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Subject: Infliximab Products [infliximab (Remicade®), Infliximab, infliximab-dyyb (Inflectra®), infliximab-abda (Renflexis®), and infliximab-axxq (Avsola®) intravenous infusions; and infliximab-dyyb (Zymfentra®) subcutaneous injection]

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DESCRIPTION:

Infliximab (Remicade) is one of five commercially available tumor necrosis factor (TNF)-alpha inhibitors, not counting biosimilars as separate products, in the United States, and was the first TNFi to be approved in August 1998. In April 2016 the first biosimilar version, infliximab-dyyb (Inflectra) [Pfizer], was approved by the FDA. In April 2017 the FDA approved another biosimilar version, infliximab-abda (Renflexis) [Merck]. A third biosimilar, infliximab-qbtx (Ixifi) [Pfizer], was FDA approved in December 2017, but the product will not be launched in the US. A fourth biosimilar, infliximab-axxq (Avsola) [Amgen], was FDA approved in December 2019. In late 2021, Janssen (the manufacturer of Remicade) released unbranded Infliximab. It is the exact same product as Remicade just without the brand name. In contrast to other TNF-alpha inhibitors that are typically administered subcutaneously, most infliximab products are administered via an intravenous (IV) infusion only. It is usually administered in a physician's office, patient's home, outpatient setting, or infusion center. However, the first subcutaneous (SC) infliximab product, infliximab-dyyb (Zymfentra), appropriate for self-administration, was approved by the FDA in October 2023. Zymfentra is essentially a SC version of IV Inflectra (both are infliximab-dyyb). 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.

Intravenous infliximab is approved by the US Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, adult and pediatric Crohn's disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and adult and pediatric ulcerative colitis. Infliximab also was granted orphan drug designation by the FDA for the treatment of juvenile rheumatoid arthritis (2002) and chronic sarcoidosis (2003). Biosimilar infliximab-dyyb (Inflectra) and infliximab-abda (Renflexis) were approved by the FDA for the same indications as Remicade with the exception of pediatric ulcerative colitis (due to Remicade's marketing exclusivity for this indication until at least 2018). In June 2019, both Renflexis and Inflectra

were granted the additional FDA-approved indication of pediatric ulcerative colitis. The initial approval of infliximab-axxq (Avsola) in December 2019 already included the pediatric ulcerative colitis indication. Infliximab shares the same labeling and indications as Remicade. Zymfentra's FDA-approval is limited to the maintenance treatment of adults with (1) moderately to severely active ulcerative colitis following treatment with an infliximab product administered IV, and (2) moderately to severely active Crohn's disease following treatment with an infliximab product administered IV. The TNF-alpha inhibitors as a class are considered to have similar efficacy and safety for the majority of indications. In 2018 the National Comprehensive Cancer Network (NCCN) began publishing its guideline Management of Immunotherapy-Related-Toxicities. Infliximab products are recommended (category 2A) for various moderate-to-severe, steroid-refractory, immunotherapy-related adverse effects including diarrhea, colitis, pneumonitis, uveitis, myalgias, myositis, elevated serum creatinine/acute kidney injury, myocarditis and inflammatory arthritis. The NCCN guideline for Hematopoietic Cell Transplantation includes infliximab products as an option (category 2A recommendation) for the treatment of steroid-refractory, acute graft-versus-host disease (GVHD). The American College of Rheumatology Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19 recommend infliximab for the treatment of MIS-C Associated with SARS-CoV-2 in certain situations.

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.

Nonradiographic Axial Spondyloarthritis (nr-axSpA)

Nonradiographic axial spondyloarthritis (nr-axSpA) falls under the same spondyloarthritis family as ankylosing spondylitis (AS). Nr-axSpA is characterized by chronic back pain and features suggestive of spondyloarthritis (SpA), although advanced sacroiliac joint damage and spine ankylosis are absent. The goals of treatment 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 NSAIDs and exercise/physical therapy.

NSAIDs are used as first line therapy for patients with active nr-axSpA, 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.(64) 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 nr-axSpA. 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

Systemic Juvenile Idiopathic Arthritis (SJIA)

Systemic juvenile idiopathic arthritis (SJIA) is a subset of juvenile idiopathic arthritis (JIA). SJIA is distinct from all other categories of JIA due to fever, rash, and visceral involvement. Disease pathogenesis and cytokine involvement in SJIA are different than other JIA categories. SJIA is now considered to be the same disease as adult onset Still's disease (AOSD) under the umbrella term Still's disease, recognizing that the previous distinction of the two disorders by age of onset (before or after 16 years of age) was mainly artificial.

SJIA has been defined as:

- Onset of symptoms occurring before the age of 16 years
- Arthritis in greater than or equal to 1 joint for at least 6 weeks' duration
- Fever of at least 2 weeks' duration (documented to be daily ["quotidian"] for at least 3 days)
- Accompanied by one or more of the following:
    - Evanescent (nonfixed) erythematous rash
    - Generalized lymphadenopathy (lymph node enlargement)
    - Hepatomegaly and/or splenomegaly

- Serositis (pericarditis, pleuritis, and/or peritonitis)

The European Alliance of Associations for Rheumatology (EULAR)/Paediatric Rheumatology European Society (PReS) 2024 guidelines strongly recommend that the presence of arthritis not be mandatory for the diagnosis of Still's disease. Arthralgia is commonly present at disease onset, but arthritis often presents later with a median delay of 1 month. Requiring arthritis to make the diagnosis leads to unnecessary treatment delays. Instead, a patient with fever for at least 7 days, rash, arthralgia/myalgia, and elevated inflammatory markers should be sufficient to facilitate rapid diagnosis and initiate early treatment.

Macrophage activation syndrome (MAS), a secondary hemophagocytic syndrome, is a life-threatening complication requiring urgent recognition and treatment. MAS presents with fever, high ferritin levels, cytopenia, elevated liver enzyme levels, low fibrinogen levels, and high triglyceride levels. As it may occur at any point during the disease course, including during treatment, careful monitoring is necessary for children with or without MAS at presentation. MAS is the most frequent complication, occurring in 15% to 20% of patients. Goals of therapy for SJIA include control of active inflammation and symptoms, and the prevention of a number of disease and/or treatment related morbidities, such as growth disturbances, joint damage, and functional limitations.

An interleukin (IL)-1 or IL-6 inhibitor should be used as initial treatment for SJIA. The IL-1/IL-6 should be initiated as early as possible when the diagnosis of SJIA is established or during a flare, irrespective of disease severity. Early initiation of an IL-1 or IL-6 inhibitor has been shown to have favorable outcomes, limit or avoid corticosteroid use, limit a chronic persistent disease course, and also does not interfere with the diagnostic work-up at onset. EULAR/PReS strongly recommends their use based on their efficacy to control all aspects of the disease, including both systemic and joint manifestations.

Glucocorticoids can be used short-term in patients with severe symptoms, risk of MAS, and/or severe pericarditis. High dose glucocorticoids are the mainstay of treatment in patients with MAS, being added on to biologic therapy. For some patients with MAS, biologic therapy combined with glucocorticoids and calcineurin inhibitors may be necessary to control the disease. Glucocorticoids may also be helpful at disease onset to control systemic and joint manifestations until IL-1 or IL-6 inhibitors can be started.

Non-steroidal anti-inflammatory drugs (NSAIDs) are sometimes used as a brief trial for initial treatment for SJIA without MAS. Studies suggest that a small proportion of patients will respond to NSAIDs alone, however many prescribers prefer that the use of NSAIDs be avoided altogether for SJIA. NSAIDs are typically only used to assist in controlling symptoms, such as fever or arthralgia. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) have historically been used, but evidence supporting their efficacy is scarce. Methotrexate is sometimes used in patients with arthritis.

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.

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.

Hidradenitis Suppurativa (HS)

Hidradenitis suppurativa (HS) is a chronic inflammatory disease causing painful, nodules to form in the folds of the skin and often secrete puss and blood. HS can be described as mild (single or few lesions in one area of the skin, Hurley Stage I), moderate (repeated cycles of enlarged lesions that break open and occur in more than one area of the skin, Hurley Stage II), and severe (widespread lesions, scarring, and chronic pain; Hurley Stage III).

Pharmacological treatment for mild HS includes topical clindamycin, oral tetracyclines, hormonal treatment, retinoids, intralesional corticosteroid injections (i.e., triamcinolone), and deroofing. Oral tetracyclines are recommended for mild to moderate HS for at least a 12-week course or as long-term maintenance. Combination clindamycin and rifampin is effective second-line therapy for mild to moderate HS, or as first-line or adjunct therapy for severe HS. Combination rifampin, moxifloxacin, and metronidazole are recommended as second or third-line therapy for moderate to severe disease.

Dapsone may be effective for a minority of patients with mild to moderate HS as long-term maintenance therapy. Oral retinoids, such as acitretin and isotretinoin, have also been used for mild HS as second or third-line therapy. Hormonal therapy may be considered in female patients for mild to moderate disease as monotherapy, or as adjunct therapy for severe disease. such as hormonal contraceptives, metformin, finasteride, and spironolactone.

Treatment recommendations for moderate to severe and refractory HS include immunosuppressants (e.g., cyclosporine and low dose systemic corticosteroids) and biologic agents. The TNF-inhibitors that are recommended are adalimumab, at doses within FDA labeling, and infliximab, but optimal doses have not been established. Anakinra and ustekinumab may be effective but require dose ranging studies to determine optimal doses for management.

INFLAMMATORY BOWEL DISEASE

Crohn's Disease (CD)

Crohn's disease (CD) is a chronic inflammatory bowel disease with genetic, immunologic, and environmental influences. It can affect any portion of the gastrointestinal tract but involves the small intestine and proximal colon most often. The most common symptom is diarrhea, but abdominal pain, fatigue, fever, weight loss, and vomiting are also prevalent. Symptoms typically occur as a chronic, intermittent course, with only a minority of patients having continuously active symptomatic disease or a prolonged remission. In most cases, CD is a chronic, progressive, destructive disease. Early diagnosis and management of CD can lead to better outcomes and less negative impact on quality of life.

