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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 NSAIDs and exercise, with the additional use of DMARDs in patients with peripheral arthritis. The American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) recommend the following pharmacological treatment for AS:

- Stable AS: First line therapy with on demand NSAIDs; there is also a conditional recommendation for continuation of TNF inhibitor as monotherapy
- Active AS:
    - First line therapy with continuous NSAIDs and physical therapy
    - TNF inhibitor recommended for patients with active AS despite an adequate trial with NSAIDs

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

Nonradiographic Axial Spondyloarthritis (nr-axSpA)

Nonradiographic axial spondyloarthritis (nr-axSpA) falls under the same spondyloarthritis family as ankylosing spondylitis (AS). Nr-axSpA includes patients with chronic back pain and features suggestive of spondyloarthritis (SpA), but do not meet the classification of AS. 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 mainstay of treatment has been NSAIDs and exercise, with the additional use of DMARDs in patients with peripheral arthritis. The American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) recommendation for nr-axSpA are the same as AS:

- Stable SpA: conditional recommendation for on-demand treatment with NSAIDs
- Active SpA:
    - First line therapy with continuous NSAIDs and physical therapy
    - TNF inhibitor conditionally recommended for patients with active SpA despite an adequate trial with NSAIDs
        - Lack of response (or intolerance) to at least 2 different NSAIDs over 1 month or incomplete response to at least 2 different NSAIDs over 2 months would be an adequate NSAID trial to judge response
    - TNF-inhibitors are conditionally recommended over secukinumab or ixekizumab
    - Secukinumab or ixekizumab are conditionally recommended over DMARDs in patients that have failed NSAIDs and have contraindications to TNF-inhibitors

- Recommendations for nonresponse to TNF therapy (all conditional):
  - Primary nonresponse: switch to secukinumab or ixekizumab over another TNF
  - Secondary nonresponse: switch to another TNF over a non-TNF biologic
  - Recommend against addition of sulfasalazine or MTX
  - Recommend against switching to a biosimilar of the failed TNF
- DMARDs (i.e., methotrexate, sulfasalazine, leflunomide, pamidronate, thalidomide, apremilast) are only conditionally recommended in patients that have failed NSAIDs and have contraindications to TNF-inhibitors
- Methotrexate is not recommended as add on therapy to TNF inhibitors in stable and active AS
- If patient has concomitant inflammatory bowel disease or recurrent uveitis, TNF-inhibitors are recommended over other biologics
- Glucocorticoids are not recommended

Rheumatoid arthritis (RA)

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

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

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

- Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modifications of treatment to minimize disease activity with the goal of reaching a predefined target (low disease activity or remission)

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

- DMARD-naïve patients with moderate-to-high disease activity initial treatment:
    - MTX monotherapy is strongly recommended over hydroxychloroquine, sulfasalazine, bDMARDs monotherapy, tsDMARD monotherapy, or combination of MTX plus a non-TNF bDMARD or tsDMARD
    - MTX monotherapy is conditionally recommended over leflunomide, dual or triple csDMARD therapy, or combination MTX plus a TNF inhibitor
- DMARD-naïve patients with low disease activity initial treatment
    - Hydroxychloroquine is conditionally recommended over other csDMARDs
    - Sulfasalazine is conditionally recommended over MTX
    - MTX is conditionally recommended over leflunomide
- Initial therapy in csDMARD-treated patients, but MTX naïve, with moderate-to high disease activity:
    - MTX monotherapy is conditionally recommended over combination MTX and a bDMARD or tsDMARD
- Treatment Modifications in patients treated with DMARDs who are not at target:
    - Addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy for patients taking maximally tolerated doses of MTX who are not at target
    - Switching to a bDMARD or tsDMARD of a different class is conditionally recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target

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

For patients who are resistant to MTX after 3 months of treatment at optimal doses (usually 25 mg per week), it is recommended to either use DMARD triple therapy with MTX plus sulfasalazine and hydroxychloroquine or combination of MTX with TNF inhibitor. Triple therapy regimen has been found to be of similar clinical efficacy to MTX with biologics in several randomized trials, including in patients with high level of disease activity or with adverse prognostic features. The use of triple therapy has been shown to be highly cost-effective compared with combining a biologic with MTX, providing comparable or near comparable clinical benefit. The use of biologic with MTX combination is preferred when

patients have high disease activity and clinical benefit from a more rapid response is needed and when patients who do not achieve satisfactory response within 3 months with non-biologic triple therapy following an inadequate response to MTX therapy.

