following criteria: (1 or 2)
      1. The patient has tried at least one oral therapy for psoriasis for at least 3 months (e.g., MTX, cyclosporine, Soriatane® [acitretin tablets]); oral methoxsalen plus ultraviolet A light (PUVA); or
      2. The patient has tried a biologic agent for at least 3 months [See Appendix A for examples]; AND
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, or products listed in Appendix A); OR

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

   c) Etanercept is prescribed by or in consultation with a dermatologist; AND
   d) Site of care medical necessity is met*.

II. Continuation of therapy: 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 Etanercept and site of care medical necessity is met*.

Enbrel is indicated for plaque psoriasis.1 Guidelines for treatment of plaque psoriasis recommend topical therapy for limited disease.18 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, acitretin (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. Erelzi (etanercept-szzs) is indicated for the treatment of Plaque Psoriasis in patients 18 years and older.

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 < 63 kg, 0.8 mg/kg weekly or ≥ 63 kg, 50 mg weekly (50mg is the maximum dose) administered subcutaneously.1

[For both Erelzi (etanercept-szzs) and Etico (etanercept-ykro) do not have dosage forms that allow dosing for weights less than 63kg. Alternative dosage forms should be utilized for patients less than 63kg]

Initial Approval/Extended Approval.

a) Initial Approval. Approve for 3 months.

b) Extended Approval. 1 year

5. Psoriatic Arthritis (PsA).

I. Initial Therapy: Approve for 3 months if Etanercept is prescribed by or in consultation with a rheumatologist or a dermatologist AND site of care medical necessity is met*.

II. Continuation of Therapy: 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 Etanercept. Site of care medical necessity is met*.

• Enbrel is indicated for PsA and can be used in combination with MTX in patients who do not respond adequately to MTX alone.1 Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with PsA and in those who were previously treated with an oral therapy.7
In clinical trials, Enbrel was effective in patients with active PsA despite therapy with a NSAID.\(^8,19\) There are few well-controlled, prospective studies with adequate duration that have evaluated the efficacy of the oral DMARDs.\(^19\) 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™ [golimumab for SC injection]) are equally effective for treatment of PsA, inhibition of radiographic progression, and improving physical function in patients with PsA. The traditional 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.\(^19-20\) This is in contrast with the newer biological 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.\(^1,19\)

**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.* Approve for 3 months.

b) *Extended Approval.* 1 year

**Other Uses with Supportive Evidence**


I. Initial Therapy: Approve for 12 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\(^\text{®}\) {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); OR

   b) Etanercept is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist; AND

   c) Site of care medical necessity is met*.

II. Continuation of therapy: Approve for 12 months 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 Etanercept and 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. 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

Initial Approval/Extended Approval.

a) Initial Approval. Approve for 1 year (12 months).

b) Extended Approval. 1 year.

7. Still’s Disease (systemic-onset RA in adults, the disease may have begun in childhood).27-28

I. Initial Therapy: Approve for 12 months 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) Etanercept is prescribed by or in consultation with a rheumatologist; AND

d) Site of care medical necessity is met*.

II. Continuation of therapy: Approve for 12 months 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 Etanercept and 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

Initial Approval/Extended Approval.

a) Initial Approval. Approve for 1 year (12 months).

b) Extended Approval. 1 year

8. Spondyloarthritis (SpA), Subtypes Other than Ankylosing Spondylitis or Psoriatic Arthritis (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]:

I. Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (a, b, AND c)

a) The patient meets one of the following: (1 or 2)

1. 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) has been tried. Note: Examples include methotrexate [MTX], leflunomide, sulfasalazine; OR

2. The patient has axial spondyloarthritis AND

b) The agent is prescribed by or in consultation with a rheumatologist. AND
II. Patients Currently Receiving an Etanercept Product. Approve for 1 year if the patient has had a response, as determined by the prescriber. Note: Examples of a response include decreased pain or stiffness, improved function or activities of daily living. The patient may not have a full response, but there should have been a recent or past response to an etanercept product. Site of care medical necessity is met*.