Patients are considered to have moderate to severe disease if they have failed to respond to treatment for mild to moderate disease, or if they present with more prominent symptoms of CD. Inflammation-related biomarkers are more likely to be abnormal, and greater endoscopic disease burden is typical. This includes larger or deeper ulcers, strictures, or extensive areas of disease and/or evidence of stricturing, penetrating, or perianal disease. The International Organization for the Study of Inflammatory Bowel Diseases characterizes patients with severe disease as having at least 10 loose stools per day, daily abdominal pain, presence of anorectal symptoms, systemic corticosteroid use within the prior year, lack of symptomatic improvement despite prior exposure to biologics and/or immunosuppressive agents, or significant impact of the disease on activities of daily living. They are also at a high risk for adverse disease-related complications, including surgery, hospitalization, and disability, based on a combination of structural damage, inflammatory burden, and impact of quality of life. Patients with severe disease may have large or deep mucosal lesions on endoscopy or imaging, presence of fistula and/or perianal abscess, presence of strictures, prior intestinal resections, presence of a stoma, and/or extensive disease (e.g., involvement of long bowel segments, pancolitis).

The choice of therapy in CD is dependent on the anatomic location of the disease, the severity of disease, and whether the treatment is needed to induce remission or maintain remission. The goal of treatment for induction of remission is to achieve clinical response and control of inflammation within 3 months of treatment initiation. After inducing clinical remission, patients should be transitioned to steroid-sparing maintenance therapy. In the absence of immunomodulator or biologic treatment, corticosteroid dependency and/or resistance occurs in up to half of patients. In general, the drug(s) used for induction of remission should be continued as maintenance therapy, with the exception of corticosteroids.

The American Gastroenterological Association (AGA) 2021 guideline provides the following recommendations and guidance:

- Biologic therapy:
    - The AGA suggest early introduction with a biologic, with or without an immunomodulator, rather than delaying their use until after failure of 5-aminosalicylates and/or corticosteroids (Conditional recommendation, low certainty of evidence)
        - Earlier therapy with a biologic may result in overtreating some patients and potentially exposing them to treatment-related risks and costs with limited benefit. However, step-up therapy comes with a potential risk of harm from disease progression related to inadequate disease therapy.

- Anti-tumor necrosis factor (TNF) (i.e., infliximab or adalimumab) and ustekinumab are recommended over no treatment for the induction and maintenance of remission
- Vedolizumab is suggested over no treatment for the induction and maintenance of remission
- AGA suggests against the use of natalizumab over no treatment for the induction and maintenance of remission
- Patients naïve to biologic therapy, the AGA recommends infliximab, adalimumab, or ustekinumab over certolizumab pegol and suggests the use of vedolizumab over certolizumab pegol for the induction of remission
- Patients with primary non-response to anti-TNF, the AGA recommends ustekinumab and suggests vedolizumab for induction of remission
- Patients with secondary non-response to infliximab, the AGA recommends use of adalimumab or ustekinumab and suggests the use of vedolizumab for the induction of remission (if adalimumab was the first line drug, there is indirect evidence to suggest using infliximab as a second-line agent)

- Corticosteroid therapy:
  - Corticosteroids are suggested over no treatment for the induction of remission, and are recommended against for maintenance of remission
    - In patients with CD involving the distal ileum and/or ascending colon who are more concerned about systemic corticosteroids and less concerned about the lower efficacy, they may reasonably choose budesonide over systematic corticosteroids for inducing remission
- Disease modifying antirheumatic drug (DMARD) therapy:
  - Patients in corticosteroid induced remission or with quiescent moderate to severe CD, the AGA suggests thiopurines for maintenance of remission
  - Subcutaneous or intramuscular methotrexate are suggested over no treatment for the induction and maintenance of remission
  - The AGA recommends against the use of 5-aminosalicylates or sulfasalazine over no treatment for the induction or maintenance of remission
  - The AGA suggests against the use of thiopurines over no treatment for achieving remission and recommends biologic drug monotherapy over thiopurine monotherapy for induction of remission
  - The AGA suggests against the use of oral methotrexate monotherapy over no treatment for the induction and maintenance of remission
- Combination therapy:
  - Patients that are naïve to biologics and immunomodulators, the AGA suggest use of infliximab in combination with thiopurines over infliximab monotherapy for the induction and maintenance of remission (combination infliximab with methotrexate may be more effective over infliximab monotherapy)
  - Patients that are naïve to biologics and immunomodulators, the AGA suggest use of adalimumab in combination with thiopurines over adalimumab monotherapy for the induction and maintenance of remission (combination adalimumab with methotrexate may be more effective over adalimumab monotherapy)
  - No recommendations are being made regarding the use of ustekinumab or vedolizumab in combination with thiopurines or methotrexate over biologic monotherapy for induction or maintenance or remission

The American College of Gastroenterology (ACG) 2025 guideline provides the following recommendations and guidance:

- Biologic therapy:
  - Biologic agents are effective for treating patients with active CD and previous inadequate response to corticosteroids, thiopurines, and/or methotrexate
  - Suggest against requiring failure of conventional therapy before initiation of advanced therapy for the management of CD (conditional recommendation, low level of evidence)
    - The risk of adverse effects and high cost of biologic agents may not be justifiable in a lower risk population
  - Recommend the following drugs for induction and maintenance of remission for moderately to severely active CD:
    - Anti-TNF agents (i.e., infliximab, adalimumab, certolizumab), vedolizumab, ustekinumab, risankizumab, mirikizumab, guselkumab
  - Recommend combination therapy of intravenous infliximab with immunomodulators (thiopurines) as compared with treatment with either immunomodulators alone or intravenous infliximab alone in patients with CD who are naïve to those agents
  - Recommend the use of risankizumab as compared with ustekinumab in patients with moderate to severe CD and prior exposure to anti-TNF therapy
  - Biosimilar infliximab, adalimumab, and ustekinumab are effective treatments for patients with moderate-to-severe CD and can be used for de novo induction and maintenance therapy
  - There are data to support the safety and efficacy of transitioning or switching to biosimilar infliximab or adalimumab for patients with CD in stable disease maintenance
- Janus kinase (JAK) inhibitor therapy:
  - Recommend upadacitinib use for induction and maintenance of remission for patients with moderate-to-severe CD who have previously been exposed to anti-TNF agents
- Corticosteroid therapy:
  - Recommend oral corticosteroids for short-term induction of remission in patients with moderately to severely active CD
    - Recommend controlled ileal release budesonide at a dose of 9 mg daily for induction of symptomatic remission in patients with mildly to moderately active ileocecal CD
  - Corticosteroids should not be used for maintaining remission, and their use should not exceed 3 continuous months without attempting to introduce a steroid-sparing agent (such as an immunomodulator)
- DMARD therapy:
  - Recommend against azathioprine or 6-mercaptopurine for induction of remission in moderately to severely active CD
    - Due to their slow onset of action of 8 to 12 weeks, thiopurines are not effective agents for induction of remission
  - Suggest azathioprine or 6-mercaptopurine for maintenance of remission in patients with moderately to severely active CD who had induction of remission with corticosteroids
  - Suggest methotrexate (up to 25 mg once weekly intramuscular or subcutaneous) for maintenance of remission in patients with moderately to severely active CD who had induction of remission with corticosteroids
  - Azathioprine, 6-mercaptopurine, or methotrexate may be used in the treatment of active CD and as adjunctive therapy for reducing immunogenicity associated with anti-TNF therapy

Ulcerative Colitis (UC)

Ulcerative colitis (UC) is a chronic inflammatory bowel disease affecting the large intestine. It typically starts with inflammation of the rectum, but often extends proximally to involve additional areas of the colon. The most common symptom is bloody diarrhea, but urgency, tenesmus, abdominal pain, malaise, weight loss, and fever can also be associated. UC commonly has a gradual onset and will present with periods of spontaneous remission and subsequent relapses.

Disease severity is based on patient-reported outcomes (e.g., bleeding, bowel habits, bowel urgency), inflammatory burden (e.g., endoscopic assessment, inflammatory markers), disease course, and disease impact. Commonly assessed symptoms include frequency and timing of bowel movements, rectal bleeding, bowel urgency, abdominal pain, bowel cramping, and weight loss. Poor prognostic factors include less than 40 years of age at diagnosis, extensive colitis, severe endoscopic disease, hospitalization for colitis, elevated C-reactive protein (CRP), and low serum albumin. Therapeutic management in UC should be guided by the extent of bowel involvement, assessment of disease activity (i.e., quiescent, mild, moderate, or severe), and disease prognosis. Treatment response should be evaluated 12 weeks after initiation of therapy to confirm efficacy and safety.

The American College of Gastroenterology (ACG) published recommendations and guidance (2025) for the management of moderate-to-severe UC:

<u>General treatment information</u>:

- Patients with mildly to moderately active UC and a number of prognostic factors associated with an increased risk of hospitalization or surgery should be treated with therapies for moderate-to-severe disease
- Patients with mildly to moderately active UC who are not responsive (or are intolerant) to 5-aminosalicylate (5-ASA) therapies (e.g., balsalazide, mesalamine, sulfasalazine) should be treated as patients with moderate-to-severe disease

<u>Corticosteroid therapy</u>:

- In patients with moderately active UC, recommend oral budesonide multi-matrix system (MMX) for induction of remission
    - In patients with moderately active UC, consider nonsystemic corticosteroids such as budesonide MMX before the use of systemic therapy
- Recommend oral systemic corticosteroids to induce remission in UC of any extent
    - In patients with severely active UC, consider systemic corticosteroids rather than topical corticosteroids
- Recommend against systemic, budesonide MMX, or topical corticosteroids for maintenance of remission

<u>Disease modifying antirheumatic drug (DMARD) therapy</u>:

- Recommend against monotherapy with thiopurines or methotrexate for induction of remission
- 5-ASA therapy could be used as monotherapy for induction of moderately but not severely active UC
- 5-ASA therapy for maintenance of remission is likely not as effective in prior severely active UC as compared with prior moderately active UC
- Suggest thiopurines for maintenance of remission in patients now in remission due to corticosteroid induction
- Suggest against using methotrexate for maintenance of remission

<u>Biologic/advanced therapy</u>:

- Recommend the following drugs for induction of remission and continuing the same drug for maintenance of remission:

- Anti-tumor necrosis factor (TNF) agents (e.g., infliximab, adalimumab, golimumab), ustekinumab, guselkumab, mirikizumab, risankizumab, vedolizumab, tofacitinib, upadacitinib, sphingosine-1-phosphate (S1P) receptor modulators (e.g., ozanimod, etrasimod)
- Most clinical trials and available data demonstrate a benefit of using the steroid-sparing therapy that induces remission to maintain that remission

- When infliximab is used as induction therapy, recommend combination therapy with a thiopurine
  - Data on combination anti-TNF and immunomodulators in moderately to severely active UC only exist for infliximab and thiopurines
- Infliximab is the preferred anti-TNF therapy for patients with moderately to severely active UC
- Recommend vedolizumab as compared to adalimumab for induction and maintenance of remission
- Patients who are primary nonresponders to an anti-TNF (defined as lack of therapeutic benefit after induction and despite sufficient serum drug concentrations) should be evaluated and considered for alternative mechanisms of disease control (e.g., in a different class of therapy) rather than cycling to another drug within the anti-TNF class
- Biosimilars to anti-TNF therapies and to ustekinumab are acceptable substitutes for originator therapies. Delays in switching should not occur and patients and clinicians should be notified about such changes