Polyarticular Juvenile Idiopathic Arthritis (PJIA)

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

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

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

- TNF, abatacept, or tocilizumab (depending on prior biologics received) over rituximab after trial of second biologic

Systemic Juvenile Idiopathic Arthritis (SJIA)

Systemic juvenile idiopathic arthritis (SJIA) is a subset of 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. Up to 40% of cases of SJIA are associated with macrophage activation syndrome (MAS), a secondary hemophagocytic syndrome that is a life-threatening complication requiring urgent recognition and treatment. MAS presents with fevers, high ferritin levels, cytopenias, elevated liver enzyme levels, low fibrinogen levels, and high triglyceride levels. As it may occur at any point during the disease course careful monitoring is necessary for children with or without MAS at presentation. Goals of therapy for SJIA includes 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.

SJIA is defined as:

- Patient age 6 months to 18 years
- Fever of at least 2 weeks duration (daily fever is not required but at some point exhibit a quotidian (daily) fever pattern, defined as a fever that rises to greater than or equal to 39 degrees Celsius at least once a day and returns to less than or equal to 37 degrees Celsius between fever peaks
- Arthritis in greater than or equal to 1 joint
- Accompanied by one or more of the following:
    - Evanescent erythematous rash
    - Generalized lymphadenopathy
    - Hepatomegaly or splenomegaly
    - Pericarditis, pleuritis and/or peritonitis

SJIA without MAS

The American College of Rheumatology conditionally recommends IL-1 or IL-6 inhibitors and/or a brief trial of scheduled non-steroidal anti-inflammatories (NSAIDs) for initial treatment for SJIA without MAS. Studies suggest that a small proportion of patients with systemic JIA will respond to NSAIDs alone. If clinical response is not rapid and complete, rapid escalation of therapy is recommended. There is no consensus on the appropriate duration of initial use of NSAIDs before escalating therapy, as many prescribers prefer that the use of NSAIDs be avoided altogether for SJIA. Oral glucocorticoids are conditionally recommended against use in this population (the recommendation is conditional, as IL-1 or IL-6 inhibitors may not always be immediately available, and glucocorticoids may help control systemic and joint manifestations until IL-1 or IL-6 inhibitors can be started. Conventional synthetic disease modifying antirheumatic drugs (DMARDs) are strongly recommended against as initial therapy in this population. For subsequent therapy IL-1 and IL-6 inhibitors are strongly recommended over a single or combination of conventional synthetic DMARDs for inadequate response to intolerance of NSAIDs and/or glucocorticoids.

SJIA with MAS

The American College of Rheumatology conditionally recommends IL-1 or IL-6 inhibitors over calcineurin inhibitors alone to achieve inactive disease and resolution of MAS. Glucocorticoids are conditionally recommended as part of initial treatment in patients with SJIA with MAS. Systemic glucocorticoids may be necessary for severely ill patients because they can have rapid onset of action. Longer-term glucocorticoids therapy in children is not appropriate because of its effects on bone health and growth.

Psoriatic Arthritis (PsA)

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

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

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

- Active PsA is defined as symptoms at an unacceptably bothersome level as reported by the patient and health care provider to be due to PsA based on the presence of one of the following:
    - Actively inflamed joints
    - Dactylitis
    - Enthesitis
    - Axial disease
    - Active skin and/or nail involvement
    - Extraarticular manifestations such as uveitis or inflammatory bowel disease
- Disease severity includes level of disease activity at a given time point and the presence/absence of poor prognostic factors and long-term damage
- Severe PsA disease includes the presence of 1 or more of the following:
    - Erosive disease
    - Elevated markers of inflammation (ESR, CRP) attributable to PsA
    - Long-term damage that interferes with function (i.e., joint deformities)
    - Highly active disease that causes a major impairment in quality of life
    - Active PsA at many sites including dactylitis, enthesitis
    - Function limiting PsA at a few sites

