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Section:	Prescription Drugs	**Effective Date:**	January 1, 2023
Subsection:	Analgesics and Anesthetics	**Original Policy Date:**	October 1, 2013
Subject:	Enbrel	**Page:**	1 of 12

Last Review Date: December 2, 2022

Enbrel

Description

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

*These medications are included in this policy but are not available on 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), polyarticular 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 TNFα, Enbrel and its biosimilars have demonstrated efficacy in managing chronic inflammatory diseases (1).

Regulatory Status
FDA-approved indications: 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.

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).

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) (3-10). Enbrel 25mg twice weekly dosing is supported by literature for patients who prefer that dosing method (11).

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 (pJIA); 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 apondylitis (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

1. Moderately to severely active Polyarticular Juvenile Idiopathic Arthritis (pJIA)
    a. Inadequate treatment 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 weekly
        ii. Age 2 – 17 and weight ≥63kg: 50 mg weekly
        iii. Age 2 – 17 and weight<63kg: 0.8 mg/kg weekly

Age 4 years of age or older

1. Chronic moderate to severe Plaque Psoriasis (PsO)
    a. Inadequate treatment 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 treatment 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 weekly
        ii. Age 4 – 17 and weight ≥63kg: 50 mg weekly
        iii. Age 4 – 17 and weight <63kg: 0.8 mg/kg weekly

Age 12 years of age or older

1. Moderately to severely active Rheumatoid Arthritis (RA)
    a. Inadequate treatment 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 weekly

2. Active Psoriatic Arthritis (PsA)
    a. Inadequate treatment 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 weekly

3. Active Ankylosing Spondylitis (AS)
    a. Inadequate treatment 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 weekly

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 (pJIA)
    a. Prescriber will be dosing the patient within the FDA labeled maintenance dose of the following:
        i. Age 18 and older: 50 mg weekly
        ii. Age 2 – 17 and weight ≥63kg: 50 mg weekly

iii. Age 2 – 17 and weight <63kg: 0.8 mg/kg weekly

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 weekly
        ii. Age 4 – 17 and weight ≥63kg: 50 mg weekly
        iii. Age 4 – 17 and weight <63kg: 0.8 mg/kg weekly

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 weekly
2. Psoriatic Arthritis (PsA)
    a. Prescriber will be dosing the patient within the FDA labeled maintenance dose of 50 mg weekly
3. Ankylosing Spondylitis (AS)
    a. Prescriber will be dosing the patient within the FDA labeled maintenance dose of 50 mg weekly

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

Diagnosis	Strength	Quantity
Rheumatoid Arthritis Psoriatic Arthritis Ankylosing Spondylitis	25mg, 50mg	12 x 50mg units per 84 days **OR** 24 x 25mg units per 84 days
Plaque Psoriasis, Age 18+	25mg, 50mg	*(50 mg twice weekly for 3 months, then 50 mg once a week)* 64 x 50mg units per 365 days **OR** 128 x 25mg units per 365 days
Plaque Psoriasis, Age 4-17 Polyarticular Juvenile Idiopathic Arthritis	25mg, 50mg	12 x 50mg units per 84 days **OR** 24 x 25mg units per 84 days

Duration 12 months

Prior – Approval *Renewal* Limits

Quantity

Diagnosis	Strength	Quantity
Rheumatoid Arthritis Psoriatic Arthritis Ankylosing Spondylitis Plaque Psoriasis, Age 18+	25mg, 50mg	12 x 50mg units per 84 days **OR** 24 x 25mg units per 84 days
Plaque Psoriasis, Age 4-17 Polyarticular Juvenile Idiopathic Arthritis	25mg, 50mg	12 x 50mg units per 84 days **OR** 24 x 25mg units per 84 days

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 (pJIA), 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.

References

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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 Addition of not to be used in combination with any other biologic DMARD or targeted synthetic DMARD Addition of not given concurrently with live vaccines per SME 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
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 Addition of Appendix 1- List of DMARDs
June 2018	Annual editorial review Addition of Appendix 2 - Examples of Contraindications to Methotrexate Addition of additional requirements to initiation criteria For diagnoses of RA and pJIA: inadequate treatment response, intolerance, or contraindication to at least ONE conventional disease-modifying antirheumatic drugs (DMARDs) For diagnosis of AS: inadequate response, intolerance, or contraindication to at least 2 NSAIDs For diagnosis of PsA: inadequate response, intolerance or contraindication to a 3-month trial of at least ONE conventional DMARD 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.
May 2021	Addition of 25mg strength to the quantity chart. Changed dosing requirement from 50mg once a week to 50mg weekly to allow members to dose 25mg twice weekly if desired.
September 2021	Annual review and reference update
March 2022	Annual editorial review and reference update
September 2022	Annual review and reference update
December 2022	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 2, 2022 and is effective on January 1, 2023.

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
spesolimab-sbzo	Spevigo
tildrakizumab-asmn	Ilumya
tocilizumab	Actemra
ustekinumab	Stelara
vedolizumab	Entyvio

Targeted synthetic disease-modifying antirheumatic drugs (DMARDs)

Generic Name	Brand Name
apremilast	Otezla
baricitinib	Olumiant

deucravacitinib	Sotyktu
tofacitinib	Xeljanz/XR
upadactinib	Rinvoq

Appendix 2 – Examples of Contraindications to Methotrexate

Contraindications to Methotrexate
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