The American Gastroenterology Association (AGA) published recommendations and guidance (2018) for the management of mild-to-moderate UC:

- In patients with moderate disease activity, suggest using high dose mesalamine (greater than 3 g/day) with rectal mesalamine for induction of remission and maintenance of remission
- Add either oral prednisone or budesonide MMX in patients that are refractory to optimized oral and rectal 5-ASA, regardless of disease extent
- If progression to moderate-to-severe disease activity occurs, or if the patient is at high risk for colectomy despite therapy, consider escalating to treatment for moderate-to-severe disease with immunomodulators and/or biologics

The American Gastroenterology Association (AGA) published recommendations and guidance (2024) for the management of moderate-to-severe UC:

<u>General treatment information</u>:

- Suggest early use of advanced therapy (e.g., biologics, ozanimod, etrasimod), with or without immunomodulator therapy (e.g., thiopurines), rather than treatment with 5-ASA and a gradual step up to biologic/immunomodulator therapy after 5-ASA treatment failure (conditional recommendation, very low certainty of evidence)
  - Patients with less severe disease or those who place a higher value on the safety of 5-ASA therapy over the efficacy of immunosuppressives may reasonably choose gradual step therapy with 5-ASA therapy

<u>DMARD therapy</u>:

- Suggest against using thiopurine monotherapy for inducing remission
- Suggest thiopurine monotherapy may be used for maintaining remission typically induced with corticosteroids
- Suggest against using methotrexate monotherapy for inducing or maintaining remission

<u>Advanced therapy</u>:

- Recommend using one of the following advanced therapies over no treatment:

- Infliximab, golimumab, vedolizumab, tofacitinib, upadacitinib, ustekinumab, ozanimod, etrasimod, risankizumab, guselkumab

- Suggest using one of the following advanced therapies over no treatment:
  - Adalimumab, filgotinib*, mirikizumab (*not currently approved by the Food and Drug Administration)
- Biosimilars of infliximab, adalimumab, and ustekinumab can be considered equivalent to their originator drug in their efficacy
- Suggest the use of infliximab in combination with an immunomodulator over infliximab or an immunomodulator alone
- Suggest the use of adalimumab or golimumab in combination with an immunomodulator over adalimumab, golimumab or immunomodulator monotherapy

Advanced therapy-naïve patients (first-line therapy):

- Suggest that a higher or intermediate efficacy medication be used rather than a lower efficacy medication
  - Higher efficacy: infliximab, vedolizumab, ozanimod, etrasimod, upadacitinib, risankizumab, guselkumab
  - Intermediate efficacy: golimumab, ustekinumab, tofacitinib, filgotinib, mirikizumab
  - Lower efficacy: adalimumab

Prior exposure to one or more advanced therapies, particularly TNF antagonists:

- Suggest that a higher or intermediate efficacy medication be used rather than a lower efficacy medication
  - Higher efficacy: tofacitinib, upadacitinib, ustekinumab
  - Intermediate efficacy: filgotinib, mirikizumab, risankizumab, guselkumab
  - Lower efficacy: adalimumab, vedolizumab, ozanimod, etrasimod

OTHER DISORDERS

Uveitis

Uveitis is characterized by inflammation of the portion of the eye known as the uvea, with the anterior portion of uvea including the iris and ciliary body and the posterior portion being the choroid. Uveitis can cause redness, pain, decreased or loss of vision, worsening field changes, and floaters involving the eye. Uveitis is subdivided into four types based on the primary anatomical location of the inflammation: anterior, intermediate, posterior, and panuveitis. Intermediate uveitis is defined by inflammation of the vitreous cavity and pars plana, posterior uveitis involves the retina and choroid, and panuveitis includes all layers. Uveitis can be caused by infections, inflammatory diseases, or trauma, or be idiopathic in nature.

The goal of treatment in uveitis is to suppress ocular inflammation and achieve an inactive disease state or drug-induced remission. Treatment of non-infectious uveitis (NIU) depends on the location of inflammation. Intermediate, posterior, and panuveitis treatment is complex and should be guided by an ophthalmologist or uveitis specialist. NIU should be treated early and aggressively to prevent complications and preserve sight, with corticosteroids being used initially to suppress inflammation. Oral corticosteroids are the mainstay of treatment, but periocular or intravitreal corticosteroid injections may also be used to limit systemic effects. Treatment with conventional systemic agents (i.e., azathioprine, mycophenolate, methotrexate[MTX], cyclosporine, tacrolimus) may be introduced to control persistent or severe inflammation, or to prevent ocular structural complications. They may also be used if there is a need for a corticosteroid-sparing effect in chronic disease or to maintain disease remission. MTX is used

most commonly, with mycophenolate being used if MTX was ineffective, not tolerated, or contraindicated. A conventional immunomodulatory agent should be used for at least three months before assuming that it is not effective.

Adalimumab, a tumor necrosis factor (TNF)-inhibitor, is generally considered for treatment in patients whose disease is inadequately controlled by corticosteroids and conventional systemic agents. TNF-inhibitors are effective in most cases, but they may eventually lose their effect and require an escalation in dose. This loss of effect is primarily due to an immune response targeting the drug itself. The concurrent use of an antimetabolite (e.g., MTX or mycophenolate) may prolong the effectiveness of the biologic.

Giant Cell Arteritis (GCA)

Giant cell arteritis (GCA) is a blood vessel disease that predominantly affects medium to large arteries in individuals older than 50 years of age, causing clinical manifestations in both cranial and extracranial locations. The cranial phenotype is characterized by headache, jaw claudication, and visual disturbance or loss. The extracranial phenotype is characterized by musculoskeletal involvement with symptoms associated with polymyalgia rheumatica, such as pain, stiffness, and limited range of motion around the shoulders, neck, and hips. Treatment should begin as soon as the diagnosis is made to prevent loss of vision or blindness.

The American College of Rheumatology/Vasculitis Foundation guidelines (2021) recommend high-dose systemic glucocorticoids as the mainstay of therapy for GCA. The guidelines provide the following recommendations for the management of GCA:

- Patients with newly diagnosed active GCA with visual symptoms/loss or critical cranial ischemia:
    - High dose IV pulse corticosteroids followed by high dose oral corticosteroids with or without a non-corticosteroid immunosuppressive agent (i.e., methotrexate or tocilizumab)
    - Taper oral corticosteroids in patients that achieve remission
    - Consider adding on or changing non-corticosteroid immunosuppressive agent in patients that have not achieved remission
- Patients with newly diagnosed active GCA without visual symptoms/loss or critical cranial ischemia:
    - High dose oral corticosteroids with or without a non-corticosteroid immunosuppressive agent (i.e., methotrexate or tocilizumab)
    - Taper oral corticosteroids in patients that achieve remission
    - Consider adding on or changing non-corticosteroid immunosuppressive agent in patients that have not achieved remission

Cryopyrin-Associated Periodic Syndromes (CAPS)/Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

Cryopyrin-associated periodic syndrome (CAPS) is a rare autosomal dominant hereditary autoimmune disorder associated with a defect in the cryopyrin protein. CAPS syndrome is caused by a gain of function mutation in the NLRP3 gene leading to over secretion of fever causing cytokine interleukin (IL)-1B. The CAPS spectrum includes mild, moderate, and severe phenotypes. The mild phenotype is called familial cold autoinflammatory syndrome (FCAS), the moderate phenotype is also known as Muckle-Wells syndrome (MWS), and the neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous articular syndrome (CINCA) describes the severe phenotype. CAPS is diagnosed clinically and genetically. There are more than 240 sequence variants of the NLRP3 gene and mutations in this gene are not inclusive of a CAPS diagnosis. The diagnostic criteria of CAPS recognize that all but a few patients with CAPS have detectable systemic inflammation and use unique CPS-specific clinical features along the whole disease spectrum to achieve reasonable specificity and sensitivity to aid clinicians in making the CAPS diagnosis. These diagnostic criteria does not include genetic confirmation

and can be applied to all CAPS subtypes regardless of NLRP3 mutation. The diagnostic criteria for CAPS are as follows:

- Raised inflammatory markers (C-reactive protein [CRP]/serum amyloid A [SAA]), AND
- The presence of at least two of the following signs/symptoms:
    - Urticaria-like rash
    - Cold/stress triggered episodes
    - Sensorineural hearing loss
    - Musculoskeletal symptoms of arthralgia/arthritis/myalgia
    - Chronic aseptic meningitis
    - Skeletal abnormalities of epiphyseal overgrowth/frontal bossing

Goals of treatment include suppressing systemic inflammation, improving functionality, preventing organ damage, and improving quality of life. IL-1 blocking therapy is the preferred treatment for CAPS and is the recommended standard of care. IL-1 blocking therapies control inflammation in the absence of corticosteroids. Current IL-1 blocking therapies include anakinra, canakinumab, and rilonacept. Each of these drugs blocks the effect of IL-1B on the IL-1 receptor and downstream signaling.

Behcet's Disease (BD)

BD is a chronic systemic inflammatory disease, defined as a variable vessel vasculitis, characterized by mucocutaneous lesions and involves numerous organ systems (e.g., mucocutaneous, musculoskeletal, ocular, vascular, neurologic, and gastrointestinal). BD has a relapsing-remitting course of disease and usually begins in the second or third decade of life. Recurring oral ulcers are seen in over 95% of patients and are typically the first clinical manifestation of the disease, usually preceding the diagnosis by an average of 6 to 7 years. No disease specific laboratory, histopathologic, or genetic findings exist to diagnose a patient with BD, and instead the diagnosis is mainly based on clinical presentation and findings. The International Study Group (ISG) criteria for the diagnosis of BD should be considered when diagnosing people with suspected BD. It is the most widely used diagnosis criteria and has been shown to have 95% sensitivity and 98% specificity. In order to meet ISG criteria, a patient must have recurrent oral ulceration, with at least three occurrences during a 12-month period.

The goal of treatment in patients with BD is to suppress inflammatory exacerbations and recurrences to prevent irreversible organ damage. Disease manifestations may improve over time in many patients. Ocular, vascular, neurological, and gastrointestinal involvement may be associated with a poor prognosis. Treatment needs to be individualized based on the type and severity of organ involvement, and a multidisciplinary approach is necessary for optimal care. Skin, mucosa, and joint involvement can impair a patient's quality of life but typically does not cause permanent damage. However, if scarring occurs due to chronic oral ulceration, vigorous treatment is needed to prevent oropharyngeal narrowing.