- Rapidly progressive disease

- Symptomatic treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, local glucocorticoid injections
- Treatment recommendations for active disease:
  - Treatment naïve patients first line options include oral small molecules (OSM), TNF biologics, IL-17 inhibitor, and IL-12/23 inhibitor
    - OSM (i.e., methotrexate [MTX], sulfasalazine, cyclosporine, leflunomide, apremilast) should be considered if the patient does not have severe PsA, does not have severe psoriasis, prefers oral therapy, has concern over starting a biologic, or has contraindications to TNF inhibitor
    - Biologics (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) are recommended as a first line option in patients with severe PsA and/or severe psoriasis
  - Previous treatment with OSM and continued active disease:
    - Switch to a different OSM (except apremilast) in patients without severe PsA or severe PS, contraindications to TNF biologics, prefers oral therapy OR add on apremilast to current OSM therapy
    - May add another OSM (except apremilast) to current OSM therapy for patients that have exhibited partial response to current OSM in patients without severe PsA or severe PS, contraindications to TNF biologics, or prefers oral therapy
    - Biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) monotherapy
  - Previous treatment with a biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) and continued active disease:
    - Switch to another biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor, abatacept, or tofacitinib) monotherapy or add MTX to the current TNF biologic

DERMATOLOGICAL DISORDERS

Psoriasis (PS)

Psoriasis (PS) is a chronic inflammatory skin condition that is often associated with systemic manifestations, especially arthritis. Diagnosis is usually clinical, based on the presence of typical erythematous scaly patches, papules, and plaques that are often pruritic and sometimes painful.

Treatment goals for psoriasis include improvement of skin, nail, and joint lesions plus enhanced quality of life.

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

- Mild to moderate (less than 5% of BSA and sparing the genitals, hands, feet, and face):
  - Candidate for intermittent therapy: topical corticosteroids, vitamin D analogs (calcipotriene and calcitriol), or tazarotene (Tazorac)

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

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

- Mild to moderate disease (less than 5% of BSA):
    - Topical corticosteroids (strength of recommendation A)
    - Off-label use of 0.1% tacrolimus for psoriasis involving the face as well as inverse psoriasis (strength of recommendation B)
    - Long-term use (up to 52 weeks) of topical vitamin D analogs including calcipotriene, calcitriol, tacalcitol, and maxacalcitol (strength of recommendation A)
    - Use of calcipotriene foam and calcipotriene plus betamethasone dipropionate gel for the treatment of mild to moderate scalp psoriasis (strength of recommendation A)
    - Use of tacalcitol ointment or calcipotriene combined with hydrocortisone for facial psoriasis (strength of recommendation B)
    - Vitamin D analogs in combination with topical corticosteroids (strength of recommendation A)
    - Topical tazarotene alone or in combination with narrowband ultraviolet B (NB-UVB) (strength of recommendation B), or topical corticosteroids (strength of recommendation A)
    - Topical salicylic acid alone or in combination with topical corticosteroids (strength of recommendation B)
    - Coal tar preparations (strength of evidence A)
- Moderate to severe disease without PsA (5% or more of BSA or psoriasis in vulnerable areas [e.g., face, genitals, hands, and feet] that adversely affects quality of life):
    - Methotrexate (adults) (strength of evidence A)
    - Methotrexate is less effective than TNF-inhibitors (strength of evidence B)
    - Combination therapy with methotrexate and NB-UVB (adult patients) (strength of evidence B)
    - Cyclosporine for patients with severe, recalcitrant (strength of recommendation A), erythrodermic, generalized pustular, and/or palmoplantar psoriasis (strength of recommendation B)

- Acitretin as monotherapy or in combination with psoralen plus ultraviolet light (PUVA) or broad band ultraviolet light (BB-UVA [strength of evidence B])
- If UV-therapy is unavailable, first line therapies include MTX, cyclosporine, acitretin, and biologics
- Apremilast (strength of recommendation A)
- TNF-α inhibiters monotherapy (strength of evidence A) or in combination with topical corticosteroids with or without a vitamin D analogue (strength of evidence B) or in combination with acitretin (strength of evidence C)
- TNF-α inhibitors should be considered as a preferred treatment option for patients with concomitant PsA
- Infliximab (strength of evidence A)
- IL-12/IL-23 Inhibitors monotherapy (strength of evidence A) or in combination with topical corticosteroids with or without a vitamin D analogue (strength of evidence C) or in combination with acitretin or methotrexate (strength of evidence B)
- IL-12/IL-23 inhibitors in combination with apremilast or cyclosporine (strength of evidence C)
- IL-17 inhibitors monotherapy (strength of evidence A)
- IL-23 inhibitors monotherapy for moderate to severe plaque psoriasis or as monotherapy for generalized pustular psoriasis (strength of evidence B)

*Strength of recommendation and descriptions

Strength of recommendation	Description
A	Recommendation based on consistent and good-quality patient-oriented evidence
B	Recommendation based on inconsistent or limited-quantity patient-oriented evidence
C	Recommendation based on consensus, opinion, case studies, or disease-oriented evidence

Biologics are routinely used when one or more traditional systemic agents fail to produce adequate response, but are considered first line in patients with moderate to severe psoriasis with concomitant severe PsA. Primary failure is defined as initial nonresponse to treatment. Primary failure to a TNF-α inhibitor does not preclude successful response to a different TNF-α inhibitor. Failure of another biologic therapy does not preclude successful response to ustekinumab.

