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Subject: Certolizumab Pegol (Cimzia®) Injection

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DESCRIPTION:

Certolizumab pegol (Cimzia) is one of five commercially available tumor necrosis factor (TNF) alpha inhibitors available, not counting biosimilars as separate products, in the United States. It was FDA approved for Crohn's disease in April 2008, for rheumatoid arthritis (RA) in May 2009, for psoriatic arthritis (PsA) in September 2013, for ankylosing spondylitis (AS) in October 2013, for plaque psoriasis in May 2018, and for non-radiographic axial spondyloarthritis (nr-AxSp) in March 2019. 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.

Biological agents exhibiting antagonistic properties for TNF bind to the cytokine with a high affinity and prevent TNF binding to receptors on immune, inflammatory, and endothelial cells. TNF-inhibitors may exert action using a variety of biologic activities that may be agent-specific or synergistic with other immunosuppressive agents. Interestingly, many individuals initially non-responsive or intolerant of one TNF-inhibitor have responded when switched to a different agent within the class. However, the TNF-alpha inhibitors as a class are considered to have similar efficacy and safety for the majority of indications. Research in this area is imperative in understanding and identifying potential risks and adverse effects associated with use. Combined data from randomized, controlled trials and safety registries have raised concerns that TNF-inhibitors increase the risk of infections and malignancies;

although, some studies have found no increased risk as compared to the frequency of infections and malignancies observed in a population predisposed to an immune-mediated inflammatory disease.

In 2015, the American College of Rheumatology (ACR) published an updated guideline for the treatment of rheumatoid arthritis (RA). The next update to the guideline is expected in late 2019 or early 2020. The guidelines support the use of a TNFi (e.g., certolizumab pegol) in the following scenarios: (1) patients with early RA if disease activity remains moderate or high despite DMARD monotherapy (with or without glucocorticoids), use combination DMARDs or a TNFi or a non-TNF biologic (all choices with or without methotrexate (MTX), in no particular order of preference); (2) patients with early RA if disease activity remains moderate or high despite DMARDs, use a TNFi over tofacitinib, (3) patients with established RA if disease activity remains moderate or high despite DMARD monotherapy, use combination traditional DMARDS or add a TNFi or a non-TNF biologic or tofacitinib (all choices with or without MTX, in no particular order of preference); and (4) patients with established RA if disease activity remains moderate or high despite TNFi therapy in patients who are currently not on DMARDs, add one or two DMARDs to TNFI therapy rather than continuation TNFi therapy alone. The avoidance of TNFi therapy and use of alternatives is recommended in certain high-risk conditions([i.e., congestive heart failure, hepatitis C infection and not receiving or requiring antiviral treatment, lymphoproliferative disorders, previously treated or untreated skin cancer, and previous serious infection).

In the 2015 TACIT pragmatic, non-inferiority, randomized controlled trial, 205 persons with established moderate to severe RA received either an anti-TNF biologic with one DMARD (e.g., methotrexate), or conventional DMARD therapy titrated upward to include combination therapy. Most persons in the DMARD group eventually received 2 or 3 DMARDs in combination (e.g., methotrexate + leflunomide). The DMARD group was shown to be non-inferior to the anti-TNF group for the primary outcome of disability measured by a patient-recorded health assessment questionnaire at 12 months with a numerical advantage towards the DMARD group. Further supporting use of combination DMARD therapy, the 2-year follow-up of the SWEFOT trial (438 persons with methotrexate-refractory RA) showed no difference in utility or QALY gain over 21 months when comparing methotrexate + infliximab vs. methotrexate + sulfasalazine + hydroxychloroquine.

While methotrexate must be avoided in women who are pregnant or trying to become pregnant, sulfasalazine has adequate data supporting safe use (pregnancy Category B), and is consider a preferred DMARD when given with folic acid if treatment is clinically necessary. Hydroxychloroquine, cyclosporine, and anti-TNF biologics are also considered to be low-risk options during pregnancy.

POSITION STATEMENT:

Site of Care: If certolizumab pegol (Cimzia) is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-46: Site of Care Policy for Select Specialty Medications.

