

## PRIOR AUTHORIZATION POLICY

**POLICY:** Inflammatory Conditions – Etanercept Products

- Enbrel® (etanercept for subcutaneous injection – Immunex/Amgen)

**TAC APPROVAL DATE:** 11/07/2018; selected revision 04/24/2019

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### OVERVIEW

Etanercept products are human soluble receptor fusion proteins which inhibit the binding of tumor necrosis factor (TNF) $\alpha$  and  $\beta$  to cell surface TNF receptors.<sup>1</sup> TNF is a proinflammatory cytokine that is involved in normal inflammatory and immune responses. At this time, Enbrel is the only etanercept product commercially available in the US. Enbrel is indicated for the following uses:

1. Rheumatoid arthritis, 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; AND
2. Juvenile idiopathic arthritis (JIA), for reducing the signs and symptoms of moderate or severe active polyarticular disease in patients aged  $\geq 2$  years<sup>1,7</sup>; AND
3. Psoriatic arthritis (PsA), for reducing the signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (PsA)<sup>1,8</sup>; AND
4. Ankylosing spondylitis (AS), for reducing signs and symptoms in patients with active disease; AND
5. Plaque psoriasis, for treatment patients 4 years of age or older with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.<sup>1,10-11</sup>

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

### Disease Overview

TNF is a naturally occurring cytokine that mediates inflammation and modulates cellular immune responses. Increased levels of TNF have been implicated in the pathology of inflammatory conditions such as psoriasis, psoriatic arthritis, and rheumatoid arthritis (RA). Increased levels of TNF are found in the synovial fluid of patients with RA, JIA, AS, and PsA; TNF has an important role in both the pathologic inflammation and the joint destruction that are characteristic of this disease. In psoriasis, increased levels of TNF are found in the blood and skin lesions. Etanercept products neutralize the biological activity of TNF $\alpha$  and inhibits binding of TNF $\alpha$  with its receptors.

### Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.<sup>12-17,20-21,70</sup>

- Rheumatoid Arthritis: 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).<sup>12</sup>
  - Juvenile Idiopathic Arthritis: In polyarticular disease, the 2011 ACR recommendations propose initial DMARD treatment with a conventional synthetic DMARD such as MTX in most patients prior to a TNFi.<sup>14</sup> TNFis may also be used as second- or third-line treatment for systemic JIA.<sup>15</sup>
  - Spondyloarthritis: Guidelines from the Assessment of SpondyloArthritis International Society (ASAS)/EULAR (2016) recommend biologics (e.g., TNFis, Cosentyx) in patients with persistently
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high disease activity despite traditional conventional treatments (e.g., nonpharmacological management, NSAIDs).<sup>38</sup> Purely axial disease should not be treated with conventional synthetic DMARDs. Guidelines from the American College of Rheumatology (ACR) and the Spondyloarthritis Research and Treatment Network (SPARTAN) [2015] recommend TNFis for patients with active disease despite treatment with an NSAID (includes patients with non-radiographic axial [nr-ax]SpA).<sup>13</sup> Predominantly axial manifestations are not recommended for a conventional synthetic DMARD prior to a TNFi. However, for symptomatic peripheral arthritis, a conventional synthetic DMARD is recommended (preferably sulfasalazine).