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

- The preferred assessment instrument for determining disease severity is BSA
- Target response after treatment initiation should be BSA ≤1% after 3 months

- Acceptable response is either a BSA ≤3% or a BSA improvement ≥75% from baseline at 3 months after treatment initiation

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 an inflammatory condition that can affect any portion of the gastrointestinal tract from the mouth to the perianal area. Choice of therapy is dependent on the anatomic location of disease, the severity of disease, and whether the treatment goal is to induce remission or maintain remission. The American Gastroenterological Association (AGA) 2021 guideline recommends the following:

- 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
    - Anti-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)

- DMARD therapy:
  - Corticosteroids are suggested over no treatment for the induction of remission, and are recommended against for maintenance of remission
  - 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 2018 American College of Gastroenterology (ACG) guidelines recommend the following:

- Mild to moderately severe disease/low risk disease:

- Sulfasalazine (in doses of 3-6 grams daily) is effective in colonic and/or ileocolonic CD, but not those with isolated small bowel disease
- 5-aminosalicylic (ASA) suppositories and enema preparations are effective for induction and maintenance of remission in rectal and sigmoid disease
- Conventional corticosteroids are primarily used for the treatment of flares, and are often used as a bridge until immunomodulators and/or biologic agents become effective
- Controlled ileal release budesonide is effective for induction of remission in ileocecal disease

- Moderate to severe disease/moderate to high risk disease
  - Corticosteroids are effective for short-term use in alleviating signs and symptoms of moderate to severely active CD, but do not induce mucosal healing and should be used sparingly
  - Azathioprine, 6-mercaptopurine, or MTX (15 mg once weekly) may be used in treatment of active disease and as adjunctive therapy for reducing immunogenicity against biologic therapy
  - TNF inhibitors should be used to treat CD that is resistant to treatment with corticosteroids and that is refractory to thiopurines or MTX
  - Vedolizumab with or without an immunomodulator should be considered for induction of symptomatic remission for patients with moderate to severely active CD and objective evidence of active disease
  - Ustekinumab should be used in patients that have failed previous treatment with corticosteroids, thiopurines, MTX, or TNF inhibitors, or in patients with no prior TNF inhibitor exposure
- Severe/fulminant disease:
  - IV corticosteroids should be used
  - TNF inhibitors can be considered
- Maintenance therapy:
  - Thiopurines or methotrexate should be considered once remission is induced with corticosteroids
  - TNF inhibitors, specifically infliximab, adalimumab, and certolizumab pegol, should be used in combination with azathioprine, MTX, or 6-mercaptopurine to maintain remission of TNF induced remission
  - Vedolizumab should be used for maintenance of remission of vedolizumab induced remission
  - Ustekinumab should be used for maintenance of remission of ustekinumab induced remission

Ulcerative Colitis (UC)

Ulcerative colitis (UC) is a chronic immune-mediated inflammatory condition affecting the large intestine associated with inflammation of the rectum, but that can extend to involve additional areas of the colon. The American College of Gastroenterology (ACG) recommends a treat-to-target approach and recommend therapeutic management should be guided by diagnosis (i.e., Montreal classification), assessment of disease activity (i.e., mild, moderate, and severe), and disease prognosis. The ACG treatment recommendations are further broken down into induction therapies and maintenance of

remission. The 2019 ACG treatment guidelines recommend the following for therapeutic management of UC:

Induction of remission:

- Mildly active disease:
  - Rectal 5-ASA at a dose of 1 g/day with or without oral 5-ASA at a dose of at least 2 g/day for left-sided UC
  - Rectal 5-ASA at a dose of 1 g/day for ulcerative proctitis
  - Oral 5-ASA at a dose of at least 2 g/day for extensive UC
  - Add oral budesonide multi-matrix (MMX) 9 mg/day for patients that are intolerant or non-responsive to oral and/or rectal and oral 5-ASA at appropriate doses
- Moderately active disease:
  - Oral budesonide multi-matrix (MMX) 9 mg/day for induction of remission
- Moderately to severely active disease:
  - Oral systemic corticosteroids, TNF inhibitors (i.e., adalimumab, golimumab, or infliximab), tofacitinib, or vedolizumab to induce remission
  - Combination of infliximab with thiopurine therapy when using infliximab for induction
  - Switch to tofacitinib or vedolizumab for induction in patients that have failed TNF inhibitors
  - Patients with initial response to TNF inhibitors that lose response should have antibody levels and serum drug levels tested to assess reason for loss of response. If serum levels are adequate, use of another TNF inhibitor is not likely to be of benefit.

Maintenance of remission:

- Previously mildly active disease:
  - Rectal 5-ASA at a dose of 1 g/day in patients with ulcerative proctitis
  - Oral 5-ASA at a dose of at least 2 g/day in patients with left-sided or extensive UC
- Previously moderately to severely active disease:
  - Thiopurines in patients that achieved remission due to corticosteroid induction
  - Continue TNF inhibitors (i.e., adalimumab, golimumab, or infliximab) for remission due to TNF induction
  - Continue vedolizumab for remission due to vedolizumab induction
  - Continue tofacitinib for remission due to tofacitinib induction

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

- Use either standard-dose mesalamine (2-3 g/day) or diazo-bonded 5-ASA for patients with extensive UC for induction of remission and maintenance of remission

- May add rectal mesalamine to oral 5-ASA in patients with extensive or left-sided UC for induction of remission and maintenance of remission
- Use high dose mesalamine (>3 g/day) with rectal mesalamine in patients with suboptimal response to standard-dose mesalamine, diazo-bonded 5-ASA, or with moderate disease activity 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

The American Gastroenterology Association (AGA) published recommendations for the management of moderate to severe UC.

- Standard of care is to continue agents initiated for induction therapy as maintenance therapy, if they are effective (excluding corticosteroids and cyclosporine)
- Adult outpatients with moderate to severe UC:
    - Infliximab, adalimumab, golimumab, vedolizumab, tofacitinib or ustekinumab are strongly recommended over no treatment
    - Biologic naïve patients:
        - infliximab or vedolizumab are conditionally recommended over adalimumab for induction of remission
        - Recommend tofacitinib only be used in the setting of a clinical or registry study
    - Previous exposure to infliximab, particularly those with primary non-response, ustekinumab or tofacitinib are conditionally recommended over vedolizumab or adalimumab for induction of remission
    - Conditionally recommend against use of thiopurine monotherapy for induction, but may be used for maintenance of remission over no treatment

OTHER DISORDERS

Uveitis

Uveitis is characterized by inflammation of the uvea, which is the middle portion of the eye; the anterior portion of the uvea includes the iris and ciliary body, and the posterior portion of the uvea is known as the choroid. Treatment of non-infectious uveitis depends on the location of inflammation. Anterior uveitis is generally treated with topical glucocorticoids, such as prednisolone ophthalmic drops. Uveitis that is primarily posterior to the lens is generally not responsive to topical medication, although some experts are increasingly using difluprednate. Oral corticosteroids continue to be the mainstay of treatment for noninfectious intermediate, posterior, and pan uveitis. Intraocular and periocular injections of triamcinolone or glucocorticoids are also options, although patients may decline the injections. Systemic treatment is generally reserved for resistant inflammation and may be indicated in patients with glaucoma who cannot be treated with local injection. If remission has been achieved for 6 to 12 months with systemic glucocorticoids, the maintenance dose may be gradually discontinued. The American Academy of Ophthalmology recommends the use of immunosuppressive agents, such as methotrexate, azathioprine, mycophenolate, cyclosporine, and tacrolimus, for patients that are

intolerant and/or resistant to systemic corticosteroids. TNF-inhibitors, such as adalimumab, are recommended if the patient is inadequately controlled by corticosteroids and non-corticosteroid systemic immunomodulatory therapies.

Giant Cell Arteritis (GCA)

Giant cell arteritis (GCA) is a blood vessel disease that commonly occurs with polymyalgia rheumatica. It is a type of vasculitis involving mostly the arteries of the scalp and head, especially the arteries over the temples. Eyesight can be affected if GCA spreads to the blood vessels that supply the eye. Treatment should begin as soon as possible to prevent loss of vision.

