09-J0000-38

Original Effective Date: 04/15/01

Reviewed: 11/09/22

Revised: 01/01/23

Subject: Etanercept (Enbrel®) Injection

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DESCRIPTION:

Etanercept (Enbrel) is one of five commercially available tumor necrosis factor (TNF)-alpha inhibitors, not counting biosimilars as separate products, available in the United States, and was first approved in November 1998. Tumor necrosis factor, a proinflammatory cytokine, initiates the body's defense response to local injury by stimulating the production of inflammatory mediators and signaling immune cells. TNF may augment host defense mechanisms when in low concentration, but large amounts of TNF can lead to excessive inflammation and tissue deterioration. In rheumatoid arthritis, activated T-cells migrate into the synovial lining of the joint where TNF is released and joint destruction begins. The intestinal mucosa from patients with Crohn's disease or ulcerative colitis has been associated with high levels of TNF as compared to healthy individuals; a similar elevation in TNF has been demonstrated in patients with psoriasis.

Etanercept is approved by the US Food and Drug Administration (FDA) for the treatment of the following conditions: ankylosing spondylitis (2003), polyarticular juvenile rheumatoid arthritis (1999), psoriatic arthritis (2002), chronic plaque psoriasis (2004), and rheumatoid arthritis (1998). In November 2016 the chronic moderate to severe plaque psoriasis indication was expanded to include pediatric patients as young as 4 years of age. At the time of approval, etancercept was the only FDA-approved *systemic* therapy for pediatric psoriasis. In August 2016 the first biosimilar to etanercept, etanercept-szzs (Erelzi), was FDA approved. A second biosimilar, etanercept-ykro (Eticovo), was approved by the FDA in April 2019. Biosimilar launches are not expected until 2029. The TNF-alpha inhibitors as a class are considered to have similar efficacy and safety for the majority of indications. Similar to other TNF-alpha inhibitors, the package labeling contains a Boxed Warning regarding potential increased risk of serious infections (e.g., tuberculosis) and certain malignancies during therapy.

RHEUMATOID DISORDERS

Ankylosing spondylitis (AS)

Ankylosing spondylitis (AS) is a form of chronic inflammatory arthritis characterized by sacroiliitis, enthesitis, and a marked propensity for sacroiliac joint and spinal fusion. AS is distinguished by universal involvement with sacroiliac joint inflammation or fusion and more prevalent spinal ankylosis. Goals of treatment for AS are to reduce symptoms, maintain spinal flexibility and normal posture, reduce functional limitations, maintain work ability, and decrease disease complications. The mainstay of treatment has been NSAIDs and exercise, with the additional use of DMARDs in patients with peripheral arthritis. The American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) recommend the following pharmacological treatment for AS:

- Stable AS: First line therapy with on demand NSAIDs; there is also a conditional recommendation for continuation of TNF inhibitor as monotherapy
- Active AS:
    - First line therapy with continuous NSAIDs and physical therapy
    - TNF inhibitor recommended for patients with active AS despite an adequate trial with NSAIDs
        - Lack of response (or intolerance) to at least 2 different NSAIDs over 1 month or incomplete response to at least 2 different NSAIDs over 2 months would be an adequate NSAID trial to judge response
    - Recommendations for nonresponse to TNF therapy (all conditional):
        - Primary nonresponse: switch to secukinumab or ixekizumab over another TNF
        - Secondary nonresponse: switch to another TNF over a non-TNF biologic
        - Recommend against addition of sulfasalazine or MTX
        - Recommend against switching to a biosimilar of the failed TNF
    - TNF-inhibitors are conditionally recommended over secukinumab or ixekizumab
    - Secukinumab or ixekizumab are conditionally recommended over DMARDs in patients that have failed NSAIDs and have contraindications to TNF-inhibitors
    - DMARDs (i.e., methotrexate [MTX], sulfasalazine, leflunomide, pamidronate, thalidomide, apremilast) are only conditionally recommended in patients that have failed NSAIDs and have contraindications to TNF-inhibitors
    - Methotrexate is not recommended as add on therapy to TNF inhibitors in stable and active AS
    - If patient has concomitant inflammatory bowel disease (IBD) or recurrent uveitis, TNF-inhibitors are recommended over other biologics
    - Glucocorticoids are not recommended

Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is the most common inflammatory autoimmune arthritis in adults. The main goal of therapy is to achieve remission, but additional goals include decrease inflammation, relieve symptoms, prevent joint and organ damage, improve physical function/overall well-being, and reduce long term complications. The choice of therapy depends on several factors, including the severity of

disease activity when therapy is initiated and the response of the patient to prior therapeutic interventions.

American College of Rheumatology (ACR) guidelines list the following guiding principles in the treatment of RA:

- RA requires early evaluation, diagnosis, and management
- Treatment decisions should follow a shared decision-making process
- Treatment decisions should be reevaluated within a minimum of 3 months based on efficacy and tolerability of the DMARD(s) chosen
- Recommendations are limited to DMARDs approved by the US FDA for treatment of RA:
    - csDMARDs: hydroxychloroquine, sulfasalazine, methotrexate (MTX), leflunomide
    - bDMARDs: TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T cell costimulatory inhibitor (abatacept), IL-6 receptor inhibitors (tocilizumab, sarilumab), anti-CD20 antibody (rituximab)
    - tsDMARDs: JAK inhibitors (tofacitinib, baricitinib, upadacitinib)
- Triple therapy refers to hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide
- Biosimilars are considered equivalent to FDA-approved originator bDMARDs
- Recommendations referring to bDMARDs exclude rituximab unless patients have had an inadequate response to TNF inhibitors (in order to be consistent with FDA approval) or have a history of lymphoproliferative disorder for which rituximab is an approved therapy
- Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modifications of treatment to minimize disease activity with the goal of reaching a predefined target (low disease activity or remission)