For the treatment of an acute exacerbation of oral ulcers, a topical corticosteroid (i.e., triamcinolone acetonide oral paste) should be used as it may help with the rapid healing of the lesions. A topical corticosteroid may also be used as adjunctive therapy with a systemic immunosuppressant in patients with more severe disease. If topical corticosteroid therapy alone is inadequate to control the disease, colchicine should be used to treat mucocutaneous lesions. Colchicine should be tried first for the prevention of recurrent mucocutaneous lesions due to its safety and tolerability. If lesions continue to recur despite colchicine, immunomodulatory or immunosuppressive agents, such as azathioprine or apremilast, can be used.

Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a non-antigen specific toxicity that occurs due to a high-level immune activation, secondary to receiving cancer immunotherapy and CAR T-cell therapy. Large numbers of lymphocytes and/or myeloid cells release inflammatory cytokines when they become

activated. Symptoms and severity depend on the level of immune activation and the inducing agent. Fever is the hallmark symptom of CRS, and potential life-threatening complications can include cardiac dysfunction, respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation. CRS severity is graded on a scale of 1 to 5, with 5 being death. The American Hematology Association recommends symptomatic treatment for grade 1 CRS and notes immunosuppressive therapy may be used to treat grade 2 with extensive co-morbidities or advanced age. Grades 3 and 4 should be treated with immunosuppression in an attempt to suppress the inflammatory cascade and prevent irreversible organ damage. Tocilizumab is recommended as the first line immunosuppressive therapy with or without corticosteroids.

Infliximab Dosing

The use of TNF-inhibitors has been associated in some patients with the development of anti-drug antibodies, which may promote adverse effects and diminish drug efficacy. The formation of anti-drug antibodies, especially drug-neutralizing antibodies, is a concern with biologic TNF inhibitors, particularly monoclonal antibody agents, infliximab and adalimumab, and most likely, biosimilars to these original drugs. Antidrug antibodies may cause allergic reactions, loss of responsiveness, and increased cost of therapy. The risk of developing antibodies appears least common with the use of etanercept, a receptor fusion protein, and most common with infliximab, a chimeric antibody construct. In drug-naïve patients, serum anti-drug antibodies are usually detected within 2 to 6 months or starting therapy and rarely after 12 months of treatment.

Neutralizing anti-infliximab antibodies, frequently associated with absent trough levels of the drug and response failure, are a significant concern with infliximab. The anti-drug antibodies are predominantly directed against the mouse portions of the infliximab molecule and are thus sometimes referred to as human anti-chimeric antibodies (HACA). Antibodies have been described in patients with RA, inflammatory bowel disease, and other disorders. HACA directed against infliximab develop in about half of the patients treated with infliximab alone, without other immunosuppressive or anti-inflammatory drug therapies. This proportion can be reduced by co-administration of MTX and other immune modulators. Infliximab was approved for use in RA in the US and Europe in combination with MTX. However, the same restriction does not apply to labeling approved for ankylosing spondylitis, inflammatory bowel disease, and psoriasis, where clinical studies of the effect of MTX co-therapy on drug immunogenicity differ considerably. Shortening drug interval or increasing regular dose has been correlated with the formation of HACA, but the loss of efficacy may also result from the inflammatory disease process no longer being driven by TNF. This seems to be the case in some patients after prolonged TNF inhibition. Some patients with RA or Crohn’s disease benefit from infliximab given at doses higher than the recommended 3 mg/kg or more frequently than 8 weeks.

Incorporating immunopharmacologic data regarding circulating drug and anti-drug antibody levels has been proposed to rationalize the usual approach to lessening clinical efficacy of infliximab, which typically either is to increase the dose or to increase the frequency with which the medication is administered. In a randomized prospective trial involving 69 patients with Crohn disease and secondary infliximab failure, the use of an algorithm for dose adjustment based upon the measurement of circulating infliximab and anti-infliximab antibody levels reduced the average treatment costs per patient by 50% without compromising clinical efficacy. Further clinical studies are needed for extrapolation to infliximab biosimilars and/or to other TNF biologics as well as to other TNF-dependent immune disease. However, testing for HACA is not widely available, and most assays measure binding of antibodies to drug but not whether this binding has neutralizing effect in vivo.

Patients who achieve an adequate response (based on clinical endoscopic and laboratory findings) to initial therapy will require repeat infusions of 5 mg/kg, usually every 8 weeks to maintain remission. Patients who have disease flare while on maintenance dosing can be managed by escalating the dose. This can be achieved by either decreasing the dosing interval (e.g., from 8 weeks to 6 weeks) or by increasing the dose (e.g., from 5 mg/kg to 10 mg/kg). The maximal dose of infliximab is 10 mg/kg every 4 weeks.

POSITION STATEMENT:

Site of Care: If intravenous infliximab products [infliximab (Remicade), Infliximab, infliximab-dyyb (Inflectra), infliximab-abda (Renflexis), or infliximab-axxq (Avsola)] are 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 subcutaneously-administered 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) of the subcutaneous formulation of infliximab products in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary. This statement does not apply to the intravenous (IV) formulation of infliximab products.

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

SUBCUTANEOUS INFLIXIMAB PRODUCTS (PHARMACY BENEFIT)

Initiation of subcutaneous infliximab-dyyb (Zymfentra) **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 subcutaneous infliximab-dyyb (Zymfentra) (starting on samples is not approvable) within the past 90 days
    b. The prescriber states the member has been treated with subcutaneous infliximab-dyyb (Zymfentra) (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. Subcutaneous infliximab-dyyb (Zymfentra) 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 subcutaneous infliximab-dyyb (Zymfentra)
            II. The prescriber has provided information in support of subcutaneous infliximab-dyyb (Zymfentra) 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., gastroenterologist for CD or UC) 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 subcutaneous infliximab-dyyb (Zymfentra)
4. Member will **NOT** be using subcutaneous infliximab-dyyb (Zymfentra) 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), 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 120 mg subcutaneously once every 2 weeks [for members new to infliximab therapy - to be started 4 weeks after the third loading dose of an IV infliximab product]

- QL: 120 mg/mL pen – 2 pens/28 days
- QL: 120 mg/mL syringe – 2 syringes/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; the start date will depend on the number of IV doses of an infliximab product already received

Table 1

Indications and Specific Criteria	
Indication	**Specific Criteria**
Moderately to severely active Crohn's disease (CD)	**ALL** of the following ("1", "2", and "3"): 1. **ONE** of the following: a. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., 6-mercaptopurine, azathioprine, corticosteroids [e.g., prednisone, budesonide EC capsule], methotrexate) used in the treatment of CD after at least a 3-month duration of therapy **OR** b. The member has an intolerance or hypersensitivity to **ONE** conventional agent used in the treatment of CD **OR** c. The member has an FDA labeled contraindication to **ALL** conventional agents used in the treatment of CD **OR** d. 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 CD **AND** 2. **ANY** of the following (submitted medical records/chart notes are required for confirmation): a. The member has tried and had an inadequate response to at least **TWO** preferred products for at least a 3-month trial per product **OR** b. The member has tried and had an inadequate response to **ONE** preferred product after at least a 3-month duration of therapy, **AND** an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to **ONE** preferred product **OR** c. The member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to at least **TWO** preferred products **OR** d. The member has an FDA labeled contraindication to **ALL** preferred products e. **ALL** preferred products are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried products for the requested indication

	The preferred CD products are: • Adalimumab-aaty • Adalimumab-adaz • Entyvio (vedolizumab) subcutaneous injection • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Selarsdi (ustekinumab-aekn) • Simlandi (adalimumab-ryvk) • Skyrizi (risankizumab-rzaa) • Stelara (ustekinumab) • Steqeyma (ustekinumab-stba) • Tremfya (guselkumab) • Yesintek (ustekinumab-kfce) **AND** 3. The member has received or will receive an infliximab IV product for induction therapy
Moderately to severely active ulcerative colitis (UC)	**ALL** of the following ("1", "2", and "3"): 1. **ONE** of the following: a. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., 6-mercaptopurine, azathioprine, balsalazide, corticosteroids, cyclosporine, mesalamine, sulfasalazine) used in the treatment of UC after at least a 3-month duration of therapy **OR** b. The member has an intolerance or hypersensitivity to **ONE** conventional agent used in the treatment of UC **OR** c. The member has an FDA labeled contraindication to **ALL** conventional agents used in the treatment of UC **OR** d. 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 UC **AND** 2. **ANY** of the following (submitted medical records/chart notes are required for confirmation): a. The member has tried and had an inadequate response to at least **TWO** preferred products for at least a 3-month trial per product

	OR b. The member has tried and had an inadequate response to **ONE** preferred product after at least a 3-month duration of therapy, **AND** an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to **ONE** preferred product **OR** c. The member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to at least **TWO** preferred products **OR** d. The member has an FDA labeled contraindication to **ALL** preferred products **OR** e. **ALL** preferred products are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried products for the requested indication **The preferred UC products are:** • Adalimumab-aaty • Adalimumab-adaz • Entyvio (vedolizumab) subcutaneous injection • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Selarsdi (ustekinumab-aekn) • Skyrizi (risankizumab-rzaa) • Simlandi (adalimumab-ryvk) • Stelara (ustekinumab) • Steqeyma (ustekinumab-stba) • Tremfya (guselkumab) • Xeljanz/Xeljanz XR (tofacitinib) • Yesintek (ustekinumab-kfce) **AND** 3. The member has received or will receive an infliximab IV product for induction therapy

Continuation of subcutaneous infliximab-dyyb (Zymfentra) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "6"):

1. An authorization or reauthorization for subcutaneous infliximab-dyyb (Zymfentra) 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 subcutaneous infliximab-dyyb (Zymfentra)
3. The prescriber is a specialist in the area of the member's diagnosis (e.g., gastroenterologist for UC) 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 subcutaneous infliximab-dyyb (Zymfentra)
5. Member will **NOT** be using subcutaneous infliximab-dyyb (Zymfentra) 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), 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 120 mg subcutaneously once every 2 weeks
        - QL: 120 mg/mL pen – 2 pens/28 days
        - QL: 120 mg/mL syringe – 2 syringes/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

INTRAVENOUS INFLIXIMAB PRODUCTS (MEDICAL BENEFIT)

Initiation of an intravenous (IV) infliximab product [infliximab (Remicade), Infliximab, infliximab-abda (Renflexis), infliximab-dyyb (Inflectra), or infliximab-axxq (Avsola)] **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "4"):