Initial Approval/Extended Approval.
 a) Initial Approval. Approve for 1 year (12 months).
 b) Extended Approval. 1 year

9. Uveitis (including other posterior uveitides and panuveitis syndromes).24,32-36
   I. Initial Therapy: Approve for 12 months if the patient meets the following criteria (a, b, and c):
      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. NOTE: An exception to the requirement for a trial of one of these therapies can be made if the patient has already had a trial of an adalimumab product [e.g., Humira] or an infliximab product [e.g., Remicade, Renflexis, Inflectra] for uveitis. These patients who have already tried a biologic for uveitis are not required to try another agent; AND
      b) Etanercept is prescribed by or in consultation with an ophthalmologist; AND
      c) Site of care medical necessity is met*.
   II. Continuation of Therapy: Approve for 12 months 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 Etanercept and site of care medical necessity is met*.

In patients with uveitis, TNF levels are increased in the serum and aqueous humor.37 Enbrel has been effective in a small number of children with chronic active uveitis (either with JRA or idiopathic) refractory to other therapies.32,36 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.24 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.36 Based on retrospective reviews, Remicade is more effective than Enbrel in the treatment of refractory uveitis in children and adults.33-35 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.37

Initial Approval/Extended Approval.
 a) Initial Approval. Approve for 1 year (12 months).
 b) Extended Approval. 1 year

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

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. 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. 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. 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. Polymyalgia Rheumatica (PMR): ACR/EULAR guidelines for the management of PMR (2015) strongly recommend against the use of TNFis for treatment of PMR. 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 immunomodulatory 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 \(\geq 6\) 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 TNFis 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. 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

Drug Policy


**FOR MEDICAL BENEFIT COVERAGE REQUESTS:**

*MMO Site of Care Medical Necessity Criteria:*

- Medications in this policy will be administered in a place of service that is a non-hospital facility based location (i.e., home infusion provider, provider’s office, free-standing ambulatory infusion center) unless at least one of the following are met†:
  1. Age less than 18* years; or
  2. Clinically unstable based upon documented medical history (e.g., patient is hemodynamically unstable); or
  3. History of a severe adverse event from previous administration of the prescribed medication; or
  4. Requested medication is being administered as follows:
     - part of a chemotherapy regimen (e.g., anti-neoplastic agent, colony stimulating factor, erythropoiesis-stimulating agent, anti-emetic) for treatment of cancer; or
     - administered with dialysis; or
  5. Physical or cognitive impairment and caregiver is not available to assist with safe administration of prescribed medication in the home; or
  6. Experiencing adverse events that are not managed by premedication or resources available at a non-hospital facility based location.

No initial doses are allowed in a hospital based outpatient facility without other above criteria being met.
* Effective 01/01/2019, age criterion applies to 18 years of older. Age at original effective date (03/01/2016) was 21 years or older.
†This criterion does not apply to Medicare or Medicare Advantage members.

Prior approval is required for HCPCS Codes J1438 and J3590†.
†When unclassified biologics (J3590) is determined to be Enbrel.

Edits and Denials:


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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.

<table>
<thead>
<tr>
<th>HCPCS Code(s):</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1438</td>
<td>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)</td>
</tr>
<tr>
<td>J3590</td>
<td>Unclassified biologics</td>
</tr>
</tbody>
</table>
Appendix A

SC – Subcutaneous; TNF – Tumor necrosis factor; IL – Interleukin; IV – Intravenous; PDE4 – Phosphodiesterase 4; JAK – Janus kinase.