ACR guidelines are broken down by previous treatment and disease activity:

- DMARD-naïve patients with moderate-to-high disease activity initial treatment:
    - MTX monotherapy is strongly recommended over hydroxychloroquine, sulfasalazine, bDMARDs monotherapy, tsDMARD monotherapy, or combination of MTX plus a non-TNF bDMARD or tsDMARD
    - MTX monotherapy is conditionally recommended over leflunomide, dual or triple csDMARD therapy, or combination MTX plus a TNF inhibitor
- DMARD-naïve patients with low disease activity initial treatment
    - Hydroxychloroquine is conditionally recommended over other csDMARDs
    - Sulfasalazine is conditionally recommended over MTX
    - MTX is conditionally recommended over leflunomide
- Initial therapy in csDMARD-treated patients, but MTX naïve, with moderate-to high disease activity:
    - MTX monotherapy is conditionally recommended over combination MTX and a bDMARD or tsDMARD

- Treatment Modifications in patients treated with DMARDs who are not at target:
    - Addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy for patients taking maximally tolerated doses of MTX who are not at target
    - Switching to a bDMARD or tsDMARD of a different class is conditionally recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target

Early use of DMARD, particularly MTX, is recommended as soon as possible following diagnosis of RA. Dosing of MTX for RA is once weekly dosing with starting doses at 7.5 mg or 15 mg once weekly. MTX dose is increased as tolerated and as needed to control symptoms and signs of RA disease. The usual target dose is at least 15 mg weekly and the usual maximum dose is 25 mg weekly. ACR defines optimal dosing for RA treatments as 1) dosing to achieve a therapeutic target derived from mutual patient-clinician consideration of patient priorities and 2) given for at least 3 months before therapy escalation or switching. For patients who are unable to take MTX, hydroxychloroquine, sulfasalazine, or leflunomide are other DMARD options. In patients resistant to initial MTX treatment, combination DMARD (e.g., MTX plus sulfasalazine or hydroxychloroquine or a TNF-inhibitor) is recommended.

For patients who are resistant to MTX after 3 months of treatment at optimal doses (usually 25 mg per week), it is recommended to either use DMARD triple therapy with MTX plus sulfasalazine and hydroxychloroquine or combination of MTX with TNF inhibitor. Triple therapy regimen has been found to be of similar clinical efficacy to MTX with biologics in several randomized trials, including in patients with high level of disease activity or with adverse prognostic features. The use of triple therapy has been shown to be highly cost-effective compared with combining a biologic with MTX, providing comparable or near comparable clinical benefit. The use of biologic with MTX combination is preferred when patients have high disease activity and clinical benefit from a more rapid response is needed and when patients who do not achieve satisfactory response within 3 months with non-biologic triple therapy following an inadequate response to MTX therapy.

Polyarticular Juvenile Idiopathic Arthritis (PJIA)

Juvenile idiopathic arthritis (JIA) is arthritis that begins before the 16th birthday and persists for at least 6 weeks with other known conditions excluded. Polyarticular juvenile idiopathic arthritis (PJIA) is a subset of JIA. The ACR defines PJIA as arthritis in more than 4 joints during their disease course and excludes systemic JIA. Treatment goals are aimed at achieving clinically inactive disease and to prevent long-term morbidities, including growth disturbances, joint contractures and destruction, functional limitations, and blindness or visual impairment from chronic uveitis.

The ACR 2019 guidelines recommend the following treatment approach for PJIA:

- NSAIDs are conditionally recommended as adjunct therapy
- DMARD therapy:
    - Methotrexate (MTX) is conditionally recommended over leflunomide and sulfasalazine
    - Subcutaneous MTX is conditionally recommended over oral MTX
- Intraarticular glucocorticoids are conditionally recommended as adjunct therapy and conditionally recommended for bridging only in patients with moderate to high disease activity

- Strongly recommend against chronic low-dose glucocorticoid use, irrespective of disease activity and/or risk factors
- Strongly recommend combination use of a DMARD and infliximab
- Initial therapy for all patients:
    - DMARD is strongly recommended over NSAID monotherapy
    - MTX monotherapy is conditionally recommended over triple DMARD therapy
    - DMARD is conditionally recommended over a biologic
    - Initial biologic therapy may be considered for patients with risk factors and involvement of high-risk joints (e.g., cervical spine, wrist, hip), high disease activity, and/or those judged by their physician to be at high risk of disabling joint damage
- Subsequent therapy:
    - Low disease activity:
        - Escalating therapy (e.g., intraarticular glucocorticoid injections, optimization of DMARD dose, trial of MTX if not already done, and adding or changing biologic agent)
    - Moderate to high disease activity:
        - Add a biologic to original DMARD over changing to a second DMARD or changing to triple DMARD therapy
        - Switch to a non-TNF biologic if currently treated with first TNF ± DMARD over switching to another TNF (unless the patient had good initial response to first TNF)
        - TNF, abatacept, or tocilizumab (depending on prior biologics received) over rituximab after trial of second biologic

Psoriatic Arthritis (PsA)

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease associated with psoriasis, most commonly presenting with peripheral arthritis, dactylitis, enthesitis, and spondylitis. Treatment involves the use of a variety of interventions, including many agents used for the treatment of other inflammatory arthritis, particularly spondyloarthritis and RA, and other management strategies of the cutaneous manifestations of psoriasis.