- Plaque Psoriasis: Guidelines are not current.<sup>16</sup> The traditional systemic agents for plaque psoriasis are MTX, Soriatane, and cyclosporine. An injectable biologic agent 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.
- Psoriatic Arthritis: Recommendations from EULAR (2015) are based on clinical presentation.<sup>17</sup> In peripheral arthritis, a biologic (usually a TNFi) should be started following inadequate response to at least one conventional synthetic DMARD (supported by long-term experience and established safety/efficacy balance of TNFis vs. other biologics). For PsA with enthesitis, dactylitis, or axial disease, the initial treatment is biologics (current practice is a TNFi). In patients who fail to respond, switching to another biologic should be considered, including switching between TNFis. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [2015] recommends TNFis for patients presenting with various manifestations of PsA (i.e., peripheral arthritis, axial disease, enthesitis, dactylitis, skin, and nail disease).<sup>70</sup>
- Ocular Inflammatory Disorders: The American Academy of Ophthalmology (AAO) [2014] note that TNFis may be used in patients with uveitis due to various causes (e.g., spondyloarthropathy-associated or human leukocyte antigen [HLA]-B27-associated uveitis, JIA-associated uveitis, and other posterior uveitides and panuveitis syndromes).<sup>21</sup> TNFis should be considered second-line in vision-threatening JIA-associated uveitis when MTX has failed or is not tolerated and may be used as corticosteroid-sparing treatment for vision-threatening chronic uveitis from seronegative spondyloarthropathy. TNFis may also be considered in other patients who have vision-threatening or corticosteroid-dependent disease who have failed first-line therapies and as a second-line immunomodulatory agent for severe ocular inflammatory conditions (including chronic and severe scleritis).
- Behcet's Disease: EULAR recommendations (2018) include TNFis for initial or recurrent sight-threatening uveitis.<sup>20</sup> For patients refractory to first-line treatments (e.g., corticosteroids), TNFis are among the treatment options for mucocutaneous manifestations, venous thrombosis, severe or refractory gastrointestinal disease, and recurrent/chronic joint involvement. Recommendations for the use of TNFis in ocular inflammatory disorders from the AAO note that TNFis may be used first-line in patients with ophthalmic manifestations of Behcet's disease and for acute exacerbations of pre-existing Behcet's disease.<sup>21</sup>
- Pyoderma Gangrenosum: Although guidelines are not current, multiple topical and systemic therapies have been used for pyoderma gangrenosum.<sup>30-33</sup> Oral prednisone is the most common initial immunosuppressant medication. Other systemic therapies include cyclosporine, MTX, azathioprine, cyclophosphamide, mycophenolate mofetil, and TNFis (infliximab, etanercept, adalimumab). In case reports, TNFis have been effective.
- Graft versus Host Disease: Guidelines (2012) generally recommend TNFis as a treatment option following a trial of first-line agent(s) [e.g., cyclosporine, intravenous methylprednisolone] for acute GVHD (grade III or IV disease).<sup>71-72</sup> A number of small studies demonstrate efficacy when etanercept was used in GVHD.<sup>22-29</sup>

- Still's Disease: There are not current guidelines for treatment of Still's disease. However, it presents in adults with features similar to those of systemic onset JIA.<sup>41</sup> In addition, there is a small trial which demonstrated efficacy of etanercept used for this condition.

### **Safety**

Etanercept products have Boxed Warnings concerning risks of serious infection and the risk of malignancy.<sup>1</sup> Prior to initiating therapy, 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 an etanercept product, and if a serious infection or sepsis develops, discontinue therapy. It is also noted that lymphoma and other malignancies have been reported in children and adolescents taking TNFs.

### **POLICY STATEMENT**

Prior authorization is recommended for prescription benefit coverage of etanercept products. Because of the specialized skills required for evaluation and diagnosis of patients as well as the monitoring required for adverse events (AEs) and long-term efficacy, initial approval requires etanercept products to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

**Automation:** None.

### **RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of etanercept products (Enbrel) is recommended in those who meet one of the following criteria:

#### **FDA-Approved Indications**

- 1. Rheumatoid Arthritis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
  - A) Initial Therapy.** Approve for 3 months if the patient meets BOTH of the following criteria (i and ii):
    - i.** The patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months (e.g., methotrexate [oral or injectable], leflunomide, hydroxychloroquine, and sulfasalazine).  
NOTE: 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 (e.g., Cimzia [certolizumab pegol SC injection], an adalimumab product [e.g., Humira], an infliximab product [e.g., Remicade, Renflexis, Inflectra], Simponi [golimumab SC injection], Simponi Aria [golimumab IV infusion], Actemra [tocilizumab IV infusion; tocilizumab SC injection], Kevzara [sarilumab SC injection], Kineret [anakinra SC injection], Orencia [abatacept IV infusion; abatacept SC injection], or a rituximab product [e.g., Rituxan]). These patients who have already tried a biologic for RA are not required to “step back” and try a conventional synthetic DMARD; AND
    - ii.** The etanercept product is prescribed by or in consultation with a rheumatologist.
  - B) Patients Currently Receiving an Etanercept Product.** Approve for 3 years 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; improved laboratory values; 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 an etanercept product.

**2. Ankylosing Spondylitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving an Etanercept Product. Approve for 3 years 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 an etanercept product.

**3. Juvenile Idiopathic Arthritis (JIA) [or Juvenile Rheumatoid Arthritis {JRA}] (regardless of type of onset)** [Note: This includes patients with juvenile spondyloarthritis/active sacroiliac arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following criteria (i and ii):

i. The patient meets one of the following conditions (a, b, c, or d):

a) The patient has tried one other agent for this condition (e.g., methotrexate [MTX], sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug [NSAID] { e.g., ibuprofen, naproxen }).

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, tocilizumab SC injection], Kineret [anakinra SC injection], or Orencia [abatacept IV infusion, abatacept SC injection]) also counts as a trial of one agent for JIA; OR

b) The patient will be starting on an etanercept product concurrently with methotrexate (MTX), sulfasalazine, or leflunomide; OR

c) The patient has an absolute contraindication to methotrexate (MTX) [e.g., pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias], sulfasalazine, or leflunomide; OR

d) The patient has aggressive disease, as determined by the prescribing physician; AND

ii. The etanercept product is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving an Etanercept Product. Approve for 3 years 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 an etanercept product.

**4. Plaque Psoriasis.** Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, and iii):

i. The patient is greater than or equal to 4 years of age; AND

ii. The patient meets one of the following conditions (a or b):

a) The patient has tried at least one traditional systemic agent for psoriasis (e.g., methotrexate [MTX], cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light [PUVA]) for at least 3 months, unless intolerant.

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., an adalimumab product [e.g., Humira], Cimzia [certolizumab pegol SC injection], an infliximab product [e.g., Remicade, Renflexis, Inflectra], Siliq [brodalumab SC injection], Cosentyx<sup>®</sup> [secukinumab SC injection], Ilumya [tildrakizumab SC injection], Stelara<sup>®</sup> [ustekinumab SC injection], Taltz<sup>®</sup> [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

- b) The patient has a contraindication to methotrexate (MTX), as determined by the prescribing physician; AND
  - iii. The etanercept product is prescribed by or in consultation with a dermatologist.
- B) Patients Currently Receiving an Etanercept Product.** Approve for 3 years 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 an etanercept product.
- 5. Psoriatic Arthritis (PsA).** Approve for the duration noted if the patient meets ONE of the following (A or B):
- A) Initial Therapy. Approve for 3 months if the etanercept product is prescribed by or in consultation with a rheumatologist or a dermatologist.
  - B) Patients Currently Receiving an Etanercept Product. Approve for 3 years 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 an etanercept product.

#### **Other Uses with Supportive Evidence**

- 6. Behcet’s Disease.** Approve for 1 year if the patient meets ONE of the following (A or B):
- A) The patient meets ONE of the following (i or ii):
    - i. The patient has tried at least one conventional therapy (e.g., systemic corticosteroids, immunosuppressants [azathioprine, methotrexate {MTX}, mycophenolate mofetil, tacrolimus, Leukeran<sup>®</sup> {chlorambucil}, cyclophosphamide, or cyclosporine], interferon alfa)
- 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 tumor necrosis factor inhibitor (e.g., an adalimumab product [e.g., an adalimumab [e.g., Humira] or infliximab [e.g., Remicade, Renflexis, Inflectra] product. These patients who have already tried a biologic for Behcet’s disease are not required to “step back” and try a conventional therapy); OR
- ii. The etanercept product is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.
- B) The patient is currently established on an etanercept product for  $\geq 90$  days and has responded to therapy, as determined by the prescriber.
- 7. Graft-Versus-Host Disease (GVHD).** Approve for 1 year if the patient meets ONE of the following (A or B):
- A) The patient meets ONE of the following (i or ii):
    - i. The patient meets one of the following conditions (i or ii):