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

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 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), 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 do not include genetic confirmation, and therefore can be applied in places where genetic testing is not available. The diagnostic criteria for CAPS are as follows:

- Raised inflammatory markers (CRP/SAA)
- 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

FCAS is characterized by episodes of rash, fever, and joint pain following generalized exposure to cold. Attacks usually occur 1 to 2 hours after exposure and last less than 24 hours. Patients experience urticaria, arthralgia, fever with chills, severe thirst, red-eyes, and headache after a general cold exposure, including air conditioning. In MWS, inflammation can occur spontaneously as well as from triggers, such as stress, cold, or exercise, with episodes lasting from one to three days. MWS shares the same characteristics as FCAS, but is also characterized by renal amyloidosis, sensorineural hearing loss, and conjunctivitis. Hearing loss, partial or complete, often develop by teenage years.

NOMID is a rare chronic inflammatory disease. NOMID is characterized by fever, urticarial rash, aseptic meningitis, deforming arthropathy, hearing loss, and intellectual disability. An urticaria-like rash develops within the first six weeks of life, and a characteristic bony overgrowth predominantly involving the knees develops in most affected children. Therapies are aimed at suppressing inflammation and have included high-dose corticosteroids, disease-modifying antirheumatic drugs, and biologic agent targeting tumor necrosis factor (TNF). Selective blockade of interleukin-1B is effective in the pathophysiology and organ-specific manifestations of NMOSD, in particular the CNS manifestations of the disease.

Treatment aims are to suppress systemic inflammation, to improve functionality, to prevent organ damage, and to increase patient's quality of life. To achieve these aims, cytokine targeting drugs are important and evidence-based treatment. Since IL-1 plays a central role in CAPS pathogenesis, the anti-IL1 treatments (anakinra, canakinumab, and rilonacept) are recommended for the whole CAPS spectrum.

Granulomatosis with Polyangiitis (GPA)

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a rare blood vessel disorder. Common symptoms for GPA include runny nose/nasal congestion, frequent nose bleeds, sinus pain, shortness of breath, and cough. Other early symptoms include fever, weight loss, fatigue, eye problems (vision and/or redness), night sweats, and numbness in fingers, toes, or limbs. Organ failure can be a result of ongoing inflammation, and without treatment, GPA can worsen rapidly, leading to life-threatening liver or kidney failure. Therapy for GPA has two main components: induction of remission with initial immunosuppressive therapy and maintenance of remission with immunosuppressive therapy for variable period to prevent relapse.

Immunosuppressive therapy is warranted in almost all patients with active GPA. Initial induction therapy in GPA depends on the severity of disease. Patients with mild disease are typically started on prednisone in combination with methotrexate (MTX). Patients with severe disease are typically started on glucocorticoids combined with either cyclophosphamide or rituximab. Patients with very severe disease can also benefit from plasma exchange. Patients that achieve remission (which usually occurs within 3 to 6 months) are typically transitioned from cyclophosphamide or rituximab, to less toxic maintenance immunosuppressants, such as MTX, azathioprine, mycophenolate mofetil, or rituximab.

Treatment resistance in GPA is defined as the presence of active disease affecting a major organ despite optimal initial immunosuppressive therapy with glucocorticoids plus either cyclophosphamide or rituximab for an adequate period of time (usually 6 months or 3 months in a patient who is dialysis dependent). The first step for management of treatment resistant GPA is to ensure that the clinical abnormalities are not due to drug toxicity, nonadherence, an inadequate regimen, progression of chronic inactive disease, infection, and/or pathogenic processes other than ongoing inflammation. Treatment strategy is dependent on initial induction therapy, whether cyclophosphamide or rituximab was used, then the other agent is tried for treatment resistant GPA. If both agents have been tried and failed, or there are contraindications to cyclophosphamide and rituximab, then mycophenolate mofetil is the next recommended option.

The role of anti-TNF therapy has unproven efficacy for GPA. Infliximab was studied in an open label study with 16 patients with acute ANCA-associated vasculitis at first presentation or relapse and in 16 patients with persistent disease despite multiple immunosuppressive regiments. Serious infections and deaths were reported despite remission achieved in 14 patients of each group.

Behcet's Disease (BD)

Behcet's disease (BD) is a type of vasculitis that involves numerous organ systems, such as the skin, mucosa, joints, eyes, veins, arteries, nervous system, and gastrointestinal system. BD runs a relapsing and remitting course, and a multidisciplinary approach is necessary for optimal care. The goal of treatment is to suppress inflammatory exacerbations and recurrences to prevent irreversible organ damage.