1. The IV infliximab product will be used for the treatment of an indication listed in Table 2, and **ALL** of the indication-specific and maximum-allowable dose criteria are met
2. The prescriber is a specialist in the area of the member's diagnosis (e.g., rheumatologist for PsA, RA; gastroenterologist for CD, UC; 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 the IV infliximab product
4. Member will **NOT** be using the IV infliximab product 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), 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)]

Approval duration: 6 months [all indications except Kawasaki disease, MIS-C Associated with SARS-CoV-2, IEC-associated enterocolitis specific to BCMA-directed CAR T-cell therapy, and immune checkpoint inhibitor-related adverse effects/toxicity – one-time dose for Kawasaki disease and MIS-C Associated with SARS-CoV-2; and 60-day approval for immune checkpoint inhibitor-related adverse effects/toxicity, IEC-associated enterocolitis specific to BCMA-directed CAR T-cell therapy, and acute GVHD]

Table 2

Indications and Specific Criteria		
Indication	**Specific Criteria**	**Maximum Allowable Dose***
Acute graft-versus-host disease (GVHD)	**ALL** of the following: 1. The member has previously received an allogeneic hematopoietic stem cell transplantation (HSCT) 2. Infliximab will be used as additional therapy in conjunction with systemic corticosteroids 3. The member has steroid-refractory disease	• 10 mg/kg once weekly for up to 8 total doses

Active ankylosing spondylitis (AS)	**ONE** of the following: 1. The member has tried and had an inadequate response to **TWO** different NSAIDs used in the treatment of AS for at least a 4-week TOTAL 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	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10
Active non-radiographic axial spondyloarthritis (nr-axSpA)	**ONE** of the following: 1. The member has tried and had an inadequate response to **TWO** different NSAIDs used in the treatment of nr-axSpA for 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** NSAIDs used in the treatment of nr-axSpA **OR**	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10

	4. The member has an FDA labeled contraindication to **ALL** NSAIDs used in the treatment of nr-axSpA **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 nr-axSpA	
Behçet's disease	**BOTH** of the following: 1. Member has **ANY** of the following: • arterial involvement (e.g., pulmonary artery aneurysms) • eye involvement (uveitis) • joint involvement • gastrointestinal involvement • mucocutaneous ulcerations • nervous system involvement • venous thrombosis 2. The member has had inadequate response(s) to, intolerable adverse effect(s) with, or contraindication(s) to treatment with the following depending on the area of involvement. If multiple areas are involved, the least restrictive requirement applies. • arterial involvement a. corticosteroids b. cyclophosphamide • eye or nervous system involvement a. none • joint involvement a. azathioprine b. colchicine • gastrointestinal involvement a. azathioprine b. corticosteroids • mucocutaneous ulcerations a. apremilast (Otezla) b. azathioprine	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10

	c. colchicine • venous thrombosis a. azathioprine b. corticosteroids	
Moderately to severely active Crohn's disease (CD)	**ONE** of the following: 1. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., 6-mercaptopurine, azathioprine, corticosteroids [e.g., prednisone, budesonide EC capsule], methotrexate) used in the treatment of CD 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 CD **OR** 3. The member has an FDA labeled contraindication to **ALL** conventional agents used in the treatment of CD **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 CD **OR** 5. The member has severe disease and/or risk factors for disease complications for which initial treatment with an infliximab product is deemed clinically necessary - provider must include additional details regarding disease severity and/or risk factors	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10
Fistulizing CD	Member has CD with one or more draining fistulas for at least 3 months	
Moderate to severe hidradenitis suppurativa (HS)	**ONE** of the following: 1. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., oral tetracyclines [doxycycline, minocycline, tetracycline]; oral contraceptives [females only]; metformin [females only]; finasteride [females only]; spironolactone [females only]; intralesional corticosteroids [triamcinolone]; clindamycin in combination with rifampin; combination of	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10

	rifampin, moxifloxacin, and metronidazole; cyclosporine, oral retinoids) used in the treatment of HS 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 HS **OR** 3. The member has an FDA labeled contraindication to **ALL** conventional agents used in the treatment of HS **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 HS	
Immune checkpoint inhibitor-related adverse effects/toxicity	**BOTH** of the following: 1. Member has been receiving treatment with an immune checkpoint inhibitor (e.g., ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, darvalumab) **AND** 2. The member has one or more of the following adverse events: a. Mild (Grade 1) diarrhea or colitis if persistent or progressive symptoms **AND** positive lactoferrin/calprotectin b. Moderate or severe diarrhea and colitis (Grades 2 to 4) if colonoscopy or flexible sigmoidoscopy shows significant ulceration or extensive non-ulcerative inflammation c. Moderate to severe esophagitis, gastritis, or duodenitis if no improvement on corticosteroids or budesonide d. Moderate or severe inflammatory arthritis if unable to taper corticosteroids after 1 week c. Myocarditis as additional immunosuppression if no improvement within 24 to 48 hours of starting high-dose methylprednisolone	• 10 mg/kg for up to 3 total doses in a 2-month period

	e. Moderate (Grade 2) pneumonitis if no improvement after 48 to 72 hours of corticosteroids f. Severe (Grade 3 or 4) pneumonitis if no improvement after 48 hours of methylprednisolone g. Severe (Grade 4) hemolytic anemia with hemolysis if no response to BOTH corticosteroids **AND** a rituximab product d. Stage 3 acute kidney injury or elevated serum creatinine if toxicity remains >stage 2 after 4 to 6 weeks of corticosteroids **OR** if creatinine increases during steroid taper (or once off steroids) e. Uveitis that is refractory to high-dose systemic corticosteroids (treatment guided by ophthalmology	
Immune effector cell (IEC)-associated enterocolitis specific to B-cell maturation antigen (BCMA)-directed CAR T-cell therapy	**BOTH** of the following: 1. The member has previously received a BCMA-directed CAR T-cell therapy [e.g., idecabtagene vicleucel (Abecma), ciltacabtagene autoleucel (Carvykti)] **AND** 2. Member has steroid-refractory diarrhea **OR** recurrent diarrhea following a steroid taper	• 10 mg/kg for up to 3 total doses in a 2-month period
Kawasaki disease	Member has had an inadequate response to, intolerable adverse effect with, or a contraindication to treatment with intravenous immunoglobulin (IVIG) [the specific adverse effect or contraindication must be provided]	• 10 mg/kg X 1 dose
Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2	**ALL** of the following: 1. Member is less than 18 years of age **AND** 2. Member has been previously infected with SARS-CoV-2 **AND** 3. Member's symptoms are severe enough that hospitalization is required **AND** 4. **EITHER** of the following: a. Member is refractory to IVIG **AND** glucocorticoids **OR**	• 10 mg/kg X 1 dose

	b. Member has contraindications to long-term use of glucocorticoids	
Psoriasis (PS)	**BOTH** of the following: 1. Member has one of the following subtypes: a. Erythrodermic psoriasis b. Plaque psoriasis c. Pustular psoriasis 2. **ONE** of the following: a. 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** b. The member has an intolerance or hypersensitivity to **ONE** conventional agent used in the treatment of PS **OR** c. The member has an FDA labeled contraindication to **ALL** conventional agents used in the treatment of PS **OR** d. 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** e. 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** f. The member's medication history indicates use of another biologic immunomodulator agent **OR** Otezla that	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10

	is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PS	
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 that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PsA	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10
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**	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10

	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** of the following conventional agents (i.e., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** 5. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of RA	
Takayasu arteritis (a.k.a., Takayasu's disease and aortic arch syndrome)	**BOTH** of the following: 1. Member's disease is refractory to, or member has intolerable adverse effect(s) with or a contraindication to oral immunosuppressive therapy (e.g., cyclophosphamide, methotrexate, azathioprine) **AND** 2. Member's disease is refractory to or member has intolerable adverse effect(s) with or a contraindication to systemic corticosteroids	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10
Moderately to severely active ulcerative colitis (UC)	**ONE** of the following: 1. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., 6-mercaptopurine, azathioprine, balsalazide, corticosteroids, cyclosporine, mesalamine, sulfasalazine) used in the treatment of UC after at least a 3-month duration of therapy **OR**	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10

	2. The member has an intolerance or hypersensitivity to **ONE** conventional agent used in the treatment of UC **OR** 3. The member has an FDA labeled contraindication to **ALL** conventional agents used in the treatment of UC **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 UC **OR** 5. The member has severe disease and/or risk factors for disease complications for which initial treatment with an infliximab product is deemed clinically necessary - provider must include additional details regarding disease severity and/or risk factors	
Uveitis	Uveitis associated with Behcet's disease – see Behcet's disease indication in Table Uveitis associated with JIA **ANY** of the following: 1. Member has severe active uveitis with sight-threatening complications **OR** 2. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., methotrexate, leflunomide) used in the treatment of PJIA for at least 3 months **OR** 3. The member has an intolerance or hypersensitivity to **ONE** conventional agent used in the treatment of PJIA **OR** 4. The member has an FDA labeled contraindication to **ALL** conventional agents used in the treatment of PJIA **OR** 5. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10

	DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PJIA Uveitis **NOT** associated with Behcet's syndrome or JIA: **ONE** of the following: 1. **BOTH** of the following: A. **ONE** of the following: i. The member has tried and had an inadequate response to **ONE** oral corticosteroid used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis after at least a 2-week duration of therapy **OR** ii. The member has tried and had an inadequate response to **ONE** periocular or intravitreal corticosteroid injection used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis **OR** iii. The member has an intolerance or hypersensitivity to **ONE** oral corticosteroids **or** periocular or intravitreal corticosteroid injections used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis **OR** iv. The member has an, FDA labeled contraindication to **ALL** oral corticosteroids and periocular/intravitreal corticosteroids used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis **AND** B. **ONE** of the following: i. The member has tried and had an inadequate response to **ONE** conventional systemic agent (i.e., azathioprine, mycophenolate,	

	methotrexate, cyclosporine, tacrolimus) used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis after at least a 3-month duration of therapy **OR** ii. The member has an intolerance or hypersensitivity to **ONE** conventional systemic agent used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis **OR** iii. The member has an FDA labeled contraindication to **ALL** conventional systemic agents used in the treatment of non-infectious intermediate uveitis, posterior **uveitis**, or panuveitis **OR** 2. 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 non-infectious intermediate uveitis, posterior uveitis, or panuveitis	
Granulomatosis with polyangiitis (GPA) [formerly known as Wegener's granulomatosis]	**ALL** of the following: 1. Member's disease has been confirmed by biopsy **AND** 2. Member's disease is active **AND** 3. Member's disease is refractory to, or member has intolerable adverse effect(s) with or a contraindication to oral immunosuppressive therapy (e.g., cyclophosphamide) **AND** 4. **EITHER** of the following ("a" or "b"): a. Member's disease is refractory to, or member has intolerable adverse effect(s) with or a contraindication to systemic corticosteroids **OR**	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10

	b. Member is dependent on systemic corticosteroids [i.e., unable to successfully taper corticosteroids to less than 10 mg of prednisone (or equivalent) within 3 months of initiation without return of symptoms]	
Orphan Indications (non-FDA approved)		
Chronic sarcoidosis	Diagnosis only	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10
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** of the conventional agents used in the treatment of PJIA **OR** 4. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PJIA	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10
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	Maximum dose supported by the FDA labeled indication or maximum dose supported in DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a
*The maximum allowable dose can be exceeded if - (1) the dose is supported in DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a for the requested indication, **OR** (2) the prescriber has provided information in support of therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)		