<table>
<thead>
<tr>
<th>Biologic or Targeted Synthetic DMARD</th>
<th>Mechanism of Action</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimzia® (certolizumab pegol for SC injection)</td>
<td>Inhibition of TNF</td>
<td>AS, ASpA, CD, PPs, PsA, RA</td>
</tr>
<tr>
<td>Enbrel® (etanercept for SC injection)</td>
<td>Inhibition of TNF</td>
<td>AS, PPs, PsA, RA</td>
</tr>
<tr>
<td>Erelzi™ (etanercept-szss for SC injection)</td>
<td>Inhibition of TNF</td>
<td>AS, CD, PPs, PsA, RA</td>
</tr>
<tr>
<td>Humira® (adalimumab for SC injection)</td>
<td>Inhibition of TNF</td>
<td>AS, CD, HS, PPs, RA, UC, UV</td>
</tr>
<tr>
<td>Amjevita™ (adalimumab-atto for SC injection)</td>
<td>Inhibition of TNF</td>
<td>AS, CD, PPs, PsA, RA, UC</td>
</tr>
<tr>
<td>Cyltezo® (adalimumab-adbm for SC injection)</td>
<td>Inhibition of TNF</td>
<td>AS, CD, PPs, PsA, RA, UC</td>
</tr>
<tr>
<td>Simponi® (golimumab for SC injection)</td>
<td>Inhibition of TNF</td>
<td>AS, CD, PsA, RA, UC</td>
</tr>
<tr>
<td>Simponi® Aria™ (golimumab for IV infusion)</td>
<td>Inhibition of TNF</td>
<td>AS, CD, PPs, PsA, RA, UC</td>
</tr>
<tr>
<td>Inflectra™ (infliximab-dyyb for IV infusion)</td>
<td>Inhibition of TNF</td>
<td>AS, CD, PPs, PsA, RA, UC</td>
</tr>
<tr>
<td>Renflexis® (infliximab-abda for IV infusion)</td>
<td>Inhibition of TNF</td>
<td>AS, CD, PPs, PsA, RA, UC</td>
</tr>
<tr>
<td>Actemra® (tocilizumab for IV infusion)</td>
<td>Inhibition of IL-6</td>
<td>CRS, GCA, RA</td>
</tr>
<tr>
<td>Actemra® (tocilizumab for SC injection)</td>
<td>Inhibition of IL-6</td>
<td>CRS, GCA, RA</td>
</tr>
<tr>
<td>Kevzara® (sarilumab for SC injection)</td>
<td>Inhibition of IL-6</td>
<td>RA</td>
</tr>
<tr>
<td>Orencia® (abatacept for IV infusion)</td>
<td>T-cell costimulation modulator</td>
<td>PsA, RA</td>
</tr>
<tr>
<td>Orencia® (abatacept for SC injection)</td>
<td>T-cell costimulation modulator</td>
<td>PsA, RA</td>
</tr>
<tr>
<td>Rituxan® (rituximab for IV infusion)</td>
<td>CD20-directed cytolytic antibody</td>
<td>Various</td>
</tr>
<tr>
<td>Kineret® (anakinra for subcutaneous SC injection)</td>
<td>Inhibition of IL-1</td>
<td>NOMID, RA</td>
</tr>
<tr>
<td>Stelara® (ustekinumab for SC injection)</td>
<td>Inhibition of IL-12/23</td>
<td>CD, PPs, PsA, UC</td>
</tr>
<tr>
<td>Stelara® (ustekinumab for IV infusion)</td>
<td>Inhibition of IL-12/23</td>
<td>CD, PPs, PsA, UC</td>
</tr>
<tr>
<td>Siliq™ (brodalumab SC injection)</td>
<td>Inhibition of IL-17A</td>
<td>PPs</td>
</tr>
<tr>
<td>Cosentyx™ (secukinumab for SC injection)</td>
<td>Inhibition of IL-17A</td>
<td>AS, PPs, PsA</td>
</tr>
<tr>
<td>Talaltz® (ixekizumab for SC injection)</td>
<td>Inhibition of IL-23</td>
<td>PPs</td>
</tr>
<tr>
<td>Ilumya™ (tildarazumab-asnm for SC injection)</td>
<td>Inhibition of IL-23</td>
<td>PPs</td>
</tr>
<tr>
<td>Tremfya® (guselkumab for SC injection)</td>
<td>Inhibition of IL-23</td>
<td>PPs</td>
</tr>
<tr>
<td>Otezla® (apremilast tablets)</td>
<td>Inhibition of PDE4</td>
<td>BD, PPs, PsA</td>
</tr>
<tr>
<td>Olumiant® (baricitinib tablets)</td>
<td>Inhibition of the JAK pathways</td>
<td>RA</td>
</tr>
<tr>
<td>Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib ER tabs)</td>
<td>Inhibition of the JAK pathways</td>
<td>PsA, RA, UC</td>
</tr>
</tbody>
</table>

Agents and associated indications are for reference only.

“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.”

AS = Ankylosing Spondylitis, ASpA = Axial Spondyloarthritis, BD = Behcet Disease, CD = Crohn’s Disease, CRS = Cytokine Release Syndrome, GCA = Giant Cell Arteritis, GVHD = Graft-Versus-Host Disease, HS = Hidradenitis Suppurativa, NOMID = Neonatal-onset Multisystem Inflammatory Disease, PPs = Plaque Psoriasis, PsA = Psoriatic Arthritis, RA = Rheumatoid Arthritis, SpA = Spondyloarthritis, UC = Ulcerative Colitis, UV = Uveitis