The American Academy of Dermatology (AAD) recommends initiating MTX in most patients with moderate to severe PsA. After 12 to 16 weeks of MTX therapy with appropriate dose escalation, the AAD recommends adding or switching to a TNF inhibitor if there is minimal improvement on MTX monotherapy.

The American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF) guidelines for PsA recommend a treat-to-target approach in therapy, regardless of disease activity, and the following:

- Active PsA is defined as symptoms at an unacceptably bothersome level as reported by the patient and health care provider to be due to PsA based on the presence of one of the following:
    - Actively inflamed joints
    - Dactylitis

- Enthesitis
- Axial disease
- Active skin and/or nail involvement
- Extraarticular manifestations such as uveitis or inflammatory bowel disease

- Disease severity includes level of disease activity at a given time point and the presence/absence of poor prognostic factors and long-term damage
- Severe PsA disease includes the presence of 1 or more of the following:
  - Erosive disease
  - Elevated markers of inflammation (ESR, CRP) attributable to PsA
  - Long-term damage that interferes with function (i.e., joint deformities)
  - Highly active disease that causes a major impairment in quality of life
  - Active PsA at many sites including dactylitis, enthesitis
  - Function limiting PsA at a few sites
  - Rapidly progressive disease
- Symptomatic treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, local glucocorticoid injections
- Treatment recommendations for active disease:
  - Treatment naïve patients first line options include oral small molecules (OSM), TNF biologics, IL-17 inhibitor, and IL-12/23 inhibitor
    - OSM (i.e., methotrexate [MTX], sulfasalazine, cyclosporine, leflunomide, apremilast) should be considered if the patient does not have severe PsA, does not have severe psoriasis, prefers oral therapy, has concern over starting a biologic, or has contraindications to TNF inhibitor
    - Biologics (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) are recommended as a first line option in patients with severe PsA and/or severe psoriasis
  - Previous treatment with OSM and continued active disease:
    - Switch to a different OSM (except apremilast) in patients without severe PsA or severe PS, contraindications to TNF biologics, prefers oral therapy OR add on apremilast to current OSM therapy
    - May add another OSM (except apremilast) to current OSM therapy for patients that have exhibited partial response to current OSM in patients without severe PsA or severe PS, contraindications to TNF biologics, or prefers oral therapy
    - Biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) monotherapy
  - Previous treatment with a biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) and continued active disease:
    - Switch to another biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor, abatacept, or tofacitinib) monotherapy or add MTX to the current TNF biologic

DERMATOLOGICAL DISORDERS

Psoriasis (PS)

Psoriasis (PS) is a chronic inflammatory skin condition that is often associated with systemic manifestations, especially arthritis. Diagnosis is usually clinical, based on the presence of typical erythematous scaly patches, papules, and plaques that are often pruritic and sometimes painful. Treatment goals for psoriasis include improvement of skin, nail, and joint lesions plus enhanced quality of life.

The American Academy of Family Physicians (AAFP) categorizes psoriasis severity into mild to moderate (less than 5% of body surface area [BSA]) and moderate to severe (5% or more of BSA). The AAFP psoriasis treatment guidelines recommend basing treatment on disease severity:

- Mild to moderate (less than 5% of BSA and sparing the genitals, hands, feet, and face):
    - Candidate for intermittent therapy: topical corticosteroids, vitamin D analogs (calcipotriene and calcitriol), or tazarotene (Tazorac)
    - Candidate for continuous therapy: calcineurin inhibitors (tacrolimus and pimecrolimus)
- Severe (5% or more of BSA or involving the genitals, hands, feet, and face):
    - Less than 20% of BSA affected: vitamin D analogs (calcipotriene and calcitriol) with or without phototherapy. These agents have a slower onset of action but a longer disease-free interval than topical corticosteroids
    - 20% or more of BSA affected: systemic therapy with MTX, cyclosporine, acitretin, or biologics. Biologics are recommended for those with concomitant PsA
- Less commonly used topical therapies include non-medicated moisturizers, salicylic acid, coal tar, and anthralin

The American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) categorize psoriasis severity as limited or mild (less than 3% of BSA), moderate (3% to 10% of BSA), or severe (great than 10% of BSA). The AAD/NPF guidelines also note that psoriasis can be considered severe irrespective of BSA when is occurs in select locations (e.g., hands, feet, scalp, face, or genital area) or when it causes intractable pruritus. The AAD psoriasis treatment guidelines recommend the following:

- Limited disease (less than 5% of BSA):
    - Topical corticosteroids are first line as either monotherapy or in conjunction with non-steroidal topical agents
    - Vitamin D analogs, calcipotriene, calcipotriol, and calcitriol, are other first line agents and are often used in combination with topical corticosteroids
    - Tazarotene is a corticosteroid sparing agent and can be used in combination with topical corticosteroids to produce a synergistic effect and longer durations of treatment benefit and remission
    - Phototherapy is another first line option for limited disease, and allows for selective targeting of localized lesions and resistant areas such as the scalp and skin folds, leaving surrounding, non-lesional skin unaffected

- Calcineurin inhibitors (tacrolimus and pimecrolimus) may also be considered first line for intertriginous, inverse, face, and genital psoriasis
- Systemic agents are considered second line and only for short term use

