

## 5.70.27

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| <b>Section:</b>    | Prescription Drugs         | <b>Effective Date:</b>       | April 1, 2021   |
| <b>Subsection:</b> | Analgesics and Anesthetics | <b>Original Policy Date:</b> | October 1, 2013 |
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**Last Review Date:** March 12, 2021

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## Enbrel

### Description

Enbrel (etanercept), Erelzi\* (etanercept – szzs), Eticovo\* (etanercept-ykro)

\*These medications are included in this policy but are not available in the market as of yet

### Background

Enbrel (etanercept) and its biosimilars are grouped within a class of medications called biologic response modifiers, or biologics. By working on the immune system, biologics block proteins that contribute to the disease process. Tumor necrosis factor (TNF) is a substance made by your body's immune system. People with inflammatory diseases such as rheumatoid arthritis (RA), plaque psoriasis (PsO), psoriatic arthritis (PsA), juvenile idiopathic arthritis (pJIA), and ankylosing spondylitis (AS) have excess TNF in their bodies. Enbrel and its biosimilars reduce levels of the active form of TNF. By limiting TNF $\alpha$ , Enbrel and its biosimilars have demonstrated efficacy in managing chronic inflammatory diseases (1).

### Regulatory Status

FDA-approved indication: Enbrel and its biosimilars are tumor necrosis factor (TNF) blockers indicated for the treatment of: (2-4)

Rheumatoid Arthritis (RA) - Enbrel and its biosimilars are indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis (RA). Enbrel and its biosimilars can be initiated in combination with methotrexate (MTX) or used alone.

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Polyarticular Juvenile Idiopathic Arthritis (pJIA) - Enbrel and its biosimilars are indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) in patients aged 2 years or older.

Psoriatic Arthritis (PsA) – Enbrel and its biosimilars are indicated for reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (PsA). Enbrel and its biosimilars can be used in combination with methotrexate (MTX) in patients who do not respond adequately to MTX alone.

Ankylosing Spondylitis (AS) – Enbrel and its biosimilars are indicated for reducing signs and symptoms in patients with active ankylosing spondylitis (AS).

Plaque Psoriasis (PsO) – Enbrel and its biosimilars are indicated for the treatment of patients 4 years or older with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy.

Enbrel and its biosimilars carry boxed warnings regarding serious infections and malignancies. Because Enbrel and its biosimilars suppress the immune system, patients are at a greater risk for getting serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. Lymphoma and other malignancies have been reported in children and adolescent patients treated with TNF blockers (2-4).

Patients should be screened for latent tuberculosis infection. Patients at risk for hepatitis B virus (HBV) infection should be evaluated for evidence of prior HBV infection. Hepatitis B virus carriers should be monitored for reactivation during and several months after therapy. Enbrel and its biosimilars should not be used in combination with other biologic agents. Enbrel and its biosimilars should not be initiated in patients with an active infection. Enbrel and its biosimilars should be discontinued if a patient develops a serious infection or sepsis during treatment (2-4).

Pancytopenia, aplastic anemia, lupus-like syndrome, anaphylaxis reactions, and congestive heart failure (new onset or worsening) may develop during Enbrel or its biosimilars therapy and therapy should be discontinued (2-4).

Use of Enbrel or its biosimilars with anakinra, abatacept, or cyclophosphamide is not recommended as the use may increase the risk of serious adverse events, including infections (2-4).

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## Off-label use:

There is sufficient medical literature to support the use of Enbrel or its biosimilars in adolescents for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) (3-14).

A study evaluating Enbrel in 3 subtypes of childhood arthritis (CLIPPER), has demonstrated efficacy of Enbrel among 122 patients with extended oligoarticular juvenile idiopathic arthritis (eoJIA), enthesitis-related arthritis (ERA), or psoriatic arthritis (PsA). The 12-week data analysis demonstrated that Enbrel was effective and well-tolerated in this combined group of patients (6).

Paller, et al. studied the same medication in children and found that Enbrel is both safe and effective to treat severe pediatric psoriasis. This was initially reported in the New England Journal of Medicine with follow-up in other journals (7-10).

