09-J0000-38

Original Effective Date: 04/15/01

Reviewed: 11/12/25

Revised: 01/01/26

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. In October 2023, the psoriatic arthritis indication was expanded to include pediatric patients as young as 2 years of age, with a new separate indication listing of juvenile psoriatic arthritis (JPsA). 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. The National Comprehensive Cancer Network

(NCCN) guidelines on the Management of Immune Checkpoint Inhibitor-Related-Toxicities now include all TNF alpha inhibitors as options to be considered for the management of moderate or severe immunotherapy-related inflammatory arthritis if unable to taper corticosteroids after 1 week. In addition, etanercept is also included as an option for the management of immunotherapy-related Stevens-Johnson syndrome or toxic epidermal necrolysis as additional immunosuppression. The NCCN guidelines on Hematopoietic Cell Transplantation include etanercept as an option for acute or chronic graft-versus-host disease (GVHD) as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options.

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 mainstays of treatment have been nonsteroidal anti-inflammatory drugs (NSAIDs) and exercise/physical therapy.

NSAIDs are used as first line therapy for patients with active AS, with continuous treatment with NSAIDs being preferred. In patients with stable disease, NSAIDs may be used on-demand to decrease the risk of adverse effects with long term use. No particular NSAID is recommended as a preferred option. Biologics should be used in patients who continue to have persistently high disease activity despite NSAIDs. Failure of standard treatment with NSAIDs can be defined as a lack of response (or intolerance) to at least 2 NSAIDs after at least a 4-week duration of therapy in total.

Tumor necrosis factor (TNF) inhibitors or interleukin (IL)-17 inhibitors are recommended as initial biologic therapy. Other present comorbidities (e.g., inflammatory bowel disease, psoriasis, uveitis) can help guide selection of the initial biologic agent/drug class. Patients who have an inadequate response to a TNF inhibitor or IL-17 inhibitor may switch to a biologic of the other drug class, or switch to a Janus kinase (JAK) inhibitor. Patients with secondary failure to a biologic (presence of antidrug antibodies) may switch to another biologic of the same or different mode of action.

Systemic glucocorticoids should generally not be used in the treatment of AS. Short-term glucocorticoid injections may be used in select patients with peripheral signs and symptoms. Conventional disease-modifying antirheumatic drugs (cDMARDs) (e.g., methotrexate, sulfasalazine, leflunomide) are not recommended as treatment due to their lack of efficacy. However, sulfasalazine may be considered in patients with peripheral arthritis.

Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that primarily affects the joints but can also damage extra-articular organs. The main goal of therapy is to achieve remission, but additional goals include decreased disease activity, prevention of systemic complications, and improved physical functioning. 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 disease-modifying antirheumatic drug(s) (DMARDs) chosen
- Recommendations are limited to DMARDs approved by the US FDA for treatment of RA:
    - Conventional synthetic DMARDs (csDMARDs): hydroxychloroquine, sulfasalazine, methotrexate (MTX), leflunomide
    - Biologic DMARDs (bDMARDs): Tumor necrosis factor (TNF) inhibitors (e.g., etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T cell costimulatory inhibitor (e.g., abatacept), Interleukin (IL)-6 receptor inhibitors (e.g., tocilizumab, sarilumab), anti-CD20 antibody* (e.g., rituximab)

        *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

    - Targeted synthetic DMARDs (tsDMARDs): Janus kinase (JAK) inhibitors (e.g., tofacitinib, baricitinib, upadacitinib)
- Triple therapy refers to hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide
- Biosimilars are considered equivalent to FDA-approved originator bDMARDs
- 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 (2021) 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.

The European Alliance of Associations for Rheumatology (EULAR) guidelines for RA (2022 update) also recommend a treat-to-target approach in therapy. MTX is recommended as first line therapy and should be initiated as soon as the diagnosis of RA is made. If MTX is not clinically appropriate, then an alternative csDMARD should be used as part of the (first) treatment strategy. If initial csDMARD therapy does not produce adequate improvement after 3 months, another csDMARD may be added or switched to as long as poor prognosis factors are absent. In the presence of poor prognosis factors, a bDMARD or JAK inhibitor should be added to csDMARD therapy. If treatment failure occurs with the initial bDMARD or JAK inhibitor, another bDMARD or JAK inhibitor should be considered. If a TNF- or IL-6 receptor inhibitor therapy was initially failed, patients may receive an agent with another mode of action or a second TNF- or IL-6 receptor inhibitor.