- Moderate to severe disease without PsA (more than 5% of BSA or psoriasis in vulnerable areas [e.g., face, genitals, hands, and feet] that adversely affects quality of life):
  - UV-therapy is considered first line as monotherapy or in combination with acitretin or MTX
  - If UV-therapy is unavailable, first line therapies include MTX, cyclosporine, acitretin, and biologics
  - Second line systemic agents include leflunomide, sulfasalazine, and tacrolimus
- Biologics are routinely used when one or more traditional systemic agents fail to produce adequate response, but are considered first line in patients with moderate to severe psoriasis with concomitant severe PsA

The National Psoriasis Foundation (NPF) medical board recommend a treat-to-target approach to therapy for psoriasis that include the following:

- The preferred assessment instrument for determining disease severity is BSA
- Target response after treatment initiation should be BSA ≤1% after 3 months
- Acceptable response is either a BSA ≤3% or a BSA improvement ≥75% from baseline at 3 months after treatment initiation

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

NOTE: The self-administered products with prerequisites for certain indications are as follows:

Table 1

Disease State	Step 1		Step 2 (Directed to ONE step 1 agent)	Step 3a (Directed to TWO step 1 agents)	Step 3b (Directed to TWO agents from step 1 and/or step 2)	Step 3c (Directed to THREE step 1 agents)
	Step 1a	Step 1b (Directed to ONE TNF inhibitor) NOTE: Please see Step 1a for preferred TNF inhibitors				
Rheumatoid Disorders						

Ankylosing Spondylitis (AS)	SQ: Cosentyx, **Enbrel**, Humira	Oral: Rinvoq, Xeljanz, Xeljanz XR	N/A	SQ: Cimzia, Simponi, Taltz	N/A	N/A
Nonradiographic Axial Spondyloarthritis (nr-axSpA)	SQ: Cimzia, Cosentyx	Oral: Rinvoq	N/A	SQ: Taltz	N/A	N/A
Polyarticular Juvenile Idiopathic Arthritis (PJIA)	SQ: **Enbrel**, Humira	Oral: Xeljanz	SQ: Actemra (Humira is required Step 1 agent)	N/A	SQ: Orencia	N/A
Psoriatic Arthritis (PsA)	SQ: Cosentyx, **Enbrel**, Humira, Skyrizi, Stelara, Tremfya Oral: Otezla	Oral: Rinvoq, Xeljanz, Xeljanz XR	N/A	SQ: Cimzia, Orencia, Simponi, Taltz	N/A	N/A
Rheumatoid Arthritis	SQ: **Enbrel**, Humira	Oral: Rinvoq, Xeljanz, Xeljanz XR	SQ: Actemra (Humira is required Step 1 agent)	Oral: Olumiant SQ: Cimzia, Kevzara, Kineret, Orencia, Simponi	N/A	N/A
Dermatological Disorders						
Hidradenitis Suppurativa (HS)	SQ: Humira	N/A	N/A	N/A	N/A	N/A
Psoriasis (PS)	SQ: Cosentyx, **Enbrel**, Humira, Skyrizi, Stelara, Tremfya Oral: Otezla	N/A	N/A	SQ: Cimzia, Ilumya	N/A	SQ: Siliq, Taltz Oral: Sotyktu
Inflammatory Bowel Disease						
Crohn's Disease	SQ: Humira, Skyrizi, Stelara	N/A	N/A	SQ: Cimzia (Humira is a required Step 1 agent)	N/A	N/A
Ulcerative Colitis	SQ: Humira, Stelara	Oral: Rinvoq, Xeljanz, Xeljanz XR	SQ: Simponi (Humira is required Step 1 agent)	N/A	Zeposia (Humira, Rinvoq, Stelara, OR Xeljanz/Xeljanz XR are	N/A

					required Step agents)	
Other						
Uveitis	SQ: Humira	N/A	N/A	N/A	N/A	N/A
Indications Without Prerequisite Biologic Immunomodulators						
Alopecia Areata (AA) Atopic Dermatitis Deficiency of IL-1 Receptor Antagonist (DIRA) Enthesitis Related Arthritis (ERA) Giant Cell Arteritis (GCA) Neonatal-Onset Multisystem Inflammatory Disease (NOMID) Systemic Juvenile Idiopathic Arthritis (SJIA) Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD	N/A	N/A	N/A	N/A	N/A	N/A

*Note: A trial of either or both Xeljanz products (Xeljanz and Xeljanz XR) collectively counts as **ONE** product

Initiation of etanercept (Enbrel) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "6"):

1. **ONE** of the following ("a", "b", or "c"):
    a. Information has been provided that indicates the member has been treated with etanercept (starting on samples is not approvable) within the past 90 days
    b. The prescriber states the member has been treated with etanercept (starting on samples is not approvable) within the past 90 days **AND** is at risk if therapy is changed
    c. **BOTH** of the following ('i" and "ii"):
        i. Etanercept will be used for the treatment of an indication listed in Table 2, and **ALL** of the indication-specific criteria are met
        ii. **EITHER** of the following ("I" or "II")