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 preferred self-administered specialty products for certain indications are:

- Ankylosing spondylitis - adalimumab (Humira), etanercept (Enbrel), and secukinumab (Cosentyx)
- Crohn's disease - adalimumab (Humira) and ustekinumab (Stelara)
- Hidradenitis suppurativa - adalimumab (Humira)
- Plaque psoriasis - adalimumab (Humira), etanercept (Enbrel), guselkumab (Tremfya), risankizumab (Skyrizi), secukinumab (Cosentyx), and ustekinumab (Stelara)
- Juvenile idiopathic arthritis [non-systemic] - adalimumab (Humira) and etanercept (Enbrel)
- Psoriatic arthritis - adalimumab (Humira), etanercept (Enbrel), secukinumab (Cosentyx), and ustekinumab (Stelara)
- Rheumatoid arthritis - adalimumab (Humira), etanercept (Enbrel), and upadacitinib (Rinvoq)
- Ulcerative colitis - adalimumab (Humira) and ustekinumab (Stelara)
- Uveitis - adalimumab (Humira)

Initiation of certolizumab pegol (Cimzia) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is 18 years of age or older
2. Certolizumab will not be used in combination with **ANY** of the following:
    a. abatacept (Orencia)
    b. adalimumab (Humira)
    c. anakinra (Kineret)
    d. apremilast (Otezla)
    e. baricitinib (Olumiant)
    f. brodalumab (Siliq)
    g. etanercept (Enbrel)
    h. golimumab (Simponi, Simponi Aria)
    i. guselkumab (Tremfya)
    j. infliximab products (Remicade, Inflectra, Renflexis)
    k. ixekizumab (Taltz)
    l. risankizumab (Skyrizi)
    m. sarilumab (Kevzara)
    n. secukinumab (Cosentyx)
    o. tildrakizumab-asmn (Ilumya)
    p. tocilizumab (Actemra)
    q. tofacitinib (Xeljanz, Xeljanz XR)
    r. upadacitinib (Rinvoq)
    s. ustekinumab (Stelara)
    t. vedolizumab (Entyvio)

3. Certolizumab will be used for treatment of an indication listed in Table 1, and **ALL** of the indication-specific criteria are met
4. The member's dosage does not exceed the following based on member weight and indication for use:
   a. Axial spondyloarthritis, Crohn's disease, psoriatic arthritis and rheumatoid arthritis:
      - Initial: 400 mg (given as 2 subcutaneous injections of 200 mg) at week 0, 2 and 4
      - Maintenance: 400 mg every 28 days (4 weeks) starting at week 8, **OR** 200 mg every other week starting at week 6
   b. Plaque psoriasis (weight ≤90 kg):
      - Initial: 400 mg (given as 2 subcutaneous injections of 200 mg) at week 0, 2 and 4
      - Maintenance: 200 mg every other week starting at week 6
   c. Plaque psoriasis (weight >90 kg):
      - 400 mg (given as 2 subcutaneous injections of 200 mg) every other week

Table 1

Indications and Specific Criteria	
Indication	**Criteria**
Axial spondyloarthritis (axSpA) [including both ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)]	When **ALL** of the following are met ("1", "2", and "3"): 1. Member has a diagnosis of axial spondyloarthritis per ASAS criteria 2. Member has had an inadequate response to, intolerable adverse effects with, or has a contraindication to at least **TWO** different NSAID therapies taken continuously for at least 2 weeks each at maximal doses* (e.g., celecoxib, diclofenac, ibuprofen, meloxicam, naproxen) [the specific adverse effect(s) and/or contraindication must be provided] 3. For the indication of ankylosing spondylitis **ONLY** (i.e., this requirement is **NOT** applicable for members with nr-axSpA) - member has had inadequate responses to **TWO** or more of the following self-administered therapies, **OR** has had intolerable adverse effects with or has contraindications to **ALL** of the following self-administered therapies† [the specific adverse effect(s) and/or contraindication(s) must be provided]: a. adalimumab (Humira) b. etanercept (Enbrel) c. secukinumab (Cosentyx)
Crohn's disease (CD)	When **ALL** of the following are met ("1", "2", and "3"): 1. Member has a diagnosis of moderately to severely active CD [e.g., Crohn's Disease Activity Index (CDAI) greater than 220 points] 2. Member has had an inadequate response to at least **ONE** or has intolerable adverse effects with or contraindications to **ALL** of the following treatments* [the specific adverse effect(s) and/or contraindication(s) must be provided]: a. azathioprine b. mercaptopurine (6-MP)