Initial dosing of MTX for RA should optimally be 15 mg once weekly, with the dose increased as tolerated and as needed to control signs and symptoms. A fast dose escalation of 5 mg/month to 25-30 mg/week has been associated with higher efficacy, but toxicity with this dosing regimen is a limiting factor. In the presence of sufficient folic acid supplementation, the MTX dose can be rapidly escalated to 25 mg once weekly. The MTX target dose is 25 mg weekly, or the highest tolerable dose.

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 American College of Rheumatology guidelines (2019) (ACR)/Arthritis Foundation recommend the following treatment approach for PJIA:

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are conditionally recommended as adjunct therapy
- Disease modifying antirheumatic drug (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- tumor necrosis factor (TNF) biologic if currently treated with first TNF-inhibitor ± DMARD over switching to another TNF-inhibitor (unless the patient had good initial response to first TNF-inhibitor)
        - TNF-inhibitor, 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 (PS), most commonly presenting with peripheral arthritis, dactylitis, enthesitis, and spondylitis. Active PsA is defined as symptoms at an unacceptably bothersome level as reported by the patient due to one of the following: actively inflamed joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and/or extraarticular manifestations such as uveitis or inflammatory bowel disease (IBD). Disease severity is based on the assessment of the level of disease activity at a given point in time, and the presence/absence of poor prognostic factors and long-term damage. Severe PsA is defined in the American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF) guidelines for PsA and includes the presence of one or more of the following:

- Erosive disease
- Elevated markers of inflammation (e.g., erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]) attributable to PsA
- Long-term damage that interferes with function (e.g., joint deformities, vision loss)
- Highly active disease that causes a major impairment in quality of life, such as:

- Active PsA at many sites including dactylitis and enthesitis
- Function-limiting PsA at a few sites

- Rapidly progressive disease

Treatment involves the use of a variety of interventions, including many agents used for the treatment of other inflammatory arthritis disorders, particularly spondyloarthritis and rheumatoid arthritis, and other management strategies of the cutaneous manifestations of psoriasis. Symptomatic treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and local glucocorticoid injections. Only patients with very mild peripheral disease may sufficiently benefit from NSAIDs as monotherapy, and instead patients are typically treated with disease-modifying antirheumatic drugs (DMARDs) and/or biologics. Efficacy of DMARD and biologic therapies should be assessed 3 months after initiation, and if adequate improvement is not seen then the treatment regimen should be updated or changed. The ACR-NPF guidelines for PsA recommend a treat-to-target approach in therapy, regardless of disease activity, and treatment recommendations for active disease are as follows:

- Treatment naïve patients:
  - First line options include oral small molecules (OSM), tumor necrosis factor (TNF) inhibitors, interleukin (IL)-17 inhibitors, and IL-12/23 inhibitors
    - OSM (i.e., methotrexate [MTX], sulfasalazine, cyclosporine, leflunomide, apremilast) should be considered if the patient does not have severe PsA, does not have severe PS, prefers oral therapy, has concern over starting a biologic, or has contraindications to TNF inhibitors
    - Biologics (e.g., TNF inhibitor, IL-17 inhibitor, IL-12/23 inhibitor) are recommended as a first line option in patients with severe PsA and/or severe PS
- Previous treatment with OSM and continued active disease:
  - Switch to a biologic (i.e., TNF inhibitor, IL-17 inhibitor, IL-12/23 inhibitor); recommended over switching to a different OSM
    - Biologic monotherapy is conditionally recommended over biologic plus MTX combination therapy
  - Switch to a different OSM (except apremilast) OR add on apremilast to current OSM therapy; recommended over adding another OSM
  - Add another OSM (except apremilast) to current OSM therapy; may consider for patients that have exhibited partial response to current OSM
  - Switch to apremilast monotherapy; may be considered instead of adding apremilast to current OSM therapy if the patient has intolerable side effects with the current OSM
- Previous treatment with a biologic and continued active disease:
  - Switch to another biologic (e.g., TNF inhibitor, IL-17 inhibitor, IL-12/23 inhibitor, abatacept, or tofacitinib) as monotherapy
  - Add MTX to the current biologic; may consider adding MTX in patients with a partial response to current biologic therapy