I. The member's age is within FDA labeling for the requested indication for etanercept

II. The prescriber has provided information in support of using etanercept for the member's age

2. The prescriber is a specialist in the area of the member's diagnosis (e.g., rheumatologist for JIA, PsA, RA; dermatologist for PS) or the prescriber has consulted with a specialist in the area of the member's diagnosis
3. Member does **NOT** have any FDA labeled contraindications to etanercept
4. Member has been tested for latent tuberculosis (TB) **AND**, if positive, the member has begun therapy for latent TB
5. Member will **NOT** be using etanercept in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (apremilast); Sotyktu (deucravacitinib); or Zeposia (ozanimod)
6. **ANY** of the following ("a", "b", or "c"):
   a. The dosage does not exceed:
      - Loading dose - 50 mg twice weekly for 3 months [for adult (≥18 years old) PS only]
      - Maintenance dose – 50 mg weekly
        - QL: 25 mg/0.5 mL single-use vial - 8 vials (4 mL)/28 days
        - QL: 25 mg multiple-dose vial kit - 8 vials/28 days
        - QL: 50 mg/mL SureClick autoinjector - 4 syringes (4 mL)/28 days
        - QL: 50 mg/mL cartridge - 4 cartridges (4 mL)/28 days
        - QL: 25 mg/0.5 mL syringe - 4 syringes (2.04) mL)/28 days
        - QL: 50 mg/mL syringe - 4 syringes (4 mL)/28 days
   b. The requested quantity (dose) is greater than program's quantity limit but does **NOT** exceed the maximum FDA labeled dose **OR** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit
   c. The requested quantity (dose) is greater that the program's quantity limit and greater than the maximum FDA labeled dose **AND** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the prescriber has provided information in support of therapy with a higher dose for the requested indication (submitted copy required; e.g., clinical trials, phase III studies, guidelines required)

Approval duration: 12 months [for adult PS only, loading dose for 3 months then maintenance dose for 9 months (12 months for total approval duration)]

Table 2

Diagnosis	Criteria
Moderately to severely active rheumatoid arthritis (RA)	**ONE** of the following: 1. The member has tried and had an inadequate response to maximally tolerated methotrexate (e.g., titrated to 25 mg weekly) for at least 3 months **OR** 2. The member has tried and had an inadequate response to another conventional agent (i.e., hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA for at least 3 months **OR** 3. The member has an intolerance or hypersensitivity to **ONE** of the following conventional agents (i.e., maximally tolerated methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** 4. The member has an FDA labeled contraindication to **ALL** of the following conventional agents (i.e., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** 5. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of RA
Active psoriatic arthritis (PsA)	**ONE** of the following: 1. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., cyclosporine, leflunomide, methotrexate, sulfasalazine) used in the treatment of PsA for at least 3 months **OR** 2. The member has an intolerance or hypersensitivity to **ONE** of the conventional agents used in the treatment of PsA **OR** 3. The member has an FDA labeled contraindication to **ALL** of the conventional agents used in the treatment of PsA **OR** 4. The member has severe active PsA (e.g., erosive disease, elevated markers of inflammation [e.g., ESR, CRP] attributable to PsA, long-term

	damage that interferes with function [i.e., joint deformities], rapidly progressive) **OR** 5. The member has concomitant severe psoriasis (PS) (e.g., greater than 10% body surface area involvement, occurring on select locations [i.e., hands, feet, scalp, face, or genitals], intractable pruritus, serious emotional consequences) **OR** 6. The member's medication history indicates use of another biologic immunomodulator agent **OR** Otezla that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PsA
Moderate to severe plaque psoriasis (PS)	**ONE** of the following: 1. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., acitretin, anthralin, calcipotriene, calcitriol, coal tar products, cyclosporine, methotrexate, pimecrolimus, PUVA [phototherapy], tacrolimus, tazarotene, topical corticosteroids) used in the treatment of PS for at least 3 months **OR** 2. The member has an intolerance or hypersensitivity to **ONE** conventional agent used in the treatment of PS **OR** 3. The member has an FDA labeled contraindication to **ALL** conventional agents used in the treatment of PS **OR** 4. The member has severe active PS (e.g., greater than 10% body surface area involvement, occurring on select locations [i.e., hands, feet, scalp, face, or genitals], intractable pruritus, serious emotional consequences) **OR** 5. The member has concomitant severe psoriatic arthritis (PsA) (e.g., erosive disease, elevated markers of inflammation [e.g., ESR, CRP] attributable to PsA, long-term damage that interferes with function [i.e., joint deformities], rapidly progressive) **OR** 6. The member's medication history indicates use of another biologic immunomodulator agent OR Otezla that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PS

Active ankylosing spondylitis (AS)	**ONE** of the following: 1. The member has tried and had an inadequate response to **TWO** different NSAIDs used in the treatment of AS for at least a 4-week total trial **OR** 2. The member has an intolerance or hypersensitivity to **TWO** different NSAIDs used in the treatment of AS **OR** 3. The member has an FDA labeled contraindication to **ALL** NSAIDs used in the treatment of AS **OR** 4. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of AS
Moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA)	**ONE** of the following: 1. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., methotrexate, leflunomide) used in the treatment of PJIA for at least 3 months **OR** 2. The member has an intolerance or hypersensitivity to **ONE** of the conventional agents used in the treatment of PJIA **OR** 3. The member has an FDA labeled contraindication to **ALL** of the conventional agents used in the treatment of PJIA **OR** 4. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PJIA
Other indications	The member has another FDA labeled indication or an indication supported in DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a

Continuation of etanercept (Enbrel) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "6"):