	c. methotrexate d. systemic corticosteroid (e.g. oral prednisone, IV methylprednisolone) 3. Member has had inadequate responses to, intolerable adverse effects with, or has contraindications to **BOTH** of the following self-administered therapies† [the specific adverse effect(s) and/or contraindications must be provided]: a. adalimumab (Humira) b. ustekinumab (Stelara)
Plaque psoriasis	When **ALL** of the following are met ("1", "2", and "3"): 1. Member's disease is moderate to severe as evidenced by **EITHER** of the following before or after systemic drug therapy ("a" or "b"): a. Psoriasis covers 10% or more of member's BSA b. Psoriasis covers less than 10% of member's BSA, but affects crucial body areas necessary for daily living activities (i.e., face, palms of hands, soles of feet, or genitals) 2. **EITHER** of the following* ("a" or "b"): a. Member has had an inadequate response to at least 3 months of continuous treatment with maximally tolerated methotrexate* (e.g., titrated to a dosage of 25 mg per week) b. **BOTH** of the following* ("i" and "ii"): i. Member has a contraindication to or intolerable adverse effects with methotrexate* [the specific contraindication and/or adverse effect(s) must be provided] ii. Member has had an inadequate response to at least 3 months of continuous treatment with **EITHER** oral cyclosporine (at a dosage of at least 4 mg/kg per day) or acitretin* (at a dosage of at least 25 mg per day), **OR** has a contraindication to and/or intolerable adverse effects(s) with **BOTH** cyclosporine and acitretin [the specific contraindication(s) and/or adverse effect(s) must be provided; pregnancy is not considered a contraindication to the use of cyclosporine] 3. Member has had inadequate responses to **THREE** or more of the following self-administered therapies, **OR** has had intolerable adverse effects with or has contraindications to **ALL** of the following self-administered therapies† [the specific adverse effects and/or contraindications must be provided]: a. adalimumab (Humira) b. etanercept (Enbrel) c. guselkumab (Tremfya) d. risankizumab (Skyrizi) e. secukinumab (Cosentyx) f. ustekinumab (Stelara)
Psoriatic arthritis (PsA) [including both axial and	When **ALL** of the following are met ("1", "2", and "3"): 1. Member's disease is active (i.e., persistent joint inflammation)

non-axial (peripheral) PsA]	2. **EITHER** of the following based on the dominate disease type*: a. **Axial PsA**: Member has had an inadequate response to, intolerable adverse effects with, or has a contraindication to at least **TWO** different NSAID therapies taken continuously for at least 2 weeks each at maximal doses* (e.g., celecoxib, diclofenac, ibuprofen, meloxicam, naproxen) [the specific adverse effect(s) or contraindications must be provided] b. **Peripheral PsA**: Member has had an inadequate response to, intolerable adverse effects with, or has a contraindication to at least **ONE** NSAID therapy taken continuously for at least 2 weeks each at maximal doses* (e.g., celecoxib, diclofenac, ibuprofen, meloxicam, naproxen) [the specific adverse effect(s) or contraindication must be provided] **AND** Member has had an inadequate response to, intolerable adverse effects with, or has a contraindication to methotrexate at the maximally tolerated dosage* (e.g., methotrexate titrated to 25 mg weekly), **OR**, if methotrexate is contraindicated or not tolerated, an inadequate response to, intolerable adverse effects with, or has a contraindication to another csDMARD* (e.g., cyclosporine, leflunomide, sulfasalazine) [the specific adverse effect(s) or contraindication must be provided] 3. Member has had inadequate responses to **TWO** or more of the following self-administered therapies, **OR** has had intolerable adverse effects with or has contraindications to **ALL** of the following self-administered therapies† [the specific adverse effect(s) and/or contraindication(s) must be provided]: • adalimumab (Humira) • etanercept (Enbrel) • secukinumab (Cosentyx) • ustekinumab (Stelara)
Rheumatoid arthritis (RA)	When **ALL** of the following are met (“1”, “2”, and “3”): **1.** Member disease is moderately to severely active **2.** Member has had an inadequate response (i.e., unable to achieve remission or low disease activity) to at least three continuous months of therapy with **TWO** or more csDMARDs* (e.g., hydroxychloroquine, methotrexate, sulfasalazine, leflunomide) used in combination at the maximally tolerated dosage (e.g., methotrexate titrated to 25 mg weekly). A trial of csDMARD monotherapy at the maximally tolerated dosage for at least three continuous months is sufficient if member has a contraindication to or intolerable adverse effect(s) with **BOTH** methotrexate **AND** either sulfasalazine or hydroxychloroquine* [the specific adverse effect(s) or contraindications must be provided; pregnancy is not considered a contraindication to the use of sulfasalazine or hydroxychloroquine] 3. Member has had inadequate responses to **TWO** or more of the following