Continuation of therapy with an IV infliximab product **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "6"):

1. An authorization or reauthorization for an IV infliximab product has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of a condition in the Preferred Agents and Drug List [except immune checkpoint inhibitor-related adverse effects/toxicity, IEC-associated enterocolitis specific to BCMA-directed CAR T-cell therapy, acute GVHD, Kawasaki disease, and MIS-C Associated with SARS-CoV-2; use the initiation criteria for these indications], **OR** the member previously met **ALL** indication-specific initiation criteria
2. The prescriber is a specialist in the area of the member's diagnosis (e.g., rheumatologist for PsA, RA; gastroenterologist for CD, UC; 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 the IV infliximab product
4. Member has had clinical benefit with the IV infliximab product
5. Member will **NOT** be using the IV infliximab product 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), 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. **EITHER** of the following ("a" or "b"):
    a. The dosage prescribed does **NOT** exceed 10 mg/kg every 4 weeks
    b. The dose is supported in DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a for the requested indication, **OR** the prescriber has provided information in support of therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy required of clinical trials, phase III studies, guidelines required)

Approval duration: 12 months

DOSAGE AND ADMINISTRATION:

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

Table 3:

FDA-approved indications and recommended dosing for IV infliximab products	
Indication	**Dosage†**
Ankylosing Spondylitis	• Initial: 5 mg/kg at weeks 0, 2, and 6 • Maintenance: 5 mg/kg every 6 weeks (beginning at week 12)
Crohn's Disease (CD): Adults and Children (greater than 6 years of age)	Adults and Children (greater than 6 years of age): • Initial: 5 mg/kg at weeks 0, 2, and 6 • Maintenance: 5 mg/kg every 8 weeks (beginning at week 14) Note: In adult members the dose may be increased to 10 mg/kg in members who initially respond but then lose their response.
Plaque Psoriasis	

Psoriatic Arthritis (PsA) Ulcerative Colitis (UC) Adults and Children (greater than 6 years of age)	• Initial: 5 mg/kg at weeks 0, 2, and 6 • Maintenance: 5 mg/kg every 8 weeks (beginning at week 14)
Rheumatoid Arthritis (RA)	• Initial: 3 mg/kg at weeks 0,2,6 • Maintenance: 3 mg/kg every 8 weeks (beginning at week 14) Incomplete response: the dose can be increased up to 10 mg/kg or treatment interval can be decreased to every 4 weeks • Should be given in combination with methotrexate
†Administered as an intravenous infusion	

Zymfentra is indicated in adults for maintenance treatment of (1) moderately to severely active ulcerative colitis following treatment with an infliximab product administered intravenously, and (2) moderately to severely active Crohn's disease following treatment with an infliximab product administered intravenously.

- Maintenance dosage starting at Week 10 and thereafter: 120 mg subcutaneously once every two weeks. To switch patients who are responding to maintenance therapy with an infliximab product administered intravenously, administer the first subcutaneous dose of Zymfentra in place of the next scheduled intravenous infusion and every two weeks thereafter.

Dose Adjustment

- Renal Impairment: dosage adjustments are not required for members with renal impairment.
- Hepatic Impairment: although specific dosage adjustments are not available, infliximab products should be used with caution in members with hepatic impairment.

Drug Availability:

- Remicade and Infliximab - 100 mg lyophilized infliximab in a single-dose vial for IV use
- Inflectra - 100 mg lyophilized infliximab-dyyb in a single-dose vial for IV use
- Renflexis - 100 mg lyophilized infliximab-abda in a single- dose vial for IV use
- Avsola - 100 mg lyophilized infliximab-axxq in a single-dose vial for IV use
- Zymfentra - 120 mg/mL prefilled syringes, prefilled syringes with needle guard, and prefilled pens in cartons of one, two, four, or six pen or syringes

PRECAUTIONS:

Boxed Warning

WARNING: SERIOUS INFECTIONS and MALIGNANCY

SERIOUS INFECTIONS

Patients treated with infliximab products are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Infliximab products should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before infliximab product use and during therapy. Treatment for latent infection should be initiated prior to infliximab product use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.

The risks and benefits of treatment with infliximab product should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with infliximab product, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including infliximab products.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including infliximab products. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis, and most were in adolescent and young adult males.

Contraindications

- Infliximab products are contraindicated in members who have experienced a severe hypersensitivity reaction to infliximab, infliximab-abda, or infliximab-dyyb, to the inactive components of the product, or to any murine proteins.
- Infliximab products at doses greater than 5 mg/kg is contraindicated in members with moderate or severe heart failure (New York Heart Association [NYHA] Functional Class III/IV).

Precautions/Warnings

- **Serious Infections:** infliximab products should not be initiated in members during an active infection. If an infection develops, monitor carefully, and discontinue infliximab if infection becomes serious. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection.
- **Invasive fungal infections:** If a member develops a systemic infection while on infliximab product 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 the infliximab product and initiate anti-viral therapy.

- **Hepatotoxicity:** rare severe hepatic reactions, some fatal or necessitating liver transplantation have occurred in those administered infliximab products. If jaundice and/or marked liver enzyme elevations occur, discontinue the infliximab product.
- **Demyelinating disease:** exacerbation of new onset may occur.
- **Cytopenia:** advise members to seek immediate medical attention if symptoms develop and consider discontinuing the infliximab product.
- **Heart failure:** worsening or new onset heart failure may occur.
- **Lupus-like syndrome:** discontinue the infliximab product if 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 an infliximab product.
- **Pregnancy and Lactation**
    - Infliximab products are classified as pregnancy category B. Developmental toxicity studies performed in animals have revealed no evidence of harm to the fetus. There are no studies in pregnant women and use during pregnancy should only occur 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 these services:

HCPCS Coding:

J1745	Injection, infliximab, excludes biosimilar, 10 mg
J1748	Injection, infliximab-dyyb (zymfentra), 10 mg
Q5103	Injection, infliximab-dyyb, biosimilar, (inflectra), 10 mg
Q5104	Injection, infliximab-abda, biosimilar, (renflexis), 10 mg
Q5121	Injection, infliximab-axxq, biosimilar, (avsola), 10 mg

ICD-10 Diagnosis Codes That Support Medical Necessity for IV infliximab products (J1745, Q5103, Q5104, and Q5121):

D86.0 – D86.9	Sarcoidosis
D89.810	Acute graft-versus-host disease
D89.812	Acute on chronic graft-versus-host disease
D89.831 – D89.839	Cytokine release syndrome
H20.00 – H20.9	Iridocyclitis
H44.111 – H44.119	Panuveitis
H44.131 - H44.139	Sympathetic uveitis
K31.6	Fistula of stomach and duodenum
K50.00 – K50.919	Crohn's disease (regional enteritis)
K51.00 – K51.919	Ulcerative colitis
K52.3	Indeterminate colitis
K60.30	Anal fistula, unspecified
K60.311 – K60.319	Anal fistula, simple
K60.321 – K60.329	Anal fistula, complex
K60.40	Rectal fistula, unspecified

K60.411 – K60.419	Rectal fistula, simple
K60.421 – K60.429	Rectal fistula, complex
K60.50	Anorectal fistula, unspecified
K60.511 – K60.519	Anorectal fistula, simple
K60.521 – K60.529	Anorectal fistula, complex
K63.2	Fistula of intestine
L40.0	Psoriasis vulgaris
L40.1	Generalized pustular psoriasis
L40.3	Pustulosis palmaris et plantaris
L40.50 – L40.59	Arthropathic psoriasis
L40.8	Other psoriasis [for erythrodermic psoriasis 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
M06.80 – M06.8A	Other specified rheumatoid arthritis
M06.9	Rheumatoid arthritis, unspecified
M08.00 – M08.09	Unspecified Juvenile rheumatoid arthritis
M08.1	Juvenile ankylosing spondylitis
M08.20 – M08.29	Juvenile rheumatoid arthritis with systemic onset
M08.3	Juvenile rheumatoid polyarthritis (seronegative)
M08.40 – M08.4A	Pauciarticular juvenile rheumatoid arthritis
M08.80 – M08.89	Other juvenile arthritis
M08.80 – M08.99	Juvenile arthritis, unspecified
M30.3	Mucocutaneous lymph node syndrome [Kawasaki]
M31.30 – M31.31	Wegener’s granulomatosis
M31.4	Aortic arch syndrome [Takayasu]
M35.2	Behçet's disease
M35.81	Multisystem inflammatory syndrome
M45.0 – M45.9	Ankylosing spondylitis
M45.A0 – M45.AB	Non-radiographic axial spondyloarthritis
M46.81 – M46.89	Other specified inflammatory spondylopathies
N82.2	Fistula of vagina to small intestine
N82.3	Fistula of vagina to large intestine
N82.4	Other female intestinal-genital tract fistulae
T45.AX5A	Adverse effect of immune checkpoint inhibitors and immunostimulant drugs, initial encounter
T45.AX5D	Adverse effect of immune checkpoint inhibitors and immunostimulant drugs, subsequent encounter

T45.AX5S	Adverse effect of immune checkpoint inhibitors and immunostimulant drugs, sequela
T80.82XA	Complication of immune effector cellular therapy, initial encounter
T80.82XD	Complication of immune effector cellular therapy, subsequent encounter
T80.82XS	Complication of immune effector cellular therapy, sequela

ICD-10 Diagnosis Codes That Support Medical Necessity for SC infliximab-dyyb (Zymfentra) (J1748):

K50.00 – K50.919	Crohn's disease (regional enteritis)
K51.00 – K51.919	Ulcerative colitis

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: No National Coverage Determination (NCD) was found at the time of the last guideline review date. The following Local Coverage Determination (LCD) was reviewed on the last guideline revised date: Infliximab (Remicade), (L33704) located at fcso.com. The Site of Care Policy for Select Specialty Medications does not apply to Medicare Advantage members.