## **Related policies**

Cimzia, Humira, Infliximab, Simponi

## **Policy**

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Enbrel and its biosimilars may be considered **medically necessary** in patients 2 years of age and older with moderately to severely active Polyarticular Juvenile Idiopathic Arthritis (JIA); in patients 4 years of age and older with chronic moderate to severe Plaque Psoriasis (PsO) who are candidates for systemic therapy or phototherapy; in patients 12 years of age and older with moderately to severely active Rheumatoid Arthritis (RA), Active Psoriatic Arthritis (PsA), or Active Ankylosing Spondylitis (AS); and if the conditions indicated below are met.

Enbrel and its biosimilars may be considered **investigational** in patients with all other indications.

## **Prior-Approval Requirements**

### **Diagnoses**

Patient must have **ONE** of the following:

**Age** 2 years of age or older

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1. Moderately to severely active Polyarticular Juvenile Idiopathic Arthritis (JIA)
  - a. Inadequate response, intolerance, or contraindication to a 3-month trial of at least **ONE** conventional disease-modifying antirheumatic drugs (DMARDs) (see Appendix 1)
  - b. Prescriber will be dosing the patient within the FDA labeled maintenance dose of the following:
    - i. Age 18 and older: 50 mg once a week
    - ii. Age 2 – 17 and weight  $\geq 63$ kg: 50 mg once a week
    - iii. Age 2 – 17 and weight  $< 63$ kg: 0.8 mg/kg once a week

**Age** 4 years of age or older

1. Chronic moderate to severe Plaque Psoriasis (PsO)
  - a. Inadequate response, intolerance, or contraindication to either conventional systemic therapy (see Appendix 1) or phototherapy
    - i. If the patient is intolerant or contraindicated to one therapy then the patient must have an inadequate response, intolerance, or contraindication to the other treatment option
  - b. Prescriber will be dosing the patient within the FDA labeled maintenance dose of the following:
    - i. Age 18 and older: 50 mg once a week
    - ii. Age 4 – 17 and weight  $\geq 63$ kg: 50 mg once a week
    - iii. Age 4 – 17 and weight  $< 63$ kg: 0.8 mg/kg once a week

**Age** 12 years of age or older

1. Moderately to severely active Rheumatoid Arthritis (RA)
  - a. Inadequate response, intolerance, or contraindication to a 3-month trial of at least **ONE** conventional disease-modifying antirheumatic drugs (DMARDs) (see Appendix 1)
  - b. Prescriber will be dosing the patient within the FDA labeled maintenance dose of 50 mg once a week
  
2. Active Psoriatic Arthritis (PsA)

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- a. Inadequate response, intolerance or contraindication to a 3-month trial of at least **ONE** conventional DMARD (see Appendix 1)
  - b. Prescriber will be dosing the patient within the FDA labeled maintenance dose of 50 mg once a week
3. Active Ankylosing Spondylitis (AS)
- a. Inadequate response, intolerance, or contraindication to **TWO** non-steroidal anti-inflammatory drugs (NSAIDs)
  - b. Prescriber will be dosing the patient within the FDA labeled maintenance dose of 50 mg once a week

**AND ALL** of the following:

1. Result for latent TB infection is negative **OR** result was positive for latent TB and patient completed treatment (or is receiving treatment) for latent TB
2. Patient is not at risk for HBV infection **OR** patient is at risk for HBV infection and HBV infection has been ruled out or treatment for HBV infection has been initiated.
3. Absence of active infection (including tuberculosis and hepatitis B virus (HBV))
4. **NOT** to be used in combination with any other biologic DMARD or targeted synthetic DMARD (see Appendix 1)
5. **NOT** given concurrently with live vaccines

## Prior – Approval *Renewal* Requirements

### Diagnoses

Patient must have **ONE** of the following:

**Age** 2 years of age or older

1. Polyarticular Juvenile Idiopathic Arthritis (JIA)
  - a. Prescriber will be dosing the patient within the FDA labeled maintenance dose of the following:
    - i. Age 18 and older: 50 mg once a week
    - ii. Age 2 – 17 and weight  $\geq 63$ kg: 50 mg once a week
    - iii. Age 2 – 17 and weight  $< 63$ kg: 0.8 mg/kg once a week

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**Age** 4 years of age or older

1. Plaque Psoriasis (PsO)
  - a. Prescriber will be dosing the patient within the FDA labeled maintenance dose of the following:
    - i. Age 18 and older: 50 mg once a week
    - ii. Age 4 – 17 and weight  $\geq 63$ kg: 50 mg once a week
    - iii. Age 4 – 17 and weight  $< 63$ kg: 0.8 mg/kg once a week