	self-administered therapies, **OR** has had intolerable adverse effects with or has contraindications to **ALL** of the following self-administered therapies[†] [the specific adverse effect(s) and/or contraindication(s) must be provided]: • adalimumab (Humira) • etanercept (Enbrel) • upadacitinib (Rinvoq
Approval duration: 6 months	

ASAS, Assessment of SpondyloArthritis International Society; NSAID, non-steroidal anti-inflammatory drug

***NOTE:** Members initiating provider administered (i.e., submitted as a medical claim with J0717) certolizumab therapy are **NOT** required to have had an inadequate response to the preferred self-administered (i.e., subcutaneous) biologic products. However, members transitioning to self-administered treatment after a single provider-administered first dose must still meet the preferred self-administered biologic product requirement.

[†]**NOTE:** If the member has had an inadequate response to previous biologic therapy, other than certolizumab pegol, that is FDA-approved for the requested indication listed in Table 1, the member is not required to have had an inadequate response to non-biologic prerequisite therapy (e.g., for RA, if member has previously had an inadequate response to etanercept, but does not have a history of an inadequate response to combination csDMARD, they do not have to try two csDMARDs in combination to meet medical necessity criteria). However, members self-administering certolizumab pegol must still meet the preferred self-administered product requirements.

Continuation of certolizumab (Cimzia) therapy **meets the definition of medical necessity** when **ALL** of the following are met ("1", "2", "3", and "4"):

1. Member has demonstrated a beneficial clinical response to certolizumab pegol therapy
2. An authorization or reauthorization for certolizumab has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of a condition listed in Table 1, **OR** the member previously met **ALL** indication-specific initiation criteria
3. Certolizumab is not used in combination with **ANY** of the following:
    a. abatacept (Orencia)
    b. adalimumab (Humira)
    c. anakinra (Kineret)
    d. apremilast (Otezla)
    e. baricitinib (Olumiant)
    f. brodalumab (Siliq)
    g. etanercept (Enbrel)
    h. golimumab (Simponi, Simponi Aria)
    i. guselkumab (Tremfya)
    j. infliximab products (Remicade, Inflectra, Renflexis)

k. ixekizumab (Taltz)
l. risankizumab (Skyrizi)
m. sarilumab (Kevzara)
n. secukinumab (Cosentyx)
o. tildrakizumab-asmn (Ilumya)
p. tocilizumab (Actemra)
q. tofacitinib (Xeljanz, Xeljanz XR)
r. upadacitinib (Rinvoq)
s. ustekinumab (Stelara)
t. Vedolizumab (Entyvio)

4. The member's certolizumab dosage does not exceed the following based on the indication for use:
   a. Axial spondyloarthritis, Crohn's disease, psoriatic arthritis, and rheumatoid arthritis - 400 mg every 28 days (4 weeks), **OR** 200 mg every other week
   b. Plaque psoriasis - 400 mg every other week

Approval duration: 1 year

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.

FDA-approved indications:

Certolizumab pegol is indication for:

- Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy
- Treatment of adults with moderately to severely active rheumatoid arthritis
- Treatment of adult patients with active psoriatic arthritis
- Treatment of adults with active ankylosing spondylitis
- Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation
- Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

Crohn's Disease:

- Initial Dose: 400 mg (given as 2 subcutaneous injections of 200 mg) initially, and at weeks 2 and 4.
- Maintenance Dose: In members who obtain a clinical response, the recommended maintenance regimen is 400 mg every 4 weeks (starting at week 8).