- a) 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
  - b) Patient is concurrently receiving at least one of these medications (e.g., high-dose systemic corticosteroids, antithymocyte globulin, cyclosporine, Thalomid® (thalidomide capsules), tacrolimus, mycophenolate mofetil) in combination with an etanercept product; AND
  - ii. The etanercept product is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.
- B) The patient is currently established on an etanercept product for  $\geq 90$  days and has responded to therapy, as determined by the prescriber.
- 8. Pyoderma Gangrenosum.** Approve for 1 year if the patient meets ONE of the following (A or B):
- A) 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
    - b) The patient has tried one other immunosuppressant (e.g., mycophenolate mofetil, cyclosporine) for at least 2 months or was intolerant to one of these agents; AND
  - ii. The etanercept product is prescribed by or in consultation with a dermatologist.
- B) The patient is currently established on an etanercept product for  $\geq 90$  days and has responded to therapy, as determined by the prescriber.
- 9. Scleritis or Sterile Corneal Ulceration.** Approve for 1 year if the patient meets ONE of the following (A or B):
- A) The patient meets BOTH of the following (i and ii):
- i. The patient has tried one other therapy for these (e.g., oral non-steroidal anti-inflammatory drugs [NSAIDs] such as indomethacin, naproxen, or ibuprofen; oral, topical [ophthalmic] or IV corticosteroids [such as prednisone, prednisolone, methylprednisolone]; methotrexate [MTX]; cyclosporine; or other immunosuppressants); AND
  - ii. The etanercept product is prescribed by or in consultation with an ophthalmologist.
- B) The patient is currently established on an etanercept product for  $\geq 90$  days and has responded to therapy, as determined by the prescriber.
- 10. Spondyloarthritis (SpA), Other Subtypes** (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 the duration noted if the patient meets ONE of the following (A or B):
- A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):
- i. The patient meets ONE of the following conditions (a or b):
    - a) 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
    - b) The patient has axial spondyloarthritis AND has objective signs of inflammation, defined as at least one of the following [(1) or (2)]:
      - (1) C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory; OR
      - (2) Sacroiliitis reported on magnetic resonance imaging (MRI); AND
  - ii. The etanercept product is prescribed by or in consultation with a rheumatologist.

- B) Patients Currently Receiving an Etanercept Product.** Approve for 1 year 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 an etanercept product.

**11. Still's Disease** (systemic-onset RA in adults, the disease may have begun in childhood). Approve for 1 year if the patient meets ONE of the following (A or B):

- A) The patient meets ALL of the following (i, ii, and iii):**
- i.** Patient has tried one corticosteroid; AND
  - ii.** Patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) such as methotrexate (MTX) given for at least 2 months or was intolerant to a conventional synthetic DMARD; AND
  - iii.** The etanercept product is prescribed by or in consultation with a rheumatologist.
- B) The patient is currently established on an etanercept product for  $\geq 90$  days and has responded to therapy, as determined by the prescriber**

**12. Uveitis (including other posterior uveitides and panuveitis syndromes).** Approve for 1 year if the patient meets the ONE of the following (A or B):

- A) The patient meets BOTH of the following (i and ii):**
- i.** The patient has tried one of the following therapies for this condition: periocular, intraocular, or systemic corticosteroids [for example, triamcinolone, betamethasone, methylprednisolone, prednisone] or immunosuppressives (e.g., methotrexate [MTX], mycophenolate mofetil, cyclosporine, azathioprine, cyclophosphamide).  
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 a another agent; AND
  - ii.** The etanercept product is prescribed by or in consultation with an ophthalmologist.
- B) The patient is currently established on an etanercept product for  $\geq 90$  days and has responded to therapy, as determined by the prescriber.**