**Age** 12 years of age or older

1. Rheumatoid Arthritis (RA)
  - a. Prescriber will be dosing the patient within the FDA labeled maintenance dose of 50 mg once a week
2. Psoriatic Arthritis (PsA)
  - a. Prescriber will be dosing the patient within the FDA labeled maintenance dose of 50 mg once a week
3. Ankylosing Spondylitis (AS)
  - a. Prescriber will be dosing the patient within the FDA labeled maintenance dose of 50 mg once a week

**AND ALL** of the following:

1. Condition has improved or stabilized with Enbrel or biosimilar
2. Absence of active infection (including tuberculosis and hepatitis B virus (HBV))
3. **NOT** to be used in combination with any other biologic DMARD or targeted synthetic DMARD (see Appendix 1)
4. **NOT** given concurrently with live vaccines

## Policy Guidelines

### Pre - PA Allowance

None

### Prior - Approval Limits

Quantity

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| Diagnosis                                   | Strength   | Quantity   |
|---|------------|--|
| Rheumatoid Arthritis                        | 50mg       | 12 units per 84 days   |
| Psoriatic Arthritis                         |            |  |
| Ankylosing Spondylitis                      |            |  |
| Plaque Psoriasis, Age 18+                   | 25mg, 50mg | 64 units per 365 days<br>(50 mg twice weekly for 3 months, then 50 mg once a week) |
| Plaque Psoriasis, Age 4-17                  | 25mg, 50mg | 12 units per 84 days   |
| Polyarticular Juvenile Idiopathic Arthritis |            |  |

**Duration** 12 months

## Prior – Approval *Renewal* Limits

### Quantity

| Diagnosis                                   | Strength   | Quantity             |
|---|------------|----------------------|
| Rheumatoid Arthritis                        | 50mg       | 12 units per 84 days |
| Psoriatic Arthritis                         |            |                      |
| Ankylosing Spondylitis                      |            |                      |
| Plaque Psoriasis, Age 18+                   | 25mg, 50mg | 12 units per 84 days |
| Plaque Psoriasis, Age 4-17                  |            |                      |
| Polyarticular Juvenile Idiopathic Arthritis |            |                      |

**Duration** 18 months

## Rationale

### Summary

Enbrel (etanercept) and its biosimilars are tumor necrosis factor (TNF) blockers indicated for the treatment of polyarticular juvenile idiopathic arthritis (JIA), moderately to severely active rheumatoid arthritis (RA), active psoriatic arthritis (PsA), active ankylosing spondylitis (AS), chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy; with a negative test for latent TB infection or is receiving treatment or has completed treatment for latent TB, not at risk for HBV infection or HBV infection has been ruled out or treatment for HBV has been initiated, absent of active infection, and not taken in combination with another biologic agent (1-4).

Prior approval is required to ensure the safe, clinically appropriate and cost-effective use of Enbrel and its biosimilars while maintaining optimal therapeutic outcomes.

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8. Long-term etanercept in pediatric patients with plaque psoriasis. Paller AS, Siegfried EC, Eichenfield LF, Pariser D, Langley RG, Creamer K, Kricorian G. *J Am Acad Dermatol*. 2010 Nov;63(5):762-8. doi: 10.1016/j.jaad.2010.04.004. Epub 2010 Jun 3.
9. Patient-reported outcomes in pediatric patients with psoriasis undergoing etanercept treatment: 12-week results from a phase III randomized controlled trial. Langley RG, Paller AS, Hebert AA, Creamer K, Weng HH, Jahreis A, Globe D, Patel V, Orlow SJ. *J Am Acad Dermatol*. 2011 Jan;64(1):64-70. doi: 10.1016/j.jaad.2010.02.060. Epub 2010 Jul 8.
10. Luu M1, Cordoro KM. The evolving role of biologics in the treatment of pediatric psoriasis. *Skin Therapy Lett*. 2013 Feb;18(2):1-4.