The European Alliance of Associations for Rheumatology (EULAR) guidelines for PsA (2023 update) also recommend a treat-to-target approach in therapy. MTX (preferred) or another conventional synthetic

disease-modifying antirheumatic drug (csDMARD) (e.g., sulfasalazine, leflunomide) should be used for initial therapy. If the treatment target is not achieved with a csDMARD, a biologic should be initiated with preference of product being based on patient specific disease characteristics. Biologics include TNF inhibitors, IL-12/23 inhibitors, IL-17A inhibitors, IL-17A/F inhibitors, IL-23 inhibitors, and cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) analogs. No order of preference of biologics is provided since none have demonstrated superiority for joint involvement, however, CTLA4 analogs are least preferred due to limited efficacy in clinical trials. The use of a Janus kinase (JAK) inhibitor (e.g., tofacitinib, upadacitinib) may be used after failure of a biologic or if biologics are not clinically appropriate for the patient. However, careful consideration should be applied prior to using a JAK inhibitor due to the increased risk of cardiovascular and malignancy events in older patients with RA and cardiovascular risk factors. A phosphodiesterase-4 (PDE4) inhibitor (i.e., apremilast) may be considered in patients with mild disease and an inadequate response to at least one csDMARD, in whom neither a biologic nor a JAK inhibitor is appropriate. Patients with an inadequate response to a biologic or JAK inhibitor may switch to a different drug within the same class or switch to a different mode of action. Adding MTX to a biologic may increase drug survival by limiting the development of antidrug antibodies, especially for TNF inhibitors.

Juvenile Psoriatic Arthritis (JPsA)

Juvenile psoriatic arthritis (JPsA) is a relatively rare condition in childhood and represents approximately 5% of the whole JIA populations. JPsA is defined by the association of arthritis and psoriasis or, in the absence of typical psoriatic lesions, with at least two of the following:

- Dactylitis
- Nail Pitting
- Onycholysis
- Family history of psoriasis in a first-degree relative.

Recent studies however have shown that this classification system could conceal more homogeneous subgroups of patients differing by age of onset, clinical characteristics, and prognosis. Little is known about genetic factors and pathogenetic mechanisms which distinguish JPsA from other JIA subtypes or from isolated psoriasis without joint involvement, especially in the pediatric population.

Psoriatic arthritis of adulthood is a well-defined, although phenotypically heterogeneous, clinical condition. In the majority of cases, it is characterized by the onset of arthritis in patients with pre-existing psoriasis. An opposite scenario is seen in children: arthritis complicates only 2% of pediatrics psoriasis, whereas in JPsA skin disease typically occurs up to 10 years after the development of arthritis, making JPsA diagnosis often challenging. JPsA can be differentiated from adult PsA by several factors as follows:

Clinical feature	**Adult PsA**	**JPsA**
Timing of psoriasis and arthritis onset	Psoriasis prior to arthritis	Arthritis prior to psoriasis
Oligoarticular peripheral arthritis	20%-55%	45%-55%
Polyarticular peripheral arthritis	20%-60%	33%-55%
Oligo-Extended peripheral arthritis	NA	15%-38%

Axial arthritis	7%-40%	10%-30%
Radiological damage	47%	25%
Enthesitis	30%-50%	12%-45%
Dactylitis	40%-50%	17%-37%
Nail involvement	41%-93%	37%-57%
Uveitis	8%	8%-13%
Human Leukocyte antigen (HLA)-B27	40%-50%	10%-25%
Antinuclear antibodies (ANA)	16%	40%-46%

Psoriasis occurs in 40%-60% of patients with JPsA, usually the classic vulgaris form, although guttate psoriasis is also observed. Psoriasis in children tends to be subtle with thin, soft plaques that may be similar to atopic eczema. Onychopathy is reported in more than half of patients with JPsA, compared with 30% in childhood psoriasis in general. Onycholysis may also be observed but is much less common than in adults.