Chronic oral ulceration can cause scaring requiring vigorous treatment to prevent oropharyngeal narrowing. The European League Against Rheumatism recommends topical measures, such as steroids, for the treatment of oral and genital ulcers. Colchicine is recommended for the prevention of recurrent mucocutaneous lesions. Patients with lesions that continue to recur despite colchicine may use immunomodulatory or immunosuppressive agents, such as azathioprine, tumor necrosis factor (TNF) inhibitors, or apremilast.

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), Olumiant (baricitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (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

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** of the conventional agents used in the treatment of CD **OR** c. The member has an FDA labeled contraindication to **ALL** of the 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** of the following preferred products for at least a 3-month trial per product: • Adalimumab-aaty • Adalimumab-adaz • Entyvio (vedolizumab) subcutaneous injection • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Simlandi (adalimumab-ryvk) • Skyrizi (risankizumab-rzaa) • Stelara (ustekinumab) **OR** b. 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** of the following preferred products: • Adalimumab-aaty • Adalimumab-adaz • Entyvio (vedolizumab) subcutaneous injection • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Simlandi (adalimumab-ryvk) • Skyrizi (risankizumab-rzaa) • Stelara (ustekinumab) **OR**

	c. The member has an FDA labeled contraindication to **ALL** of the following: • Adalimumab-aaty • Adalimumab-adaz • Entyvio (vedolizumab) subcutaneous injection • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Simlandi (adalimumab-ryvk) • Skyrizi (risankizumab-rzaa) • Stelara (ustekinumab) **OR** d. **ALL** of the following are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried agents for the requested indication: • Adalimumab-aaty • Adalimumab-adaz • Entyvio (vedolizumab) subcutaneous injection • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Simlandi (adalimumab-ryvk) • Skyrizi (risankizumab-rzaa) • Stelara (ustekinumab) 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** of the conventional agents used in the treatment of UC **OR** c. The member has an FDA labeled contraindication to **ALL** of the 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** of the following preferred products for at least a 3-month trial per product: • Adalimumab-aaty • Adalimumab-adaz • Entyvio (vedolizumab) subcutaneous injection • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Simlandi (adalimumab-ryvk) • Skyrizi (risankizumab-rzaa) • Stelara (ustekinumab) • Tremfya (guselkumab) • Xeljanz/Xeljanz XR (tofacitinib) **OR** b. 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** of the following preferred products: • Adalimumab-aaty • Adalimumab-adaz • Entyvio (vedolizumab) subcutaneous injection

	• Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Simlandi (adalimumab-ryvk) • Skyrizi (risankizumab-rzaa) • Stelara (ustekinumab) • Tremfya (guselkumab) • Xeljanz/Xeljanz XR (tofacitinib) c. The member has an FDA labeled contraindication to **ALL** of the following: • Adalimumab-aaty • Adalimumab-adaz • Entyvio (vedolizumab) subcutaneous injection • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Skyrizi (risankizumab-rzaa) • Simlandi (adalimumab-ryvk) • Stelara (ustekinumab) • Tremfya (guselkumab) • Xeljanz/Xeljanz XR (tofacitinib) **OR** d. **ALL** of the following are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried agents for the requested indication: • Adalimumab-aaty • Adalimumab-adaz • Entyvio (vedolizumab) subcutaneous injection • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Skyrizi (risankizumab-rzaa) • Simlandi (adalimumab-ryvk)

	• Stelara (ustekinumab) • Tremfya (guselkumab) • Xeljanz/Xeljanz XR (tofacitinib) 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), Olumiant (baricitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (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 (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (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, and immune checkpoint inhibitor-related adverse effects – 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 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 trial **OR** 2. The member has an intolerance or hypersensitivity to **TWO** different NSAIDs used in the treatment of AS **OR** 3. The member has an FDA labeled contraindication to **ALL** NSAIDs used in the treatment of AS **OR** 4. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of AS	• 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 trial **OR** 2. The member has an intolerance or hypersensitivity to **TWO** NSAIDs used in the treatment of nr-axSpA **OR** 3. The member has an FDA labeled contraindication to **ALL** NSAIDs used in the treatment of nr-axSpA **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 nr-axSpA	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10
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	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10