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:

Crohn's Disease: is an inflammatory bowel disease characterized by severe, chronic inflammation of the intestinal wall or any portion of the gastrointestinal tract. The lower portion of the small intestine (ileum) and the rectum are most commonly affected by this disorder. Symptoms may include watery diarrhea and abdominal pain. The symptoms of Crohn's Disease can be difficult to manage and diagnosis is often delayed.

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).

Enterocutaneous fistula: a fistula between the intestine and skin of the abdomen.

Hidradenitis suppurativa (HS) (a.k.a., acne inversa): a chronic, inflammatory, recurrent, debilitating skin disease of the hair follicle that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillae, inguinal and anogenital regions. HS may have a large impact on quality of life, often causing depression, impaired

sexual health, and embarrassment. Squamous cell carcinoma may arise from chronic (10-30 years of evolution) lesions. The main goals of treatment are to prevent the formation of new lesion, treat new lesions, and eliminate existing nodules and sinus tract to limit or prevent scar formation.

Immune checkpoint inhibitors: drugs that target molecules on certain immune cells that need to be activated (or inactivated) to start an immune response. Some types of cancer cells use these "checkpoints" to avoid being attacked by the body's own immune system. Examples include CTLA-4 inhibitors [e.g., ipilimumab (Yervoy)]; PD-1 inhibitors (e.g., pembrolizumab (Keytruda), nivolumab (Opdivo)]; and PD-L1 inhibitors (e.g., atezolizumab (Tecentriq)].

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-Severe Crohn's Disease: Moderate-severe disease applies to members who have failed to respond to treatment for mild-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.

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.

Remission: Remission refers to members who are asymptomatic or without inflammatory sequelae and includes members who have responded to acute medical intervention or have undergone surgical resection without gross evidence of residual disease. Members requiring steroids to maintain well-being are considered to be "steroid-dependent" and are usually not considered to be "in remission."

Rheumatoid arthritis: usually strikes between ages 20 and 50. Inflammation begins in a joint, usually those of the fingers and hands, resulting in pain, swelling, redness, and eventually joint deformity. It is considered an autoimmune disease, which can affect the entire body, causing fatigue, weight loss, weakness, fever, and loss of appetite. It affects each person differently, with symptoms ranging from mild to debilitating. In many cases, it is difficult to control. In about one in six cases, rheumatoid arthritis becomes severely debilitating and can shorten the life of the person affected.

Severe-Fulminant Disease: Severe-fulminant disease refers to members with persisting symptoms despite the introduction of steroids as outpatients, or individuals presenting with high fever, persistent vomiting, and evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess.

Ulcerative colitis: a chronic inflammatory disease of the colon that is of unknown cause and is characterized by diarrhea with discharge of mucus and blood, cramping abdominal pain, and inflammation and edema of the mucous membrane with patches of ulceration.

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
Canakinumab (Ilaris) Injection, 09-J1000-14
Certolizumab Pegol (Cimzia), 09-J0000-77
Etanercept (Enbrel), 09-J0000-38
Etrasimod (Velsipity), 09-J4000-72
Golimumab (Simponi, Simponi Aria), 09-J1000-11
Guselkumab (Tremfya), 09-J2000-87
Ixekizumab (Taltz), 09-J2000-62
Mirikizumab (Omvoh), 09-J4000-71
Natalizumab (Tysabri) Injection, 09-J0000-73
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) Tablets, 09-J1000-86
Ustekinumab (Stelara), 09-J1000-16
Upadacitinib (Rinvoq), 09-J3000-51
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 4: Conventional Synthetic DMARDs

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

Table 5: Grading of Severity of Rheumatoid Arthritis

Severity	Criteria
Mild	Joint pain Inflammation of at least 3 joints No inflammation in tissues other than the joints Usually, a negative result on a rheumatoid factor test An elevated erythrocyte sedimentation rate (ESR) or C reactive protein (CRP) level No evidence of bone or cartilage damage on x-rays
Moderate	Between 6 and 20 inflamed joints Usually no inflammation in tissues other than the joints An elevated ESR or CRP levels A positive rheumatoid factor test or anti-cyclic citrullinated peptide (anti-CCP) antibodies Evidence of inflammation but no evidence of bone damage on x-rays

Severe	More than 20 persistently inflamed joints or a rapid loss of functional abilities Elevated ESR or CRP levels Anemia related to chronic illness Low blood albumin level A positive rheumatoid factor test, often with a high level Evidence of bone and cartilage damage on x-ray Inflammation in tissues other than joints

REFERENCES:

1. Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part I: Diagnosis, evaluation, and the use of complementary and procedural management. J Am Acad Dermatol. 2019 Jul;81(1):76-90. doi: 10.1016/j.jaad.2019.02.067. Epub 2019 Mar 11.
2. Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part II: Topical, intralesional, and systemic medical management. J Am Acad Dermatol. 2019 Jul;81(1):91-101. Epub 2019 Mar 11.
3. American College of Rheumatology. Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19 (Version 3). Available at: https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf. Accessed 10/29/24.
4. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis. Arthritis Rheumatol. 2019 Jun;71(6):864-877. Epub 2019 Apr 25.
5. 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.
6. Avsola (infliximab-axxq) [package insert]. Amgen Inc., Thousand Oaks, CA: September 2025.
7. 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.
8. Bautista-Molano W, Fernández-Ávila DG, et al. Pan American League of Associations for Rheumatology recommendations for the management of axial spondyloarthritis. Nat Rev Rheumatol. 2023 Nov;19(11):724-737. doi: 10.1038/s41584-023-01034-z. Epub 2023 Oct 6.
9. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018 Jun 10;36(17):1714-1768.
10. Brunello F, Tirelli F, Pegoraro L, et al. New Insights on Juvenile Psoriatic Arthritis. Front Pediatr. 2022 May 26;10:884727.
11. 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.
12. Chauhan K, Tyagi M. Update on non-infectious uveitis treatment: anti-TNF-alpha and beyond. Front Ophthalmol (Lausanne). 2024 Aug 2; 4:1412930.
13. Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol. Aug 2021; 73(8): 1366-1383.

14. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2025. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 10/29/25.
15. Coates LC, Soriano ER, Corp N, et al; GRAPPA Treatment Recommendations domain subcommittees. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. Nat Rev Rheumatol. 2022 Aug;18(8):465-479. Epub 2022 Jun 27. Erratum in: Nat Rev Rheumatol. 2022 Dec;18(12):734.
16. Del Galdo F, Lescoat A, Conaghan PG, et al. EULAR recommendations for the treatment of systemic sclerosis: 2023 update. Ann Rheum Dis. 2025 Jan;84(1):29-40.
17. Dick AD, Rosenbaum JT, Al-Dhibi HA, et al. Guidance on Noncorticosteroid Systemic Immunomodulatory therapy in noninfectious Uveitis. Ophthalmology. 2018;125(5):757-773.
18. Di Gennaro S, Di Matteo G, Stornaiuolo G, et al. Advances in the Diagnosis and Treatment of Enthesitis-Related Arthritis. Children (Basel). 2023 Oct 2;10(10):1647.
19. 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. 2013 Mar;27(3): e305-11.
20. 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.
21. 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.
22. 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.
23. Fautrel B, Mitrovic S, De Matteis A, et al. EULAR/PReS recommendations for the diagnosis and management of Still's disease, comprising systemic juvenile idiopathic arthritis and adult-onset Still's disease. Ann Rheum Dis. 2024 Oct 15:ard-2024-225851. Epub ahead of print.
24. FDA Orphan Drug Designations and Approvals [Internet]. Washington, D.C. [cited 2025 Oct 29]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/.
25. Feuerstein JD, Ho EY, Shmidt E, Singh H, Falck-Ytter Y, Sultan S, Terdiman JP; American Gastroenterological Association Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. Gastroenterology. 2021 Jun;160(7):2496-2508.
26. Feuerstein JD, Isaacs KL, Schneider Y, et al.; AGA Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology. 2020 Apr;158(5):1450-1461. 2020 Jan 13.
27. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2021 Jul;73(7):924-939.
28. Friedman CF, Proverbs-Singh TA, and Postow MA. Treatment of the Immune-Related Adverse Effects of Immune Checkpoint Inhibitors: A Review. JAMA Oncol. 2016 Jun 30.
29. Gener G, Canoui-Poitrine F, Revuz JE, et al. Combination therapy with clindamycin and rifampicin for hidradenitis suppurativa: a series of 116 consecutive patients. Dermatology. 2009;219(2):148-54.
30. Giardina A, Ferrante A, Ciccia F, et al. One year study of efficacy and safety of infliximab in the treatment of patients with ocular and neurological Behcet’s disease refractory to standard immunosuppressive drugs. Rheumatol Int 2011; 31:33-7.

31. Gorelik M, Chung SA, Ardalan K, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Kawasaki Disease. Arthritis Care Res (Hoboken). Apr 2022; 74(4): 538-548.
32. Gossec L, Kerschbaumer A, Ferreira RJO, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2023 update. Ann Rheum Dis. 2024 May 15;83(6):706-719.
33. 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.
34. Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker JNWN. Psoriasis. Lancet. 2021;397(10281): 1301-1315.
35. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis. 2018 Jun;77(6):808-818. Epub 2018 Apr 6.
36. Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2019 Jul 3. pii: annrheumdis-2019-215672. [Epub ahead of print].
37. Holland GN, Acharya N, Fitzgerald JD, Goldstein DA, Kempen JH. Strategies for Managing Uveitis, Part 2: Treatment of Adults With Chronic Disease. EyeNet Magazine. Published online November 1, 2023:33-35.
38. Inflectra (infliximab-dyyb) [package insert]. Pfizer Laboratories Div Pifzer Inc. New York (NY): September 2025.
39. Infliximab [package insert]. Janssen Biotech, Inc. Horsham (PA): March 2025.
40. Ingram JR, Woo PN, Chua SL, et al. Interventions for hidradenitis suppurativa. Cochrane Database Syst Rev. 2015 Oct 7;(10):CD010081
41. Ko CW, Singh S, Feuerstein JD, et al; American Gastroenterological Association Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Management of Mild-to-Moderate Ulcerative Colitis. Gastroenterology. 2019 Feb;156(3):748-764.
42. 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.
43. 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.
44. Lichtenstein GR, Loftus EV, Afzali A, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2025 Jun 3;120(6):1225-1264.
45. Maz M, Chung SA, Abril A, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. Arthritis Care Res (Hoboken). 2021 Aug;73(8):1071-1087.
46. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. Circulation 2017;135: e927-e999.
47. Menter A, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. J Am Acad Dermatol. 2020 Jan;82(1):161-201. Epub 2019 Nov 5. Erratum in: J Am Acad Dermatol. 2020 Mar;82(3):574.

48. Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. J Am Acad Dermatol. 2020 Jun;82(6):1445-1486.
49. Menter A, Korman NJ, Elmets CA, et al. 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.
50. Menter A, Strober BE, Kaplan DH et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol. 2019 Apr;80(4):1029-1072. Epub 2019 Feb 13.
51. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 10/29/25.
52. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 10/29/25.
53. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Hematopoietic Cell Transplantation (HCT). Version 3.2025 – September 24, 2025. Available at https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf. Accessed 10/29/25.
54. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Management of CAR T-Cell and Lymphocyte Engager-Related Toxicities. Version 1.2026 - October 23, 2025. Available at https://www.nccn.org/professionals/physician_gls/pdf/cellular_tox.pdf. Accessed 10/29/25.
55. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Management of Immune Checkpoint Inhibitor-Related-Toxicities. Version 1.2026 - October 23, 2025. Available at https://www.nccn.org/professionals/physician_gls/pdf/ici_tox.pdf. Accessed 10/29/25.
56. Okada A, Goto H, Ohno S, et al. Multicenter study of infliximab for refractory uveoretinitis in Behcet disease. Arch Opthalmol 2012;130(5):592-98.
57. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis. Arthritis Care Res (Hoboken). 2022 Apr;74(4):521-537. Epub 2022 Mar 1.
58. 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.
59. 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.
60. Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis. 2022 Oct 19: ard-2022-223297. Epub ahead of print.
61. Remicade (infliximab) [package insert]. Janssen Biotech, Inc. Horsham (PA): February 2025.
62. Renflexis (infliximab-abda) [package insert]. Organon; Jersey City (NJ): October 2025.
63. Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Rheumatol. 2019 Jun;71(6):846-863. Epub 2019 Apr 25
64. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline Update: Ulcerative Colitis in Adults. Am J Gastroenterol. 2025 Jun 3;120(6):1187-1224.

65. 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.
66. Sbidian E, Chaimani A, Garcia-Doval, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2021 Apr 19;4(4):CD011535. Update in: Cochrane Database Syst Rev. 2022 May 23;5:CD011535.
67. 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.
68. Scott DL, Kinglsey GH. Tumor necrosis factor inhibitors in rheumatoid arthritis. N Engl J Med 2006; 355:704-12.
69. Serra R, Butrico L, Fugetto F, et al. Updates in Pathophysiology, Diagnosis and Management of Takayasu Arteritis. Ann Vasc Surg. 2016 May 27.
70. 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.
71. Smolen JS, Landewé RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023 Jan;82(1):3-18. Epub 2022 Nov 10. Erratum in: Ann Rheum Dis. 2023 Mar;82(3):e76.
72. Tracey D, Klareskog L, Sasso EH, et al. Tumor necrosis factor antagonist mechanism of action: a comprehensive review. Pharmacol Ther 2008; 117:244-79.
73. 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.
74. 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 Oct;71(10):1285-1299. Epub 2019 Aug 21.
75. Yalniz FF, Hefazi M, McCullough K, et al. Safety and Efficacy of Infliximab Therapy in the Setting of Steroid-Refractory Acute Graft-versus-Host Disease. Biol Blood Marrow Transplant. 2017 Sep;23(9):1478-1484.
76. Zymfentra (infliximab-dyyb) [package insert]. Celltrion USA Inc. Jersey City (NJ): May 2025.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/12/25.

GUIDELINE UPDATE INFORMATION:

04/25/01	Medical Coverage Guideline developed.
04/25/02	Reviewed, revised coverage for Crohn's disease.
08/15/02	Revised coverage for Crohn's disease.
04/01/05	Revised with updates: Added maintenance therapy to fistulizing Crohn's. Added coverage for psoriatic arthropathy and ankylosing spondylitis. Updated dosing.
11/15/05	Revised; added coverage for ulcerative colitis, updated dosage and administration, deleted warnings and contraindications section, updated references and Internet links.

01/01/06	CPT coding update: deleted expired codes 90780, 90781 and added new codes 90765, 90766.
11/15/06	Scheduled review: added psoriasis indication and ICD-9 code, updated code descriptions and updated references.
01/01/07	MCG revised to include Medicare Part D as a program exception.
02/15/07	Revised by adding CPT-4 codes 96413 & 96415.
06/15/07	Review and revision to guideline; consisting of reformatting, removed ICD-9 codes 557.0 and 619.1, added ICD-9 code 714.2, added statement saying Remicade® is a first line agent and updated references.
05/15/08	Review and revision to guideline; consisting of reformatting, added black box warning.
01/01/09	Annual HCPCS coding update: deleted 90765 and 90766; added 96365 and 96366.
05/15/09	Revision to guideline; consisting of adding maximum dose for each indication.
09/15/09	Review and revision to guideline; consisting of updating boxed warning, updating the references, and rewording dosing maximums within the position statement.
04/15/10	Revision to guideline; consisting of adding specific continuation criteria.
09/15/10	Review and revision to guideline; consisting of updating boxed warnings, precautions and references.
01/15/11	Revision to guideline; consisting of adding ICD-10 codes.
09/15/11	Review and revision to guideline; consisting of updating coding and references.
09/15/12	Review and revision to guideline; consisting of modifying continuation criteria, updating dosage, precautions, exceptions and references.
01/15/13	Revision to guideline; consisting of revising, reformatting and updating the position statement; revising and reformatting dosage/administration, precautions, and description sections; updating references.
04/15/13	Revision to guideline; consisting of adding Orphan Drug Indications and duration of approval.
09/15/13	Review and revision to guideline; consisting of updating program exceptions and reformatting position statement.
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 revising position statement, updated references, coding, and related guidelines.
09/15/15	Review and revision to guideline; consisting of updating description section, position statement, warnings/precautions, billing/coding, and references.
10/01/15	Revision consisting of update to Program Exceptions section.
11/01/15	Revision: ICD-9 Codes deleted.
07/01/16	Revision to guideline consisting of updating HCPCS codes.
09/15/16	Review and revision to guideline consisting of updating description section, position statement, warnings/precautions, billing/coding, definitions, and references.
10/01/16	Revision: ICD-10 code updates.
01/01/17	Revision: updated HCPCS code J1745 description.
07/01/17	Revision to guideline consisting of updating the position statement for infliximab-dyyb (Inflectra).
07/15/17	Revision to guideline consisting of updating the position statement for infliximab-dyyb (Inflectra) and addition of infliximab-abda (Renflexis). MCG title renamed to “Infliximab Products.”
10/15/17	Review and revision to guideline consisting of updating description, position statement, definitions, related guidelines, and references.
01/15/18	Review and revision to guideline; consisting of revising position statement.
04/01/18	Addition of HCPCS codes Q5103 and Q5104 and removal of Q5102.
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, coding/billing, and references based on the new NCCN guideline for management of immunotherapy-related toxicities.
10/15/18	Review and revision to guideline consisting of updating the position statement, definitions, 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.
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.
03/15/20	Revision to guideline consisting of updating the description section, position statement, dosage/administration, billing/coding, and references based on the FDA-approval and inclusion of infliximab-axxq (Avsola).
07/01/20	Revision to guideline consisting of updating the description, position statement, billing/coding, definitions, and other sections.
01/01/21	Review and revision to guideline consisting of updating the position statement, billing/coding, and references.
07/01/21	Revision to guideline consisting of updating the position statement as it relates to preferred products and “Other” section.
10/01/21	Revision: Addition of new ICD-10 code range M45.A0 – M45.AB.
01/01/22	Review and revision to guideline consisting of updating the position statement, billing/coding, and references.
03/15/22	Revision to guideline consisting of updating the position statement and other section.
04/01/22	Revision to guideline consisting of updating the description section, position statement, dosage/administration, and references based on the addition of unbranded Infliximab.
07/15/22	Revision to guideline consisting of updating the position statement regarding revised maximum dosage limits.
01/01/23	Review and revision to guideline consisting of updating the description section (NCCN information), position statement, other section, and references. New drugs were added to the list of drugs that are not permitted for use in combination. For CD and UC, added allowance for infliximab products to be used first-line for members with severe disease and/or risk factors for disease complications.
04/15/23	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 other section. 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, position statement, billing/coding, other section, and references. Increased the maximum dosages from 5 mg/kg to 10 mg/kg per dose regardless of indication. Updated immune checkpoint inhibitor-related adverse effects criteria. 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, position statement, dosage/administration, billing/coding, related guidelines, other section, and references. Zymfentra added to the guidelines as a non-preferred, self-administered Step 3c (triple stepped) agent for CD and UC. Position statement divided into one section for “SUBCUTANEOUS INFLIXIMAB PRODUCTS (PHARMACY BENEFIT)” and one section for “INTRAVENOUS INFLXIMAB PRODUCTS (MEDICAL BENEFIT)” as criteria are different. Removal of latent TB testing requirement. New drugs added to the list of Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy. New HCPCS code for Zymfentra.
10/01/24	Revision to guideline consisting of updating the position statement and billing/coding. Renflexis added as a co-preferred infliximab product. Simlandi (for CD) and Simlandi and Skyrizi (for UC) added to the list of prerequisite agents that must be tried prior to the use of Zymfentra. Updated dosing for immune checkpoint inhibitor-related adverse effect. New ICD-10 codes related to fistulas and adverse effect of immune checkpoint inhibitors.

01/01/25	Review and revision to guideline consisting of updating the position statement, other section, and references. Zymfentra moved from a step 3c agent (triple step) to a step 3a agent (double step) for CD and UC. Adalimumab-aaty, Adalimumab-adaz, and Entyvio SC added among the prerequisite therapies for Zymfentra for CD and UC. Tremfya added among the prerequisite therapies for Zymfentra for UC. Revised wording regarding maximum dosage exceptions for Zymfentra. Update to original Table 1 which is now a link out from the Position Statement. Table titles updated. New drugs were added to the list of drugs that are not permitted for use in combination.
05/15/25	Revision: Tremfya added among the preferred agents for CD for Zymfentra SC.
07/01/25	Revision: Added Selarsdi, Steqeyma and Yesintek among the preferred agents for CD and UC for Zymfentra SC.
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, billing/coding, and references. IEC-associated enterocolitis specific to BCMA-directed CAR T-cell therapy added as an indication for infliximab IV. New ICD-10 codes. Revised criteria for Immune checkpoint inhibitor-related toxicity.
05/15/26	Revision to guideline consisting of clarifying the approval duration and start date for Zymfentra subcutaneous injection following IV treatment with an infliximab product.