1. An authorization or reauthorization for etanercept has been previously approved by Florida Blue

2. Member has had clinical benefit with etanercept therapy
3. The prescriber is a specialist in the area of the member's diagnosis (e.g., rheumatologist for JIA, PsA, RA; dermatologist for PS) or the prescriber has consulted with a specialist in the area of the member's diagnosis
4. Member does **NOT** have any FDA labeled contraindications to etanercept
5. Member will **NOT** be using etanercept in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (apremilast); Sotyktu (deucravacitinib); or Zeposia (ozanimod)
6. **ANY** of the following ("a", "b", or "c"):
    a. The dosage does not exceed 50 mg weekly
        - QL: 25 mg/0.5 mL single-use vial - 8 vials (4 mL)/28 days
        - QL: 25 mg multiple-dose vial kit - 8 vials/28 days
        - QL: 50 mg/mL SureClick autoinjector - 4 syringes (4 mL)/28 days
        - QL: 50 mg/mL cartridge - 4 cartridges (4 mL)/28 days
        - QL: 25 mg/0.5 mL syringe - 4 syringes (2.04) mL)/28 days
        - QL: 50 mg/mL syringe - 4 syringes (4 mL)/28 days
    b. The requested quantity (dose) is greater than program's quantity limit but does **NOT** exceed the maximum FDA labeled dose **OR** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit
    c. The requested quantity (dose) is greater that the program's quantity limit and greater than the maximum FDA labeled dose **AND** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the prescriber has provided information in support of therapy with a higher dose for the requested indication (submitted copy required, e.g., clinical trials, phase III studies, guidelines required)

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Table 3:

FDA-approved indications and recommended dosing

Indication	Dosage
Plaque Psoriasis (adult, ≥18 years old)	• First 3 months: 50 mg twice weekly (given 3 to 4 days apart) • After 3 months: 50 mg once weekly
Plaque Psoriasis (pediatric, 4 to 17 years old)	• Less than 63 kg (138 lbs.): 0.8 mg/kg per week • 63 kg or more: 50 mg once weekly
Polyarticular Juvenile Idiopathic Arthritis (PJIA) (2 years and older)	
Ankylosing Spondylitis	50 mg once weekly
Psoriatic Arthritis (PsA)	
Rheumatoid Arthritis (RA)	

Methotrexate, glucocorticoids, NSAIDs, or analgesics may be continued during treatment with etanercept.

Dose Adjustments: dosage adjustments are not required for members with hepatic or renal impairment.

Drug Availability:

Etanercept is supplied in the following dosage forms and strengths:

- 50 mg single-use prefilled syringe
- 50 mg single-use prefilled SureClick Autoinjector
- 50 mg Enbrel Mini single-dose prefilled cartridge (used in the AutoTouch Reusable Autoinjector)
- 25 mg single-use prefilled syringe
- 25 mg multiple-use vial

Store refrigerated at 36°F to 46°F (2°C to 8°C). **DO NOT SHAKE**. Store in the original carton to protect from light or physical damage. For convenience, storage of an individual dose tray containing Enbrel multi-use vial and diluent syringe at room temperature at 68°F to 77°F (20°C to 25°C) for a maximum single period of 14 days is permissible, with protection from light, sources of heat, and humidity.

PRECAUTIONS:

Boxed Warning

- **Infections:** tuberculosis (TB), invasive fungal, and other opportunistic infections, some fatal, have occurred. Perform test for latent TB; if positive, start treatment for TB prior to starting therapy. Monitor all patients for active TB, even if initial tuberculin skin test is negative.
- **Malignancy:** lymphoma and other malignancies, some fatal have been reported in children and adolescent individuals treated with TNF blockers including etanercept.

Contraindications

- Enbrel is contraindicated in members with sepsis.

Precautions/Warnings

- **Serious Infections:** etanercept should not be initiated in members during an active infection. If an infection develops, monitor carefully, and discontinue etanercept if infection becomes serious.
- **Invasive fungal infections:** If a member develops a systemic infection while on etanercept therapy, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic
- **Anaphylaxis:** anaphylaxis or serious allergic reactions may occur.
- **Hepatitis B virus reactivation:** members who are HBV caries should be monitored during and several months after therapy. If reactivation occurs during therapy, discontinue etanercept and initiate anti-viral therapy.
- **Demyelinating disease:** exacerbation of new onset may occur
- **Cytopenia, pancytopenia:** advise members to seek immediate medical attention if symptoms develop and consider discontinuing etanercept.
- **Heart failure:** worsening or new onset heart failure may occur.
- **Lupus-like syndrome/Autoimmune hepatitis:** discontinue etanercept if either syndrome develops.
- **Drug Interactions:** avoid concomitant use with abatacept (Orencia®) and anakinra (Kineret®), due to increased risk of serious infection.
- **Live vaccines:** Avoid administration of live vaccines (e.g., varicella and MMR) in members taking etanercept.
- **Pregnancy and Lactation**
    - Etanercept is classified as pregnancy category B. Developmental toxicity studies performed in animals have revealed no evidence of harm to the fetus. Use during pregnancy should occur only if clearly needed.
    - Because many immunoglobulins are secreted in milk and the potential for serious adverse reactions exists, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

BILLING/CODING INFORMATION:

The following codes may be used to report Etanercept (Enbrel®).

HCPCS Coding:

J1438	injection, etanercept, 25 mg

ICD-10 Diagnosis Codes That Support Medical Necessity:

D89.810	Acute graft-versus-host disease
D89.811	Chronic graft-versus-host disease
D89.812	Acute on chronic graft-versus-host disease
D89.813	Graft-versus-host disease, unspecified
L40.0	Psoriasis vulgaris