Nonsteroidal anti-inflammatory drugs and oral glucocorticoids, as well as intra-articular glucocorticoids, are indicated as initial steps for symptom relief and bridge therapies. Disease modifying antirheumatic drugs (DMARDs) represent the mainstay second line treatment of children with polyarthritis. The most used is methotrexate which is recommended over leflunomide or sulfasalazine. Biologic agents should be considered in case of DMARDs failure or intolerance, presence of risk factors, or high disease activities.

DERMATOLOGICAL DISORDERS

Psoriasis (PS)

Psoriasis (PS) is a chronic inflammatory skin and systemic disorder. It is a complex disease that affects the skin and joints and is associated with numerous comorbidities, including obesity and inflammatory bowel disease. Psoriasis vulgaris, or plaque psoriasis, is a cutaneous form that often presents with pink plaques with silvery scale on the scalp, elbows, knees, or presacral region, but any area of the skin may be involved. Plaque psoriasis is the most common form (affecting 90% of adults with psoriasis), but others include guttate, erythrodermic, pustular, inverse, nail, and psoriatic arthritis (PsA). PS is clinically diagnosed based on the presence of cutaneous and systemic symptoms, and treatment is similar for most forms but is guided by the body surface area (BSA) involved. The American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) categorize psoriasis severity as mild (less than 3% of BSA), moderate (3% to 10% of BSA), or severe (greater than 10% of BSA). The AAD/NPF guidelines also note that psoriasis can be considered severe irrespective of BSA when it causes serious emotional consequences, occurs in select locations (e.g., hands, feet, scalp, face, or genital area), or when it causes intractable pruritus.

Topical therapies are most commonly used to treat mild to moderate PS, but they may be used in combination with phototherapy, systemic, or biologic therapies for the treatment of moderate to severe PS. Topical therapies alone can be sufficient for managing limited disease and also have fewer significant adverse effects compared to systemic treatment options. However, topical therapies may be inadequate to obtain and maintain skin clearance, and systemic therapies may be warranted. Conventional systemic agents are widely used as monotherapy or in combination with biologics for moderate to severe disease,

and they are beneficial for widespread disease and ease of administration. Biologics are routinely used when one or more conventional agents fail to produce an adequate response but are considered first line in patients with severe PS or patients with concomitant severe PsA. The NPF medical board recommends a treat-to-target approach to therapy for psoriasis that includes the following:

- The preferred assessment instrument for determining treatment response is BSA
- The preferred time to perform initial evaluation of treatment response is after 3 months
- Target response after treatment initiation should be BSA less than or equal to 1% after 3 months
- Acceptable response is either a BSA less than or equal to 3% or a BSA improvement greater than or equal to 75% from baseline at 3 months after treatment initiation

Selection of treatment is based on several factors including benefit-risk assessment, clinical presentation, disease severity, and comorbidities. The AAD/NPF psoriasis treatment guidelines support the following treatment options:

- Topical therapies:
    - Topical corticosteroids (TCS)
    - Topical calcineurin inhibitors (TCIs), such as tacrolimus and pimecrolimus
    - Vitamin D analogues (e.g., calcipotriene and calcitriol)
    - Tazarotene (topical retinoid)
    - Coal tar preparations
    - Topical anthralin
- Psoralen plus ultraviolet light (PUVA) phototherapy
- Systemic non-biologic therapies:
    - Methotrexate (MTX)
    - Cyclosporine
    - Acitretin
    - Apremilast
- Biologic therapies:
    - Tumor necrosis factor (TNF)-α inhibitors (e.g., adalimumab, certolizumab, etanercept, infliximab)
    - Interleukin (IL)-17 inhibitors (e.g., brodalumab, ixekizumab, secukinumab)
    - IL-23 inhibitors (e.g., guselkumab, risankizumab, tildrakizumab)
    - IL-12/IL-23 Inhibitors (e.g., ustekinumab)

      *Note: Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics was published in 2019. No specific biologic drug/class is recommended as first-line for all patients with psoriasis, and instead choice of therapy should be individualized based on patient specific factors. Additional biologic drugs have since received FDA approval for psoriasis that are not discussed.