Plaque Psoriasis:

- 400 mg (given as 2 subcutaneous injections of 200 mg) every other week
- For some patients (with body weight ≤90 kg), 400 mg (given as 2 subcutaneous injections of 200 mg each) initially and at Weeks 2 and 4, followed by 200 mg every other week can be considered.

Rheumatoid Arthritis, Active Psoriatic Arthritis, Ankylosing Spondylitis, and Non-radiographic Axial Spondyloarthritis:

- Initial Dose: 400 mg (given as 2 subcutaneous injections of 200 mg) initially, and at weeks 2 and 4.
- Maintenance Dose: 200 mg every other week (starting at week 6). 400 mg every 4 weeks can be considered (starting at week 8).

Administration: Certolizumab is administered by subcutaneous injection. Rotate injection sites and do not give injections into areas where the skin is tender, bruised, red, or hard. When a 400 mg dose is needed (given as 2 subcutaneous injections of 200 mg), injections should occur at separate sites in the thigh or abdomen

Powder for solution: Prepare the lyophilized powder and administer by a health care provider.

Prefilled syringe: A member may self-inject certolizumab if a health care provider determines that it is appropriate, with medical follow-up, as necessary, after proper training in subcutaneous injection technique. Instruct members using certolizumab to inject the full amount in the syringe (1 mL).

Drug Availability: certolizumab is available as:

- Lyophilized powder for reconstitution – contains 200 mg vials of lyophilized powder for reconstitution and supplies needed for reconstitution
- Prefilled syringe for injection – contains two 200 mg/mL syringes
- Starter kit – contains six 200 mg/mL prefilled syringes to provide for the three 400 mg inial induction doses on week 0, 2, and 4

Refrigerate intact carton between 2 to 8 °C (36 to 46 °F). Do not freeze. Do not separate contents of carton prior to use. Protect solution from light.

PRECAUTIONS:

Boxed Warning

- **Infections:** Increased risk of serious infections leading to hospitalization or death including 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. Discontinue treatment if a patient develops a serious infection or sepsis.
- **Malignancy**: lymphoma and other malignancies, some fatal have been reported in children and adolescent individuals treated with TNF blockers including certolizumab. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescents and young adults with inflammatory bowel disease. Certolizumab pegol is not indicated for use in pediatric patients.

Contraindications

- Serious hypersensitivity reaction to certolizumab pegol or to any of the excipients

Precautions/Warnings

- **Serious Infections:** certolizumab should not be initiated in members during an active infection. If an infection develops, monitor carefully, and discontinue certolizumab if infection becomes serious.
- **Invasive fungal infections:** If a member develops a systemic infection while on certolizumab 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 certolizumab 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 certolizumab.
- **Heart failure:** worsening or new onset heart failure may occur.
- **Lupus-like syndrome:** discontinue certolizumab if syndrome develops.
- **Drug Interactions:** avoid concomitant use with abatacept (Orencia®) and anakinra (Kineret®), due to increased risk of serious infection.
- **Laboratory tests:** may interfere with certain aPTT tests
- **Live vaccines:** Avoid administration of live vaccines (e.g., varicella and MMR) in members taking certolizumab.
- **Pregnancy and Lactation**
    - Certolizumab is classified as pregnancy category B. Developmental toxicity studies performed in animals have revealed no evidence of harm to the fetus.
    - 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 describe:

HCPCS Coding:

J0717	Injection, certolizumab pegol, 1 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when self-administered)

ICD-10 Diagnosis Codes That Support Medical Necessity:

K50.00 – K50.919	Crohn's disease [regional enteritis]
L40.0	Psoriasis vulgaris
L40.50 – L40.59	Arthropathic psoriasis
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
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. The Site of Care Policy for Select Specialty Medications does not apply to Medicare Advantage members.