L40.50 – L40.59	Arthropathic psoriasis
L73.2	Hidradenitis suppurativa
M05.00 – M05.09	Felty's syndrome
M05.10 – M05.19	Rheumatoid lung disease with rheumatoid arthritis
M05.20 – M05.29	Rheumatoid vasculitis with rheumatoid arthritis
M05.30 – M05.39	Rheumatoid heart disease with rheumatoid arthritis
M05.40 – M05.49	Rheumatoid myopathy with rheumatoid arthritis
M05.50 – M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis
M05.60 – M05.69	Rheumatoid arthritis with involvement of other organs and systems
M05.70 – M05.79	Rheumatoid arthritis with rheumatoid factor without organ or systems involvement
M05.80 – M05.89	Other rheumatoid arthritis with rheumatoid factor
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.00 – M06.09	Rheumatoid arthritis without rheumatoid factor
M06.20 – M06.29	Rheumatoid bursitis
M06.30 – M06.39	Rheumatoid nodule
M06.80 – M06.89	Other specified rheumatoid arthritis
M06.9	Rheumatoid arthritis, unspecified
M08.09	Unspecified Juvenile rheumatoid arthritis, multiple sites
M08.1	Juvenile ankylosing spondylitis
M08.3	Juvenile rheumatoid arthritis (seronegative)
M08.89	Other juvenile arthritis, multiple sites
M 45.0 – M45.9	Ankylosing spondylitis
M46.81 – M46.89	Other specified inflammatory spondylopathies

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

DMARDs: An acronym for disease-modifying antirheumatic drugs. These are drugs that modify the rheumatic disease processes, and slow or inhibit structural damage to cartilage and bone. These drugs are unlike symptomatic treatments such as NSAIDs that do not alter disease progression. DMARDs can

be further subcategorized. With the release of biologic agents (e.g., anti-TNF drugs), DMARDs were divided into either: (1) conventional, traditional, synthetic, or non-biological DMARDs; or as (2) biological DMARDs. However, with the release of newer targeted non-biologic drugs and biosimilars, DMARDs are now best categorized as: (1) conventional synthetic DMARDs (csDMARD) (e.g., MTX, sulfasalazine), (2) targeted synthetic DMARDs (tsDMARD) (e.g., tofacitinib, apremilast), and (3) biological DMARDs (bDMARD), which can be either a biosimilar DMARD (bsDMARD) or biological originator DMARD (boDMARD).

Plaque psoriasis: It is the most common form of psoriasis. It affects 80 to 90% of people with psoriasis. Plaque psoriasis typically appears as raised areas of inflamed skin covered with silvery white scaly skin. These areas are called plaques.

Psoriatic arthritis (PsA): joint inflammation that occurs in about 5% to 10% of people with psoriasis (a common skin disorder). It is a severe form of arthritis accompanied by inflammation, psoriasis of the skin or nails, and a negative test for rheumatoid factor. Enthesitis refers to inflammation of entheses, the site where ligaments or tendons insert into the bones. It is a distinctive feature of PsA and does not occur with other forms of arthritis. Common locations for enthesitis include the bottoms of the feet, the Achilles' tendons, and the places where ligaments attach to the ribs, spine, and pelvis.

Rheumatoid arthritis: An inflammatory disease of the synovium, or lining of the joint which results in pain, stiffness, and swelling of multiple joints. The inflammation may extend to other joints and cause bone and cartilage erosion, joint deformities, movement problems, and activity limitations**.**

RELATED GUIDELINES:

Abatacept (Orencia), 09-J0000-67
Adalimumab (Humira), 09-J0000-46
Anakinra (Kineret), 09-J0000-45
Apremilast (Otezla) Tablet, 09-J2000-19
Baricitinib (Olumiant), 09-J3000-10
Brodalumab (Siliq) Injection, 09-J2000-74
Certolizumab Pegol (Cimzia), 09-J0000-77
Golimumab (Simponi, Simponi Aria), 09-J1000-11
Guselkumab (Tremfya), 09-J2000-87
Infliximab Products [infliximab (Remicade), infliximab-dyyb (Inflectra), and infliximab-abda (Renflexis)], 09-J0000-39
Ixekizumab (Taltz), 09-J2000-62
Risankizumab (Skyrizi), 09-J3000-45
Rituximab (Rituxan), 09-J0000-59
Sarilumab (Kevzara), 09-J2000-87
Secukinumab (Cosentyx), 09-J2000-30
Tildrakizumab-asmn (Ilumya), 09-J3000-04
Tocilizumab (Actemra) Injection, 09-J1000-21
Tofacitinib (Xeljanz, Xeljanz XR) Oral Solution, Tablet and Extended-Release Tablet, 09-J1000-86
Upadacitinib (Rinvoq), 09-J3000-51
Ustekinumab (Stelara), 09-J1000-16

[Vedolizumab (Entyvio) Injection, 09-J2000-18]

OTHER:

Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy

Actemra (tocilizumab)

Adbry (tralokinumab-ldrm)

Arcalyst (rilonacept)

Avsola (infliximab-axxq)

Benlysta (belimumab)

Cimzia (certolizumab)

Cinqair (reslizumab)

Cosentyx (secukinumab)

Dupixent (dupilumab)

Enbrel (etanercept)

Entyvio (vedolizumab)

Fasenra (benralizumab)

Humira (adalimumab)

Ilaris (canakinumab)

Ilumya (tildrakizumab-asmn)

Inflectra (infliximab-dyyb)

Infliximab

Kevzara (sarilumab)

Kineret (anakinra)

Nucala (mepolizumab)

Orencia (abatacept)

Remicade (infliximab)

Renflexis (infliximab-abda)

Riabni (rituximab-arrx)

Rituxan (rituximab)

Rituxan Hycela (rituximab/hyaluronidase human)

Ruxience (rituximab-pvvr)

Siliq (brodalumab)

Simponi (golimumab)

Simponi Aria (golimumab)

Skyrizi (risankizumab-rzaa)

Stelara (ustekinumab)

Taltz (ixekizumab)