Primary failure for biologics is defined as initial nonresponse to treatment. Primary failure to a tumor necrosis factor (TNF)-α inhibitor does not preclude successful response to a different TNF-α inhibitor, and failure of another biologic therapy does not preclude successful response to ustekinumab. All biologics may lose efficacy in a patient who initially responds favorably to the medication (secondary failure), and loss of efficacy may be attributed to the presence of antidrug antibodies. The concomitant use of MTX with a biologic may increase drug survival by limiting antibody formation.

For the treatment of PS in the pediatric patient population, topical corticosteroids are the mainstay option based on extensive clinical experience that supports efficacy. Topical calcineurin inhibitors are also a treatment option and may be preferred for psoriasis of the face, genitalia, and body folds. Vitamin D analogues are recommended as a treatment option for childhood plaque psoriasis and are considered safe, effective, and generally well tolerated. Other topical therapies that may be used for the treatment of pediatric psoriasis include tazarotene, anthralin, and coal tar. Phototherapy may be efficacious and well tolerated for pediatric patients with generalized psoriasis or localized psoriasis refractory to topical agents. Systemic non-biologic therapies, such as methotrexate, cyclosporine, and acitretin, are options for moderate to severe psoriasis. Biologic therapies (e.g., adalimumab, etanercept, infliximab, ustekinumab) have also shown efficacy in moderate to severe plaque psoriasis in this patient population.

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 list of self-administered products with prerequisites for certain indications can be found at Preferred Agents and Drug List.

Initiation of etanercept (Enbrel) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "5"):

1. **ONE** of the following ("a", "b", or "c"):
    a. 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 1, and **ALL** of the indication-specific criteria are met
        ii. **EITHER** of the following if the member has an FDA-approved indication ("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 for the requested indication

2. The prescriber is a specialist in the area of the member's diagnosis (e.g., rheumatologist for JIA, PsA, JPsA, 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 will **NOT** be using etanercept in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib), Rinvoq/Rinvoq LQ (upadacitinib), and Xeljanz/Xeljanz XR (tofacitinib)]; Otezla/Otezla XR (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
5. **ANY** of the following ("a", "b", "c", or "d"):
    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 pens (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 member has an FDA labeled indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):
        i. The requested quantity (dose) does **NOT** exceed the maximum FDA labeled dose 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
        ii. **ALL** of the following ("1", "2", and "3"):
            1. The requested quantity (dose) exceeds the FDA maximum labeled dose for the requested indication
            2. The member has tried and had an inadequate response to at least a 3-month trial of the maximum FDA labeled dose for the requested indication (medical records required)
            3. **EITHER** of the following ("a" or "b"):
                a. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose 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

b. The requested quantity (dose) exceeds the maximum FDA labeled dose **AND** the maximum compendia supported dose for the requested indication, AND there is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

c. The member has a compendia supported indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):

   i. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose 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

   ii. The requested quantity (dose) exceeds the maximum compendia supported dose for the requested indication, **AND** there is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

d. The member does **NOT** have an FDA labeled indication **NOR** a compendia supported indication for the requested agent, **AND BOTH** of the following ("i" and "ii"):

   i. 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

   ii. There is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

Compendia Allowed: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use

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 1

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) after at least a 3-month duration of therapy **OR** 2. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA after at least a 3-month duration of therapy **OR**