## Policy History

| Date           | Action  |
|----------------|---|
| October 2013   | Addition to PA  |
| December 2013  | Annual editorial review by the PMPC   |
| September 2014 | Age limit lowered to 12 and older for RA, PsA, AS and PsO and renewal limit to 18 months  |
| June 2015      | Annual review and reference update  |
| September 2016 | Annual editorial review<br>Addition of not to be used in combination with any other biologic DMARD or targeted synthetic DMARD<br>Addition of not given concurrently with live vaccines per SME<br>Policy number change from 5.18.07 to 5.70.27 |
| November 2016  | Addition of Erelzi (biosimilar) to criteria and change to 4 years of age and older for PsO  |



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| December 2016  | Annual editorial review  |
| March 2017     | Annual review  |
| June 2017      | Annual review  |
| December 2017  | Annual review  |
| March 2018     | Annual editorial review and reference update<br>Addition of Appendix 1- List of DMARDs   |
| June 2018      | Annual editorial review<br>Addition of Appendix 2 - Examples of Contraindications to Methotrexate<br>Addition of additional requirements to initiation criteria<br>For diagnoses of RA and pJIA: inadequate treatment response, intolerance, or contraindication to at least ONE conventional disease-modifying antirheumatic drugs (DMARDs)<br>For diagnosis of AS: inadequate response, intolerance, or contraindication to at least 2 NSAIDs<br>For diagnosis of PsA: inadequate response, intolerance or contraindication to a 3-month trial of at least ONE conventional DMARD<br>For diagnosis of PsO: if the patient is intolerant or contraindicated to either therapy then the other treatment option needs to be tried |
| September 2018 | Annual editorial review and reference update   |
| March 2019     | Annual review  |
| May 2019       | Addition of the biosimilar Eticovo   |
| June 2019      | Annual review  |
| September 2019 | Annual review and reference update   |
| December 2019  | Annual review  |
| March 2020     | Annual review and reference update   |
| September 2020 | Annual review  |
| December 2020  | Annual editorial review and reference update. Added requirements to dose within the FDA labeled maintenance dosing. Added PA quantity limits.  |
| March 2021     | Annual editorial review. Appendix 1 updated.   |

## Keywords

**This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 12, 2021 and is effective on April 1, 2021.**

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### Appendix 1 - List of DMARDs

#### Conventional disease-modifying antirheumatic drugs (DMARDs)

| Generic Name       | Brand Name                  |
|--------------------|-----------------------------|
| azathioprine       | Azasan, Imuran              |
| cyclophosphamide   | Cytoxan                     |
| cyclosporine       | Neoral, Gengraf, Sandimmune |
| hydroxychloroquine | Plaquenil                   |
| leflunomide        | Arava                       |
| methotrexate       | Rheumatrex, Trexall         |
| mycophenolate      | Cellcept                    |
| sulfasalazine      | Azulfidine, Sulfazine       |

#### Biological disease-modifying antirheumatic drugs (DMARDs)

| Generic Name       | Brand Name                          |
|--------------------|-------------------------------------|
| abatacept          | Orencia                             |
| adalimumab         | Humira                              |
| anakinra           | Kineret                             |
| brodalumab         | Siliq                               |
| certolizumab       | Cimzia                              |
| etanercept         | Enbrel                              |
| golimumab          | Simponi/Simponi Aria                |
| guselkumab         | Tremfya                             |
| infliximab         | Remicade/Avsola/Inflectra/Renflexis |
| ixekizumab         | Taltz                               |
| risankizumab-rzaa  | Skyrizi                             |
| rituximab          | Rituxan/Riabni/Ruxience/Truxima     |
| sarilumab          | Kevzara                             |
| secukinumab        | Cosentyx                            |
| tildrakizumab-asmn | Ilumya                              |
| tocilizumab        | Actemra                             |
| ustekinumab        | Stelara                             |
| vedolizumab        | Entyvio                             |

#### Targeted synthetic disease-modifying antirheumatic drugs (DMARDs)

| Generic Name | Brand Name |
|--------------|------------|
| apremilast   | Otezla     |
| baricitinib  | Olumiant   |
| tofacitinib  | Xeljanz/XR |
| upadactinib  | Rinvoq     |

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## Appendix 2 – Examples of Contraindications to Methotrexate

| <b>Contraindications to Methotrexate</b>                                     |
|--|
| 1. Alcoholism, alcoholic liver disease or other chronic liver disease        |
| 2. Breastfeeding   |
| 3. Blood dyscrasias (e.g., thrombocytopenia, leukopenia, significant anemia) |
| 4. Elevated liver transaminases  |
| 5. History of intolerance or adverse event                                   |
| 6. Hypersensitivity  |
| 7. Interstitial pneumonitis or clinically significant pulmonary fibrosis     |
| 8. Myelodysplasia  |
| 9. Pregnancy or planning pregnancy (male or female)                          |
| 10. Renal impairment   |
| 11. Significant drug interaction   |