Effective Date **2/15/2024**
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Coverage Policy Number **IP0241**

Etanercept

Table of Contents

Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for etanercept (**Enbrel®**).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Etanercept (Enbrel) is considered medically necessary when ONE of the following is met:

1. **Ankylosing Spondylitis.** Individual meets **BOTH** of the following criteria:
   A. Documentation of **ONE** of the following:
      i. Failure, contraindication, or intolerance to **ONE** non-steroidal anti-inflammatory drug (NSAID)
      ii. Already tried a biologic or targeted synthetic DMARD for Ankylosing Spondylitis
   B. Medication is prescribed by, or in consultation with a rheumatologist

2. **Behcet's Disease.** Individual meets **BOTH** of the following criteria:
   A. Documentation of **ONE** of the following:
      i. Failure, contraindication, or intolerance to **ONE** systemic conventional therapy
      ii. Already tried a biologic for Behcet's Disease
   B. Medication is prescribed by, or in consultation with, a rheumatologist, dermatologist, ophthalmologist, gastroenterologist or neurologist

3. **Graft-Versus-Host Disease.** Individual meets **BOTH** of the following criteria:
   A. Documented failure, contraindication, or intolerance to **ONE** conventional systemic treatment (for example, corticosteroids, antithymocyte globulin, other immunosuppressants
   B. Medication is prescribed by, or in consultation with, an oncologist, hematologist, or a physician affiliated with a transplant center

4. **Non-Radiographic Axial Spondyloarthritis**. Individual meets **ALL** of the following criteria:
   A. Has objective signs of inflammation, defined as **ONE** of the following:
      i. C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory
      ii. Sacroiliitis reported on magnetic resonance imaging (MRI)
   B. **ONE** of the following (i or ii):
      i. Documented failure, contraindication, or intolerance to **ONE** non-steroidal anti-inflammatory drug (NSAID)
      ii. Already tried a biologic or targeted synthetic DMARD (tsDMARD) for Non-Radiographic Axial Spondylarthritis
   C. Medication is prescribed by, or in consultation with, a rheumatologist

5. **Plaque Psoriasis.** Individual meets **ALL** of the following criteria:
   A. 4 years of age or older
   B. Body Surface Area (BSA) of greater than 5%, OR BSA less than 5% and there is and there is involvement of the scalp, face, the palms and soles, or genitals
   C. Documentation of **ONE** of the following:
      i. Failure, contraindication, or intolerance to **ONE** of the following:
         a. Topical therapy (for example, topical corticosteroids, topical vitamin D analogs, Tazorac)
         b. Systemic therapy (for example, methotrexate, cyclosporine, Soriatane)
         c. Phototherapy
      ii. Already tried a biologic or targeted synthetic DMARD (tsDMARD) for Plaque Psoriasis
   D. Medication is prescribed by, or in consultation with, a dermatologist

6. **Polyarticular Juvenile Idiopathic Arthritis (includes Juvenile Rheumatoid Arthritis, Juvenile Spondyloarthropathy/Active Sacroiliac Arthritis).** Individual meets **BOTH** of the following criteria:
   A. 2 years of age or older
   B. Medication is prescribed by, or in consultation with, a rheumatologist

7. **Psoriatic Arthritis**. Individual meets the following criterion:
   A. Medication is prescribed by, or in consultation with, a rheumatologist or dermatologist

8. **Pyoderma Gangrenosum.** Individual meets **BOTH** of the following criteria:
   A. Documented failure, contraindication, or intolerance to conventional systemic therapy (for example, mycophenolate mofetil, cyclosporine or corticosteroid)
   B. Medication is prescribed by, or in consultation with, a dermatologist or rheumatologist

9. **Rheumatoid Arthritis**. Individual meets **BOTH** of the following criteria:
   A. Documentation of **ONE** of the following:
      i. Failure, contraindication, or intolerance to **ONE** conventional synthetic disease-modifying anti-rheumatic drug (csDMARD)
      ii. Already tried a biologic or targeted synthetic DMARD (tsDMARD) for Rheumatoid Arthritis

B. Medication is prescribed by, or in consultation with, a rheumatologist

10. **Spondyloarthritis (non-axial disease): Reactive Arthritis (Reiter's disease) and Undifferentiated Arthritis.** Individual meets **ALL** of the following criteria:
    A. Arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet
    B. Documentation of **ONE** of the following:
        i. Failure, contraindication, or intolerance to **ONE** conventional synthetic disease-modifying anti-rheumatic drug (csDMARD)
        ii. Already tried a biologic for non-axial spondyloarthritis
    C. Medication is prescribed by, or in consultation with, a rheumatologist

11. **Still's Disease.** Individual meets **BOTH** of the following criteria:
    A. **ONE** of the following:
        i. **Documentation of BOTH** of the following:
            a. Failure, contraindication, or intolerance to **ONE** corticosteroid
            b. Failure (after at least a 2 month trial), contraindication, or intolerance to **ONE** conventional synthetic disease-modifying antirheumatic drug (DMARD)
        ii. Already tried a biologic for Still's Disease
    B. Medication is prescribed by, or in consultation with, a rheumatologist

Coverage varies across plans and may require the use of preferred products. Refer to the customer's benefit plan document for coverage details.