	3. The member has an intolerance or hypersensitivity to **ONE** conventional agent (i.e., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** 4. The member has an FDA labeled contraindication to **ALL** 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 after at least a 3-month duration of therapy **OR** 2. The member has an intolerance or hypersensitivity to **ONE** conventional agent used in the treatment of PsA **OR** 3. The member has an FDA labeled contraindication to **ALL** 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, vision loss], 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/Otezla XR 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, calcipotriene, calcitriol, coal tar, cyclosporine, methotrexate, pimecrolimus, PUVA [phototherapy], tacrolimus, tazarotene, topical corticosteroids) used in the treatment of PS after at least a 3-month duration of therapy **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, vision loss], rapidly progressive) **OR** 6. The member's medication history indicates use of another biologic immunomodulator agent **OR** Otezla/Otezla XR 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 after at least a 4-week TOTAL duration of therapy **OR** 2. The member has tried and had an inadequate response to **ONE** NSAID used in the treatment of AS after at least a 4-week duration of therapy **AND** an intolerance or hypersensitivity to **ONE** additional NSAID used in the treatment of AS **OR** 3. The member has an intolerance or hypersensitivity to **TWO** different NSAIDs used in the treatment of AS

	OR 4. The member has an FDA labeled contraindication to **ALL** NSAIDs used in the treatment of AS **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 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 after at least a 3-month duration of therapy **OR** 2. The member has an intolerance or hypersensitivity to **ONE** conventional agent used in the treatment of PJIA **OR** 3. The member has an FDA labeled contraindication to **ALL** 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
Juvenile psoriatic arthritis (JPsA)	**ONE** of the following: 1. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., methotrexate, leflunomide, sulfasalazine) used in the treatment of JPsA after at least a 3-month duration of therapy **OR** 2. The member has an intolerance or hypersensitivity to **ONE** conventional agent used in the treatment of JPsA **OR** 3. The member has an FDA labeled contraindication to methotrexate **OR** 4. The member has severe active JPsA (e.g., erosive disease, elevated markers of inflammation [e.g., ESR, CRP] attributable to JPsA, long-term damage that interferes with function [i.e., joint deformities, vision loss], 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 medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of JPsA
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 [Note: members not previously approved for the requested agent will require initial evaluation review]
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, JPsA, 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), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib), Rinvoq/Rinvoq LQ (upadacitinib), and Xeljanz/Xeljanz XR (tofacitinib)]; Otezla/Otezla XR (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
6. **ANY** of the following ("a", "b", "c", or "d"):
    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 pens (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 member has an FDA labeled indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):

   i. The requested quantity (dose) does **NOT** exceed the maximum FDA labeled dose 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

   ii. **ALL** of the following ("1", "2", and "3"):

      1. The requested quantity (dose) exceeds the FDA maximum labeled dose for the requested indication

      2. The member has tried and had an inadequate response to at least a 3-month trial of the maximum FDA labeled dose for the requested indication (medical records required)

      3. **EITHER** of the following ("a" or "b"):

         a. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose 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

         b. The requested quantity (dose) exceeds the maximum FDA labeled dose **AND** the maximum compendia supported dose for the requested indication, **AND** there is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

c. The member has a compendia supported indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):

   i. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose 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

   ii. The requested quantity (dose) exceeds the maximum compendia supported dose for the requested indication, **AND** there is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

d. The member does **NOT** have an FDA labeled indication **NOR** a compendia supported indication for the requested agent, **AND BOTH** of the following ("i" and "ii"):

   i. 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

   ii. There is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

Compendia Allowed: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use

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 2:

<table>
<tr><th colspan="2">FDA-approved indications and recommended dosing</th></tr>
<tr><th>Indication</th><th>Dosage</th></tr>
<tr><td>Plaque Psoriasis (adult, ≥18 years old)</td><td>• First 3 months: 50 mg twice weekly (given 3 to 4 days apart)
• • After 3 months: 50 mg once weekly</td></tr>
<tr><td>Plaque Psoriasis (pediatric, 4 to 17 years old)</td><td rowspan="3">• Less than 63 kg (138 lbs.): 0.8 mg/kg per week
• • 63 kg or more: 50 mg once weekly</td></tr>
<tr><td>Polyarticular Juvenile Idiopathic Arthritis (PJIA) (2 years and older)</td></tr>
<tr><td>Juvenile psoriatic arthritis (JPsA) (pediatric, 2 to 17 years old)</td></tr>
<tr><td>Ankylosing Spondylitis</td><td rowspan="3">• 50 mg once weekly</td></tr>
<tr><td>Psoriatic Arthritis (PsA) (adult, ≥18 years old)</td></tr>
<tr><td>Rheumatoid Arthritis (RA)</td></tr>
</table>