#### **CONDITIONS NOT RECOMMENDED FOR APPROVAL**

Etanercept products (Enbrel) have 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. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

- 1. Concurrent Use with a Biologic DMARD or Targeted Synthetic DMARD.** Etanercept products 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.<sup>47</sup> **Note:** This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with etanercept products.
- 2. Crohn's Disease.** In a double-blind, placebo-controlled trial etanercept (Enbrel) was not effective for the treatment of moderate to severe Crohn's disease.<sup>49</sup> However, arthritis (spondyloarthritis, ankylosing spondylitis) may be associated with Crohn's disease and etanercept products may be effective for spondyloarthritis in these patients.<sup>50</sup>

- 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 an etanercept product.<sup>51</sup> In this case series, an etanercept product 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 etanercept was given for at least 3 months.<sup>52</sup> All patients had exacerbation of disease and etanercept was stopped. In a 1-year, double-blind study, patients were randomized to receive etanercept 50 mg weekly (n = 11) or placebo (n = 5).<sup>53</sup> All patients who received placebo were judged as treatment failures whereas five patients in the etanercept group were successfully weaned off of prednisone. More studies are needed demonstrating the efficacy of etanercept and its long-term effects.<sup>54</sup> In a 6-month, open-label study of etanercept in patients with refractory juvenile dermatomyositis (n = 9), minimal improvement was noted in disease activity with some patients experiencing worsening disease.<sup>55</sup>
  - 4. Hidradenitis Suppurativa.** A prospective, randomized, double-blind, placebo-controlled study assigned patients (n = 20) to treatment with etanercept 50 mg twice weekly or placebo for 12 weeks.<sup>56</sup> Following 12 weeks of treatment, all patients received open-label etanercept for an additional 12 weeks. The study found no statistically significant difference between etanercept 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 etanercept for treatment of hidradenitis suppurativa.<sup>57</sup>
  - 5. Polymyalgia Rheumatica (PMR).** ACR/EULAR guidelines for the management of PMR (2015) strongly recommend against the use of TNFis for treatment of PMR.<sup>58</sup> This recommendation is based on lack of evidence for benefit as well as considerable potential for potential harm. While etanercept has been evaluated in small numbers of patients with PMR, efficacy has not been established.<sup>59-61</sup>
  - 6. Sarcoidosis.** Evidence does not support use of etanercept in ocular or pulmonary disease. 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.<sup>21</sup> A discretionary recommendation (indicating trade-offs are less certain) is that etanercept 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 etanercept or placebo for 6 months.<sup>62</sup> Patients had received ≥ 6 months of therapy with MTX and were currently on corticosteroids. For most of the patients, therapy with etanercept was not associated with significant improvement. In a prospective, open-label trial in patients with Stage II or III progressive pulmonary sarcoidosis, treatment with etanercept was frequently associated with early or late treatment failure.<sup>63</sup> This trial was ended early because an excessive number of patients (n = 11/17) had disease progression on etanercept. Recommendations for best practice in the management of pulmonary and systemic sarcoidosis mention Humira and Remicade as therapeutic options for management of disease.<sup>64</sup>
  - 7. 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
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arteritis) do not mention the use of TNFis.<sup>65</sup> 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.<sup>66</sup> In a double-blind trial patients with biopsy proven giant cell arteritis with AEs due to corticosteroids were randomized to etanercept 25 mg twice weekly (n = 8) or placebo (n = 9) for 12 months.<sup>67</sup> 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 etanercept patients and 22.2% of placebo patients were able to control the disease without corticosteroid therapy (not statistically significant). But patients on etanercept 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 etanercept (n = 9).<sup>68</sup> Five patients who were initially treated with etanercept 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 etanercept.