	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 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** of the conventional agents used in the treatment of CD **OR** 3. The member has an FDA labeled contraindication to **ALL** of the conventional agents used in the treatment of CD **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'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	
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 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** of the conventional agents used in the treatment of HS **OR** 3. The member has an FDA labeled contraindication to **ALL** of the 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	• 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 HS	
Immune checkpoint inhibitor-related adverse effects	**ALL** 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) c. Myocarditis d. Moderate or severe pneumonitis (Grade 2 or greater) e. Severe or life-threatening acute kidney injury and elevated serum creatinine (Grade 3 or 4) f. Moderate or severe inflammatory arthritis g. Uveitis **AND** 3. **EITHER** of the following: a. Member has had an inadequate response to, intolerable adverse effects with, or a contraindication to an adequate trial of systemic corticosteroid treatment **OR** b. Member has been unable to taper off systemic steroids after at least 2 weeks of treatment	• 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	• 10 mg/kg X 1 dose

	immunoglobulin (IVIG) [the specific adverse effect or contraindication must be provided]	
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** b. Member has contraindications to long-term use of glucocorticoids	• 10 mg/kg X 1 dose
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, anthralin, calcipotriene, calcitriol, coal tar products, 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** of the	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10

	conventional agents used in the treatment of PS **OR** c. The member has an FDA labeled contraindication to **ALL** of the 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], rapidly progressive) **OR** f. The member's medication history indicates use of another biologic immunomodulator agent **OR** Otezla that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PS	
Active 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** of the conventional agents used in 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

	OR 3. The member has an FDA labeled contraindication to **ALL** of the conventional agents used in the treatment of PsA **OR** 4. The member has severe active PsA (e.g., erosive disease, elevated markers of inflammation [e.g., ESR, CRP] attributable to PsA, long-term damage that interferes with function [i.e., joint deformities], rapidly progressive) **OR** 5. The member has concomitant severe psoriasis (PS) (e.g., greater than 10% body surface area involvement, occurring on select locations [i.e., hands, feet, scalp, face, or genitals], intractable pruritus, serious emotional consequences) **OR** 6. The member's medication history indicates use of another biologic immunomodulator agent **OR** Otezla that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PsA	
Moderately to severely active rheumatoid arthritis (RA)	**ONE** of the following: 1. The member has tried and had an inadequate response to maximally tolerated methotrexate (e.g., titrated to 25 mg weekly) after at least a 3-month duration of therapy **OR** 2. The member has tried and had an inadequate response to another conventional agent (i.e., hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA 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

	3. The member has an intolerance or hypersensitivity to **ONE** of the following conventional agents (i.e., maximally tolerated methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** 4. The member has an FDA labeled contraindication to **ALL** of the following conventional agents (i.e., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** 5. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of RA	
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** of the conventional agents used in the treatment of UC **OR** 3. The member has an FDA labeled contraindication to **ALL** of the 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** of the conventional agents used in 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

	OR 4. The member has an FDA labeled contraindication to **ALL** of the 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 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 oral corticosteroids 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 periocular or intravitreal corticosteroid injections in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis **OR** iii. The member has an intolerance or hypersensitivity to 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 **BOTH** oral corticosteroids and periocular/intravitreal corticosteroids **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** 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]	• Initial: 10 mg/kg at weeks 0, 2, and 6 • Maintenance: 10 mg/kg every 4 weeks starting at week 10
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	**ONE** of the following: 1. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., methotrexate, leflunomide)	• Initial: 10 mg/kg at weeks 0, 2, and 6

idiopathic arthritis (PJIA)	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** of the conventional agents used in the treatment of PJIA **OR** 3. The member has an FDA labeled contraindication to **ALL** of the conventional agents used in the treatment of PJIA **OR** 4. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PJIA	• 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, 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 (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (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)	• Initial: 5 mg/kg at weeks 0, 2, and 6 • Maintenance: 5 mg/kg every 8 weeks (beginning at week 14)

Ulcerative Colitis (UC) Adults and Children (greater than 6 years of age)	
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 – M05.79	Rheumatoid arthritis with rheumatoid factor without organ or systems involvement
M05.80 – M05.89	Other rheumatoid arthritis with rheumatoid factor
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.00 – M06.09	Rheumatoid arthritis without rheumatoid factor

M06.20 – M06.29	Rheumatoid bursitis
M06.30 – M06.39	Rheumatoid nodule
M06.4	Inflammatory polyarthropathy
M06.80 – M06.89	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

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.

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

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/13/24.

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.