Employer Group - Standard/Performance, Value/Advantage, Legacy, Cigna Total Savings Prescription Drug List Covered Alternatives:	
Condition	**Criteria**
Ankylosing Spondylitis	**Preferred** [requires prior authorization]
Polyarticular Juvenile Idiopathic Arthritis	
Plaque Psoriasis - Adult, Pediatric and Adolescent	
Psoriatic Arthritis - Adult, Pediatric and Adolescent	
Rheumatoid Arthritis	

Individual and Family Plan Prescription Drug List Covered Alternatives:	
Condition	**Criteria**
Ankylosing Spondylitis	**Preferred** [requires prior authorization]
Polyarticular Juvenile Idiopathic Arthritis	
Plaque Psoriasis - Adult, Pediatric and Adolescent	
Psoriatic Arthritis - Adult, Pediatric and Adolescent	
Rheumatoid Arthritis	

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of etanercept (Enbrel) is considered medically necessary for **ALL** covered diagnoses when the above medical necessity criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration is up 12 months.
Reauthorization approval duration is up 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (tsDMARD).** Etanercept products should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition. Combination therapy is generally not recommended due to a higher rate of AEs with combinations and lack of data supportive of additional efficacy.

   This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, 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.[25] However, arthritis (spondyloarthropathy, ankylosing spondylitis) may be associated with Crohn's disease and etanercept products may be effective for spondyloarthropathy in these patients.[26]

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.[27] 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 (methotrexate, azathioprine, cyclosporine), the cytotoxic drugs were discontinued and etanercept was given for at least 3 months.[28] 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).[29] 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.[30] 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.[31]

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.[32] 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.[33]

5. **Polymyalgia Rheumatica (PMR).** ACR/EULAR guidelines for the management of PMR (2015) strongly recommend against the use of TNFis for treatment of PMR.[34] 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.[35-37]

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 infliximab or adalimumab may be considered as second-line immunomodulatory therapy for patients failing or intolerant of standard immunomodulatory agents.[8] 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.[38] Patients had received ≥ 6 months of therapy with methotrexate 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.[39] 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 infliximab and adalimumab as therapeutic options for management of disease.[40]

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 arteritis) do not mention the use of TNFis.[41] 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.[42] 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.[43] 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, there was not a statistically significant difference in the proportion of patients able to control disease without corticosteroid therapy with etanercept (50%) vs. placebo (22.2%). However, 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 infliximab (n = 21) or etanercept (n = 9).[44] Five patients who were initially treated with etanercept were switched to infliximab. Therapy with TNFis 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, methotrexate, corticosteroids) depending on disease severity.[45] 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 adverse event 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.[1]

Background

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**, for reducing the signs and symptoms of moderate or severe active polyarticular disease in patients aged ≥ 2 years.
- **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.
- **Psoriatic arthritis**, ± methotrexate for reducing the signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis.
- **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.

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.

- **Spondyloarthritis:** 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).[5] 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.
- **Juvenile Idiopathic Arthritis (JIA):** There are guidelines from the ACR/Arthritis Foundation for the treatment of JIA (2019) specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[3] TNFis are the biologics recommended for polyarthritis, sacroiliitis, enthesitis. Actemra® (tocilizumab intravenous, tocilizumab subcutaneous) and Orencia® (abatacept intravenous, abatacept intravenous) are also among the biologics recommended for polyarthritis. Biologics are recommended following other therapies (e.g., following DMARDs for active polyarthritis or following a nonsteroidal anti-inflammatory drug [NSAID] for active JIA with sacroiliitis or enthesitis). However, there are situations where initial therapy with a biologic may be preferred over other conventional therapies (e.g., if there is involvement of high-risk joints such as the cervical spine, wrist, or hip; high disease activity; and/or those judged to be at high risk of disabling joint damage). TNFis may also be used as second- or third-line treatment for systemic JIA.[4]
- **Plaque Psoriasis:** Guidelines from the American Academy of Dermatologists (AAD) and National Psoriasis Foundation (NPF) [2019] recommend etanercept as a monotherapy treatment option for adults with moderate to severe disease.[7]
- **Psoriatic Arthritis:** 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.[8]
- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic DMARD for a patient taking the maximum tolerated dose of methotrexate who is not at target.[22]

Other Uses with Supportive Evidence

There are guidelines and/or published data supporting the use of etanercept products in the following conditions:

- **Behcet's Disease:** The European Union Against Rheumatism (EULAR) recommendations (2018) include TNFis for initial or recurrent sight-threatening uveitis.[9] 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 American Academy of Ophthalmology (AAO) [2014] 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.[8] In particular, the monoclonal antibodies (adalimumab or infliximab products) are recommended for vision-threatening ocular manifestations of Behcet's disease.
- **Graft-Versus-Host Disease:** Guidelines for hematopoietic cell transplantation from the National Comprehensive Cancer network (NCCN) [version 4.2021 – September 9, 2021] list etanercept among the agents used for steroid-refractory acute and chronic disease.[46]
- **Pyoderma Gangrenosum:** Although guidelines are not current, multiple topical and systemic therapies have been used for pyoderma gangrenosum. Oral prednisone is the most common initial immunosuppressant medication.[10-13] Other systemic therapies include cyclosporine, methotrexate,

azathioprine, cyclophosphamide, mycophenolate mofetil, and TNFis (i.e., infliximab, etanercept, and adalimumab products). In case reports, TNFis have been effective.

- **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.[24] In addition, there is a small trial which demonstrated efficacy of etanercept used for this condition.

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APPENDIX

Table 1. Approved TNFis for Targeted Indications.

	Rheumatology					Dermatology	Gastroenterology	
	RA	JIA	AS	nr-axSpA	PsA	PsO	CD	UC
Tumor Necrosis Factor Inhibitors								
Cimzia	√	--	√	√	√	√	√	--
Enbrel	√	√	√	--	√	√	--	--
Humira	√	√	√	--	√	√	√	√
Infliximab Products	√	--	√	--	√	√	√	√
Simponi Subcutaneous	√	--	√	--	√	--	--	√
Simponi Aria	√	√	√	--	√	--	--	--

TNFis – Tumor necrosis factor inhibitor; RA – Rheumatoid arthritis; JIA – Juvenile idiopathic arthritis; AS – Ankylosing spondylitis; nr-axSpA – Non-radiographic spondyloarthritis; PsA – Psoriatic arthritis; PsO – Plaque psoriasis; CD – Crohn's disease; UC – Ulcerative colitis.

Table 2. Approved IL-17, IL-23, and IL-12/23 Blockers for Targeted Indications.

	Rheumatology			Dermatology	Gastroenterology	
	Ankylosing Spondylitis	nr-axSpA	Psoriatic Arthritis	Plaque Psoriasis	Crohn's Disease	Ulcerative Colitis
Interleukin-17 Blockers						
Cosentyx	√	√	√	√	--	--
Siliq	--	--	--	√	--	--
Taltz	√	√	√	√	--	--
Interleukin-23 Blockers						
Ilumya	--	--	--	√	√	--
Skyrizi Intravenous	--	--	--	--	√#	--
Skyrizi Subcutaneous	--	--	√	√	√^	--
Tremfya	--	--	√	√	--	--
Interleukin-12/23 Blockers						
Stelara Subcutaneous	--	--	√	√	√^	√^
Stelara Intravenous	--	--	--	--	√#	√#

IL – Interleukin; nr-axSpA – Non-radiographic spondyloarthritis; ^ Maintenance dosing only; # Induction dosing only.

Table 3. Approved Oral tsDMARDs for Targeted Indications.

	Rheumatology				Dermatology	Gastro-enterology
	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	Psoriatic Arthritis	Plaque Psoriasis	Ulcerative Colitis
	Janus Kinases Inhibitors					
Olumiant	√	--	--	--	--	--
Rinvoq	√	--	√	√	--	√
Xeljanz tablets	√	√#	√	√	--	√
Xeljanz oral solution	--	√#	--	--	--	--
Xeljanz XR	√	--	√	√	--	√
Phosphodiesterase Type 4 Inhibitor						
Otezla	--	--	--	√	√	--
Sphingosine 1-Phosphate Receptor Modulator						
Zeposia	--	--	--	--	--	√

tsDMARDs – Targeted synthetic disease-modifying antirheumatic drugs; # Indicated in polyarticular JIA.

Table 4. Other Approved Biologics for Targeted Indications.

	Rheumatology		
	Rheumatoid Arthritis	**Juvenile Idiopathic Arthritis**	**Psoriatic Arthritis**
Interleukin-6 Blockers			
Actemra Intravenous	√	√^	--
Actemra Subcutaneous	√	√^	--
Kevzara	√	--	--
Interleukin-1 Blocker			
Kineret	√	--	--
T-Cell Costimulation Modulator			
Orencia Intravenous	√	√#	√
Orencia Subcutaneous	√	√#	√
CD20-Directed Cytolytic Antibody			
Rituximab Intravenous Products	√	--	--

^ Indicated in polyarticular and systemic JIA; # Indicated in polyarticular JIA.