8. **Wegener's Granulomatosis.** Etanercept 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 etanercept or placebo in combination with standard therapies (e.g., cyclophosphamide, MTX, corticosteroids) depending on disease severity.<sup>69</sup> 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 etanercept 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 etanercept and 57.1% on placebo had at least one severe or life-threatening AE or died. Six of the etanercept patients and none of the controls developed solid malignancies. Use of etanercept in patients with Wegener's granulomatosis who are receiving immunosuppressant drugs is not recommended.<sup>1</sup>
9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

## REFERENCES

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**HISTORY**

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	Under Conditions Not Recommended for Coverage, list polymyositis and dermatomyositis along with inclusion body myositis under Inflammatory Myopathies. Remove the following from the Conditions Not Recommended for Approval (not needed): Autoimmune Mucocutaneous Blistering Diseases (pemphigus vulgaris, mucous membrane pemphigoid [cicatricial pemphigoid]; Immune-Mediated Cochleovestibular Disorders; Sjögren’s syndrome; Systemic Sclerosis (Scleroderma).	10/19/2016
Annual revision	For RA, Kevzara was added as an example of an agent that may have been tried prior to Enbrel. Throughout the policy, criteria that mentioned Humira, Remicade, and Rituxan were reworded as adalimumab, infliximab, and rituximab products, respectively, with the innovator names listed as examples of these products; Renflexis and Inflectra were also added to criteria as examples of an infliximab product. Criteria were clarified for Behcet’s disease, JIA, and uveitis. For these conditions, the criterion that directs patients to previous therapy prior to approval of etanercept was reworded to clarify its intent such that patients are now directed to conventional agents with a note that prior use of a biologic would count towards this requirement. Previously, criteria were worded more generally and both conventional and biologic therapies were listed together. For plaque psoriasis, Siliq and Tremfya were added as examples of an agent that may have been tried prior to Enbrel. For initial therapy of plaque psoriasis, add criteria to require that patients are greater than or equal to 4 years of age.	10/11/2017
Annual revision	<p><b>Patients Established on Enbrel:</b> Remove this criterion for patients currently established on therapy for <math>\geq 90</math> days. Patients currently taking an etanercept product are now addressed in the criteria section for each specific indication.</p> <ul style="list-style-type: none"> <li>• Add a requirement that the patient must have responded to initial therapy for the following indications: Behcet’s disease, GVHD, pyoderma gangrenosum, scleritis or sterile corneal ulcerations, Still’s disease, SpA, and uveitis.</li> </ul> <p><b>Previous Therapies:</b> For these indications, add the following agents to the list of therapies the patient may have tried prior to etanercept:</p> <ul style="list-style-type: none"> <li>• PsO: Cimzia, Illumya</li> <li>• JIA: Actemra SC</li> </ul> <p><b>Behcet’s disease:</b> Modify criteria to change previous therapy from biologic to more specifically say TNFi.</p> <p><b>Conditions Not Recommended for Coverage:</b> Ocular and Pulmonary Sarcoidosis were combined into one condition (Sarcoidosis) which is not recommended for coverage.</p> <p><b>Other:</b> Policy name was changed to Inflammatory Conditions – Etanercept Products. Throughout the policy, references to Enbrel were reworded to say etanercept products.</p>	11/07/2018
Selected revision	<p><b>Spondyloarthritis (SpA), Other Subtypes:</b> This off-label approval condition was reworded (previously listed as Spondyloarthritis, Subtypes Other than Ankylosing Spondylitis or Psoriatic Arthritis). There is a note which directs to criteria for FDA-approved subtypes of SpA (AS, PsA). Criteria were changed to approve for 3 months for patients starting therapy (previously was 1 year). For patients with primarily axial disease, a criterion was added to require objective signs of inflammation, defined as C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory or sacroiliitis reported on magnetic resonance imaging. For patients currently receiving therapy, examples of a response to therapy were added; the requirement that patients be on an etanercept product for <math>\geq 90</math> days was removed.</p>	04/24/2019

\* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>; TAC – Therapeutic Assessment Committee; DMARD – Disease-modifying anti-rheumatic drug; FDA – Food and Drug Administration; SpA – Spondyloarthritis; PMR – Polymyalgia rheumatic; MTX – Methotrexate.