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/mL single-use prefilled syringe
- 50 mg/mL single-use prefilled SureClick Autoinjector
- 50 mg/mL Enbrel Mini single-dose prefilled cartridge (used in the AutoTouch Reusable Autoinjector)
- 25 mg/0.5 mL single-use prefilled syringe
- 25 mg/0.5 mL single-use vial
- 25 mg multiple-use vial (lyophilized powder for reconstitution)

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
L51.1	Stevens-Johnson syndrome [for immunotherapy-related adverse effect ONLY]
L52.2	Toxic epidermal necrolysis [Lyell] [for immunotherapy-related adverse effect ONLY]
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 – M05.7A	Rheumatoid arthritis with rheumatoid factor without organ or systems involvement
M05.80 – M05.8A	Other rheumatoid arthritis with rheumatoid factor
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M05.A	Abnormal rheumatoid factor and anti-citrullinated protein antibody with rheumatoid arthritis
M06.00 – M06.0A	Rheumatoid arthritis without rheumatoid factor
M06.20 – M06.29	Rheumatoid bursitis
M06.30 – M06.39	Rheumatoid nodule
M06.4	Inflammatory polyarthropathy [for immunotherapy-related inflammatory arthritis ONLY]
M06.80 – M06.8A	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
M45.0 – 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.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

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 Products, 09-J0000-46
Anakinra (Kineret), 09-J0000-45
Apremilast (Otezla) Tablet, 09-J2000-19
Baricitinib (Olumiant), 09-J3000-10
Bimekizumab (Bimzelx), 09-J4000-70
Brodalumab (Siliq) Injection, 09-J2000-74
Certolizumab Pegol (Cimzia), 09-J0000-77
Deucravacitinib (Sotyktu), 09-J4000-37
Golimumab (Simponi, Simponi Aria), 09-J1000-11
Guselkumab (Tremfya), 09-J2000-87
Infliximab Products, 09-J0000-39
Ixekizumab (Taltz), 09-J2000-62
Risankizumab (Skyrizi), 09-J3000-45
Rituximab Products, 09-J0000-59
Sarilumab (Kevzara), 09-J2000-87
Secukinumab (Cosentyx), 09-J2000-30
Tildrakizumab-asmn (Ilumya), 09-J3000-04
Tocilizumab Products (Actemra, Tofidence, Tyenne), 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), 09-J2000-18

OTHER:

NOTE: The list of biologic immunomodulator agents not permitted as concomitant therapy can be found at Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.

Table 3: 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 4: 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 11/12/25.

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.
04/15/23	Update to Table 1 in Position Statement. New drugs were added to the list of drugs that are not permitted for use in combination.
07/01/23	Revision to guideline consisting of updating the position statement and other section. Amjevita and Hadlima added as Step 1a agents. Humira biosimilar products added to list of Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.
01/01/24	Review and revision to guideline consisting of updating the description section (NCCN and FDA label info), position statement, dosage/administration, other section, billing/coding, and references. New indication of juvenile psoriatic arthritis (JPsA). Update to Table 1 in Position Statement. New drugs were added to the list of drugs that are not permitted for use in combination.
07/01/24	Revision to guideline consisting of updating the description section, position statement, related guidelines, and other section. New indication for juvenile psoriatic arthritis. Removal of latent TB testing requirement. New drugs added to the list of Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.
10/01/24	Updates to Table 1.
01/01/25	Review and revision to guideline consisting of updating the description, position statement, other section, and references. Update to original Table 1 which is now a link out from the Position Statement. Table titles updated. Revised wording regarding maximum dosage exceptions. New drugs added to the list of drugs that are not permitted for use in combination.
10/01/25	Revision: Added ICD-10 code M05.A. Updated ICD-10 code ranges for RA.
01/01/26	Review and revision to guideline consisting of updating the description, position statement, and references.