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:

Axial PsA (a.k.a., psoriatic spondylitis): a subset of psoriatic arthritis that affects the spine (i.e., spondylitis) and/or spinal joints (e.g., the sacroiliac joint between the sacrum and ilium of pelvis). Axial PsA shares similar clinical findings to patients with ankylosing spondylitis (AS); however, patients with axial PsA are often less symptomatic, have asymmetric disease, and tend to have less severe disease. In addition, the psoriatic plaques or nail changes present in patients with axial PsA are absent in patients with AS. About 5% of PsA patients have exclusively axial involvement, and 20 to 50% have both spinal and peripheral involvement, with peripheral joint involvement being the predominant pattern.

Axial Spondyloarthritis (SpA): an inflammatory disease where the main symptom is back pain, and where the x-ray changes of sacroiliitis may or may not be present. In ankylosing spondylitis (AS), the x-ray changes are clearly present. In non-radiographic axial spondyloarthritis (nr-axSpA); the x-ray changes are not present but you have symptoms. It is thought that nr-axSpA may be an earlier form of AS.

Crohn's disease: a chronic granulomatous inflammatory disease of unknown etiology, involving any part of the gastrointestinal tract from mouth to anus, but commonly involving the terminal ileum with scarring and thickening of the bowel wall. It frequently leads to intestinal obstruction and fistula and abscess formation and has a high rate of recurrence after treatment.

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., baricitinib, tofacitinib, apremilast), and (3) biological DMARDs (bDMARD), which can be either a biosimilar DMARD (bsDMARD) or biological originator DMARD (boDMARD).

Mild-Moderate Crohn's Disease: Mild-moderate Crohn's disease applies to ambulatory members able to tolerate oral alimentation without manifestations of dehydration, toxicity (high fevers, rigors, prostration), abdominal tenderness, painful mass, obstruction, or >10% weight loss**.**

Moderate to Severe Crohn's Disease: Moderate to severe disease applies to patients who have failed to respond to treatment for mild to moderate disease or those with more prominent symptoms of fevers, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia.

Monoclonal antibody: derived from a single cell; pertaining to a single clone. Widely used to measure proteins and drugs in the serum, type tissue and blood, identify infectious agents, identify classification and follow-up therapy of leukemias and lymphomas, and identify tumor antibodies.

Non-axial or peripheral PsA: a subset of psoriatic arthritis that does NOT affect the spine or spinal joints [e.g. elbow, wrist, knees, hands, feet, and digits (dactylitis)]. Peripheral involvement may be polyarticular (5 or more joints affected) or oligoarticular (a.k.a., pauciarticular) (4 or fewer joints affected). Approximately 95% of patients with PsA have involvement of the peripheral joints, predominantly the polyarticular form, whereas a minority has the oligoarticular form.

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 that 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

Etanercept (Enbrel), 09-J0000-38

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

Natalizumab (Tysabri) IV, 09-J0000-73

Psoralens with Ultraviolet A (PUVA), 02-10000-16

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) IV, 09-J1000-21

Tofacitinib (Xeljanz, Xeljanz XR), 09-J1000-86

Ustekinumab (Stelara), 09-J1000-16

Vedolizumab (Entyvio), 09-J2000-18

OTHER:

Table 2: 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

Assessment of Spondyloarthritis International Society (ASAS) Diagnostic Criteria for Axial Spondylarthritis (SpA)

Patients with chronic (≥3 months) back pain, the onset of which occurs at <45 years of age, AND EITHER of the following:

1. Imaging arm:
    a. Sacroiliitis on imaging*****

    AND

    b. ≥1 SpA feature
2. Clinical arm:
    a. HLA-B27 positive

    AND

    b. ≥2 other SpA features

SpA features:

- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's/colitis
- Good response to NSAIDs
- Family history of SpA
- HLA-B27
- Elevated CRP

*****Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA, or definite radiographic sacroiliitis according to modified New York criteria

Table 3: 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

REFERENCES:

1. Armstrong AW, Siegel MP, Bagel J, et al. From the Medical Board of the National Psoriasis Foundation: Treatment targets for plaque psoriasis. J Am Acad Dermatol. 2017 Feb;76(2):290-298.
2. Bansback N, Phibbs CS, Sun H, et al; CSP 551 RACAT Investigators.Triple Therapy Versus Biologic Therapy for Active Rheumatoid Arthritis: A Cost-Effectiveness Analysis. Ann Intern Med. 2017 Jul 4;167(1):8-16.
3. Callhoff J, Sieper J, Weiß A, et al. Efficacy of TNFα blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. Ann Rheum Dis. 2015 Jun;74(6):1241-8.
4. Cimzia (certolizumab pegol) [package insert]. UCB Pharma Inc., Smyrna (GA): March 2019.
5. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: www.clinicalpharmacilogy-ip.com. Accessed 8/2/19.
6. Coates LC, Kavanaugh A, Mease PJ et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis: Treatment Recommendations for Psoriatic Arthritis 2015. Arthritis Rheumatol 2016;68:1060–71.
7. Dogra S, Jain A, Kanwar AJ. Efficacy and safety of acitretin in three fixed doses of 25, 35 and 50 mg in adult patients with severe plaque type psoriasis: a randomized, double blind, parallel group, dose ranging study. J Eur Acad Dermatol Venereol. 2012;27:305-311.
8. Dogra S, Krishna V, Kanwar AJ. Efficacy and safety of systemic methotrexate in two fixed doses of 10 mg or 25 mg orally once weekly in adult patients with severe plaque-type psoriasis: a prospective, randomized, double-blind, dose-ranging study. Clin Exp Dermatol. 2012 Oct;37(7):729-34.
9. Elmets CA, Leonardi CL, Davis DM, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol. 2019 Apr;80(4):1073-1113. Epub 2019 Feb 13.
10. Elmets CA, Lim HW, Stoff H, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy. J Am Acad Dermatol. Epub 2019 July 25.
11. FDA Orphan Drug Designations and Approvals [Internet]. Washington, D.C. [cited 2019 August 28]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/.
12. Graudal N, Hubeck-Graudal T, Tarp S, et al. Effect of combination therapy on joint destruction in rheumatoid arthritis: a network meta-analysis of randomized controlled trials. PLoS One. 2014 Sep 22;9(9):e106408.
13. Heydendael VM, Spuls PI, Opmeer BC, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med 2003;349:658-65.

14. Hsu S, Papp KA, Lebwohl MG, et al. Consensus guidelines for the management of plaque psoriasis. Arch Dermatol 2012;148(1):95-102.

15. Kalb RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol 2009;60:824-37.

16. Krause ML, Amin A, and Makol A. Use of DMARDs and biologics during pregnancy and lactation in rheumatoid arthritis: what the rheumatologist needs to know. Ther Adv Musculoskelet Dis. 2014 Oct; 6(5): 169–184.

17. Kroon FP, van der Burg LR, Ramiro S, et al. Non-steroidal anti-inflammatory drugs (NSAIDs) for axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis). Cochrane Database Syst Rev. 2015 Jul 17;7:CD010952.

18. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018 Apr;113(4):481-517.

19. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis:Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol. 2009 Sep;61(3):451-85

20. Menter A, Korman, NJ, Elmets, CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: Case-based presentations and evidence-based conclusions. J Am Acad Dermatol 2011; 65:137-74.

21. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 8/28/19.

22. Peper SM, Lew R, Mikuls T, et al. Rheumatoid Arthritis Treatment After Methotrexate: The Durability of Triple Therapy Versus Etanercept. Arthritis Care Res (Hoboken). 2017 Oct;69(10):1467-1472.

23. Rahimi R, Nikfar S, Rezaie A, et al. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. Reprod. Toxicol;2008:25,271–275.

24. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019 Mar;114(3):384-413

25. Rudwaleit M, van der Heijde D, Landewé R, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011 Jan;70(1):25-31.

26. Sbidian E, Chaimani A, Garcia-Doval , et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2017 Dec 22;12:CD011535.

27. Scott DL, Ibrahim F, Farewell V, et al. Tumour necrosis factor inhibitors versus combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis: TACIT non-inferiority randomised controlled trial. BMJ. 2015 Mar 13;350:h1046.

28. Scott DL, Kinglsey GH. Tumor necrosis factor inhibitors in rheumatoid arthritis. N Engl J Med 2006;355:704-12.

29. Singh JA, Guyatt G, Ogdie A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis Rheumatol. 2019 Jan;71(1):5-32. Epub 2018 Nov 30.

30. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2016 Jan;68(1):1-25.

31. Smith CH, Jabbar-Lopez JK, Yiu ZZ, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. Br J Dermatol 2017; 177: 628-136.

32. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017 Jun;76(6):960-977.
33. Tracey D, Klareskog L, Sasso EH, et al. Tumor necrosis factor antagonist mechanism of action: a comprehensive review. Pharmacol Ther 2008;117:244-79.
34. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017 Jun;76(6):978-991.
35. van Vollenhoven RF, Geborek P, Forslind K, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet. 2012 May 5;379(9827):1712-20.
36. Ward MM, Deodhar A, Gensler LS, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Rheumatol. 2019 Aug 22. [Epub ahead of print]

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Committee on 11/13/19.

GUIDELINE UPDATE INFORMATION:

09/15/08	New Medical Coverage Guideline.
01/01/09	Annual HCPCS coding update: deleted code 90772; added codes 96372.
04/01/09	Annual HCPCS coding update: added HCPCS code C9249 & deleted J3490.
04/15/09	Revision; consisting adding ICD-9 codes.
06/15/09	Revision; consisting of adding rheumatoid arthritis indication and updating boxed warning.
10/15/09	Review and revision; consisting of updating administration and dosage section and references.
01/01/10	Annual HCPCS coding update: added HCPCS code J0718 and deleted code C9249.
04/15/10	Revision; consisting of adding specific continuation criteria.
08/15/10	Review and revision; consisting of updating precautions and references.
01/15/11	Revision; consisting of adding ICD-10 codes.
08/15/11	Review and revision to guideline; consisting of updating precautions, coding and references.
08/15/12	Review and revision to guideline; consisting of reformatting position statement, updating precautions and references.
10/15/12	Revision to guideline; consisting of modifying continuation criteria.
01/15/13	Revision to guideline; consisting of reformatting position statement; revising and reformatting description, dosage/administration, and precautions sections.
03/07/13	Revision to guideline; additions to position statement.
04/15/13	Revision to guideline; consisting of revising position statement to include duration of approval.
09/15/13	Review and revision to guideline; consisting of reformatting position statement; updating related guidelines, references, program exceptions, and coding.
01/01/14	Revision to guideline; consisting of updating position statement, coding, and references.
04/15/14	Revision to guideline; consisting of updating position statement.
09/15/14	Review and revision to guideline; consisting of updating position statement, references,

	and coding.
09/15/15	Review and revision to guideline; consisting of updating description section, position statement, dosage/administration, warnings/precautions, billing/coding, related guidelines, and references.
12/15/15	Revision to guideline consisting of updating the position statement.
09/15/16	Review and revision to guideline consisting of updating description section, position statement, billing/coding, and references.
11/15/16	Revision to guideline consisting of updating position statement with ustekinumab prerequisite therapy requirement for Crohn's disease 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. Secukinumab is now a preferred product for psoriatic arthritis and axial spondyloarthritis, and use of three preferred products is required. Tofacitinib (Xeljanz, Xeljanz XR) added as prerequisite therapy for rheumatoid arthritis when certolizumab pegol is used as self-administered therapy.
07/01/18	Revision to guideline consisting of updating the position statement.
07/15/18	Revision to guideline consisting of updating the description section, position statement, dosage/administration, warnings/precautions, billing/coding, related guidelines, definitions, and references based on a new FDA-approved indication of plaque psoriasis.
10/15/18	Review and revision to guideline consisting of updating the position statement, related guidelines, and references.
05/15/18	Revision to guideline consisting of updating the description section and dosage/administration section based on the new FDA-approved indication of non-radiographic axial spondyloarthritis.
07/15/19	Revision to guideline consisting of updating the position statement.
09/01/19	Revision to guideline consisting of updating the position statement.
10/15/19	Review and revision to guideline consisting of updating the statement and references.
11/11/19	Revision to guideline consisting of adding a reference to the Site of Care Policy for Select Specialty Medications and updating the Program Exceptions.
01/01/20	Revision to guideline consisting of updating the position statement due to changes in preferred and non-preferred products.