Tezspire (tezepelumab-ekko)

Tremfya (guselkumab)

Truxima (rituximab-abbs)

Tysabri (natalizumab)

Xolair (omalizumab)

Table 4: Conventional Synthetic DMARDs

Generic Name	Brand Name
Auranofin (oral gold)	Ridaura
Azathioprine	Imuran
Cyclosporine	Neoral, Sandimmune
Hydroxychloroquine	Plaquenil
Leflunomide	Arava
Methotrexate	Rheumatrex, Trexall
Sulfasalazine	Azulfidine, Azulfidine EN-Tabs

Table 5: Grading of Severity of Rheumatoid Arthritis

Severity	Criteria
Mild	Joint pain Inflammation of at least 3 joints No inflammation in tissues other than the joints Usually, a negative result on a rheumatoid factor test An elevated erythrocyte sedimentation rate (ESR) or C reactive protein (CRP) level No evidence of bone or cartilage damage on x-rays
Moderate	Between 6 and 20 inflamed joints Usually no inflammation in tissues other than the joints An elevated ESR or CRP levels A positive rheumatoid factor test or anti-cyclic citrullinated peptide (anti-CCP) antibodies Evidence of inflammation but no evidence of bone damage on x-rays
Severe	More than 20 persistently inflamed joints or a rapid loss of functional abilities Elevated ESR or CRP levels Anemia related to chronic illness Low blood albumin level A positive rheumatoid factor test, often with a high level Evidence of bone and cartilage damage on x-ray Inflammation in tissues other than joints

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/09/22.

GUIDELINE UPDATE INFORMATION:

04/15/01	New Medical Coverage Guideline.
05/15/03	Annual review.
10/15/03	Added active ankylosing spondylitis to the When Services Are Covered section.
01/01/05	Revised psoriasis language in the When Services Are Covered Section.
02/15/06	Updated when services are covered added statement: For reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis. Deleted warnings and contraindications, added DMARD table under Other.
12/15/06	Reviewed; reformatted, added CPT-4 and ICD-9 coding, related guidelines, and updated links and references. MCG revised to include Medicare Part D as a program exception.
08/15/07	Reviewed: reformatted, maintained current coverage and limitations, updated related guidelines, updated internet links and updated references.
10/15/07	Revision; consisting of updating ICD-9 coding.
05/15/08	Revision; consisting of adding a black box warning under “PRECAUTIONS”.
10/15/08	Review and revision consisting of; updating description section, reformatted and updated references.
01/01/09	Annual HCPCS coding update: deleted code 90772; added code 96372.
10/15/09	Review and revision consisting of updating precautions, related guidelines and reference sections.
04/15/10	Revision; consisting of adding specific continuation criteria.
09/15/10	Review and revision; consisting of updating precautions and references.
01/15/11	Revision; consisting of adding ICD-10 codes.
04/01/11	Revision; consisting of adding dosage limitations.
09/15/11	Review and revision to guideline; consisting of updating references.
09/15/12	Review and revision to guideline; consisting of modifying continuation criteria, updating precautions, coding and references.
01/15/12	Revision to guideline; consisting of revising and reformatting the position statement and description, dosage/administration, and precautions sections; updating references.
04/15/13	Revision to guideline; consisting of revising position statement to include duration of approval and Orphan Drug indications.
09/15/13	Review and revision to guideline; consisting of revising position statement to include treatment of compendia supported off-label indications, updating references, program exceptions, and coding.
04/15/14	Revision to guideline; consisting of adding clarification statement and reformatting position statement.
09/15/14	Review and revision to guideline; consisting of reformatting position statement, updating references, coding and related guidelines.

09/15/15	Review and revision to guideline; consisting of updating description, position statement, dosage/administration, coding/billing, related guidelines, and references.
11/01/15	Revision: ICD-9 Codes deleted.
09/15/16	Review and revision to guideline consisting of updating description, position statement, dosage/administration, coding/billing, definitions, related guidelines, and references.
01/15/17	Revision to guideline consisting of updating description, position statement, dosage/administration, and references based on new pediatric plaque psoriasis indication.
10/15/17	Review and revision to guideline consisting of updating description, position statement, definitions, related guidelines, and references.
01/01/18	Revision to guideline consisting of updating the preferred self-administered biologic products according to indication for use.
07/01/18	Revision to guideline consisting of updating the position statement.
10/15/18	Review and revision to guideline consisting of updating the position statement, related guidelines, and references.
10/15/19	Review and revision to guideline consisting of updating the description section, position statement, billing/coding, related guidelines, and references.
01/01/20	Revision to guideline consisting of updating the position statement “Note” due to changes in preferred products.
07/01/20	Revision to guideline consisting of updating the description, position statement, billing/coding, and definitions.
01/01/21	Review and revision to guideline consisting of updating the position statement and references.
03/15/21	Revision to guideline consisting of updating Table 1 in the position statement.
09/15/21	Update to Table 1 in Position Statement.
11/15/21	Revision to guideline consisting of updating the position statement.
01/01/22	Review and revision to guideline consisting of updating the description, position statement, related guidelines, other section, and references.
02/15/22	Update to Table 1 in Position Statement.
03/15/22	Revision to guideline consisting of updating the position statement and other sections.
05/15/22	Update to Table 1 in Position Statement.
07/15/22	Update to Table 1 in Position Statement.
09/15/22	Update to Table 1 in Position Statement.
01/01/23	Review and revision to guideline consisting of updating the position statement, other section, and references. New drugs were added to the list of drugs that are not permitted for use in combination.