**APPENDIX**

<b>Brand (generic name)</b>	<b>Mechanism of Action</b>
<b>Cimzia</b> <sup>®</sup> (certolizumab pegol SC injection)	Inhibition of TNF
<b>Enbrel</b> <sup>®</sup> (etanercept SC injection)	Inhibition of TNF
<b>Erelzi</b> <sup>™</sup> (etanercept-szsz SC injection)	Inhibition of TNF
<b>Humira</b> <sup>®</sup> (adalimumab SC injection)	Inhibition of TNF
<b>Amjevita</b> <sup>®</sup> (adalimumab-atto SC injection)	Inhibition of TNF
<b>Cyltezo</b> <sup>®</sup> (adalimumab-adbm SC injection)	Inhibition of TNF
<b>Simponi</b> <sup>®</sup> (golimumab SC injection)	Inhibition of TNF
<b>Simponi</b> <sup>®</sup> <b>Aria</b> <sup>™</sup> (golimumab IV infusion)	Inhibition of TNF
<b>Remicade</b> <sup>®</sup> (infliximab IV infusion)	Inhibition of TNF
<b>Inflectra</b> <sup>™</sup> (infliximab-dyyb IV infusion)	Inhibition of TNF
<b>Renflexis</b> <sup>®</sup> (infliximab-abda IV infusion)	Inhibition of TNF
<b>Actemra</b> <sup>®</sup> (tocilizumab IV infusion)	Inhibition of IL-6
<b>Actemra</b> <sup>®</sup> (tocilizumab SC injection)	Inhibition of IL-6
<b>Kevzara</b> <sup>®</sup> (sarilumab SC injection)	Inhibition of IL-6
<b>Orencia</b> <sup>®</sup> (abatacept IV infusion)	T-cell costimulation modulator
<b>Orencia</b> <sup>®</sup> (abatacept SC injection)	T-cell costimulation modulator
<b>Rituxan</b> <sup>®</sup> (rituximab IV infusion)	CD20-directed cytolytic antibody
<b>Truxima</b> <sup>®</sup> (rituximab-abbs IV injection)	CD20-directed cytolytic antibody
<b>Kineret</b> <sup>®</sup> (anakinra SC injection)	Inhibition of IL-1
<b>Stelara</b> <sup>®</sup> (ustekinumab SC injection)	Inhibition of IL-12/23
<b>Stelara</b> <sup>®</sup> (ustekinumab IV infusion)	Inhibition of IL-12/23
<b>Siliq</b> <sup>™</sup> (brodalumab SC injection)	Inhibition of IL-17
<b>Cosentyx</b> <sup>™</sup> (secukinumab SC injection)	Inhibition of IL-17A
<b>Taltz</b> <sup>®</sup> (ixekizumab SC injection)	Inhibition of IL-17A
<b>Ilumya</b> <sup>™</sup> (tildrakizumab-asmn SC injection)	Inhibition of IL-23
<b>Skyrizi</b> <sup>™</sup> (risankizumab SC injection)	Inhibition of IL-23
<b>Tremfya</b> <sup>™</sup> (guselkumab SC injection)	Inhibition of IL-23
<b>Entyvio</b> <sup>™</sup> (vedolizumab IV infusion)	Integrin receptor antagonist
<b>Otezla</b> <sup>®</sup> (apremilast tablets)	Inhibition of PDE4
<b>Olumiant</b> <sup>®</sup> (baricitinib tablets)	Inhibition of the JAK pathways
<b>Xeljanz</b> <sup>®</sup> , <b>Xeljanz XR</b> (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways

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