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Subject: Tocilizumab (Actemra) Injection and Infusion and tocilizumab-bavi (Tofidence) Infusion

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DESCRIPTION:

Tocilizumab (Actemra) is a monoclonal antibody that binds to and ultimately blocks soluble and membrane-bound interleukin-6 (IL-6). Interleukin-6 is a proinflammatory cytokine that affects the function of neutrophils, T-cells, B-cells, monocytes, and osteoclasts and is over-expressed in the synovial tissue in patients with rheumatoid arthritis (RA). Additionally, IL-6 has been linked to other inflammatory conditions including systemic juvenile idiopathic arthritis (SJIA) and polyarticular juvenile idiopathic arthritis (PJIA). Tocilizumab was initially approved by the US Food and Drug Administration (FDA) in January 2010 to reduce the signs and symptoms of moderate to severe RA in adults who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonists. The indication was revised in October 2012 to persons with an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). In 2011, tocilizumab was approved alone or in combination with methotrexate for the treatment of active SJIA in children 2 years of age or older and in April 2013 tocilizumab was granted approval for the treatment of active PJIA in children 2 years of age or older. In May 2017, subcutaneous tocilizumab was FDA-approved for the treatment of giant cell arteritis (GCA) in adult patients in combination with a tapering course of glucocorticoids. It is the first FDA-approved treatment for this disease. In February 2022, the GCA indication was expanded to include the use of IV tocilizumab. The subcutaneous formulation of tocilizumab was first approved in October 2013 for RA. In May 2018, the subcutaneous formulation was approved for the treatment of PJIA. In September 2018, the subcutaneous formulation was approved for the treatment of SJIA. In March 2021, the subcutaneous formulation was approved for the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD) for slowing the rate of decline in pulmonary function in adult patients. The subcutaneous formulation is now FDA-approved for the treatment of RA, PJIA, SJIA, SSc-ILD, and GCA. In August 2017, coinciding with approval of the first chimeric antigen receptor (CAR) T-cell therapy tisagenlecleucel (Kymriah), IV tocilizumab was FDA-approved for the treatment of CAR T-cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients 2 years of age and older. Tocilizumab was granted orphan drug designation by the FDA for the treatment of CAR T cell-induced CRS early in the same month. Actemra also received orphan designation (but not an FDA-approved indication) for the treatment of systemic sclerosis in 2013.

In 2018 the National Comprehensive Cancer Network (NCCN) began publishing its guideline Management of Immunotherapy-Related-Toxicities. Tocilizumab is recommended (category 2A) for additional disease modifying antirheumatic therapy for management of moderate or severe immunotherapy-related inflammatory arthritis if no improvement after holding immunotherapy and treating with oral corticosteroids or if unable to taper corticosteroids, additional disease modifying antirheumatic therapy for polymyalgia rheumatica if unable to taper prednisone or no improvement in symptoms, and additional therapy for management of immunotherapy-related giant cell arteritis (urgent referral to rheumatology even in mild cases. NCCN also includes recommendation for the use of IV tocilizumab for cytokine release syndrome (CRS) or neurotoxicity related to blinatumomab or CAR T-cell therapy. Tocilizumab is also recommended for acute graft-versus-host disease (GVHD) and Castleman's Disease. In June 2021, the IV use of Actemra was granted an Emergency Use Authorization (EUA) by the FDA for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). In December 2022, IV Actemra was granted FDA-approval for the treatment of hospitalized adult patients with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. The EUA still applies for pediatric patients 2 to less than 18 years of age. In September 2023, the FDA approved the first biosimilar to IV Actemra, tocilizumab-bavi (Tofidence). Tofidence is approved for the treatment of moderately to severely active RA, PJIA, and SJIA. The FDA approval of Tofidence was based on a comprehensive analytical, non-clinical and clinical data package submitted by Biogen to the FDA in September 2022.

RHEUMATOID DISORDERS

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 aged 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

<u>SJIA without MAS</u>

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.

OTHER DISORDERS

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

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.

Systemic Sclerosis (Scleroderma)-Associated Interstitial Lung Disease (ILD)

Systemic sclerosis (SSc) is a connective tissue disease (CTD) that affects numerous organ systems, including skin, blood vessels, heart, lungs, kidneys, gastrointestinal, and musculoskeletal. Pulmonary disease is the leading cause of death in patients with systemic sclerosis, and ILD is a common manifestation that tends to occur early in the course of systemic sclerosis

The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) collaborated on classification criteria for the diagnosis of systemic sclerosis, in which they note that systemic sclerosis associated ILD is diagnosed when there is radiographic evidence of diffuse parenchymal lung disease in patients with systemic sclerosis. The ACR/EULAR criteria note that ILD is defined as pulmonary fibrosis seen on HRCT or chest radiography, most pronounced in the basilar portions of the lungs.

The American College of Rheumatology (ACR) published a treatment algorithm for systemic sclerosis and related conditions. The ACR recommends the following treatment options for ILD associated with systemic sclerosis

Induction therapy:

- Mycophenolate mofetil (MMF) as first line therapy
- IV cyclophosphamide (CYC) as second line therapy
- Rituximab as third line therapy
- Lung transplant or hemopoietic stem cell transplant for select patients as fourth line therapy

Maintenance therapy:

- MMF as first line therapy
- Azathioprine as second line therapy
- IV or oral CYC as third line therapy

Recent recommendations from the ACR suggest early first line treatment with tocilizumab based on the efficacy and safety from phase II and phase III clinical trials. MMF and CYC are alternative options, but do not have clinical trial data showing efficacy and safety for patients with subclinical ILD. Patients that have clinical evidence of skin and/or musculoskeletal manifestations and inactive disease, MMF, CYC, and nintedanib are the preferred first line options for patients with SSc-ILD. Patients with clinical

evidence of skin and/or musculoskeletal manifestations and active disease, tocilizumab, MMF, and CYC are suggested as initial therapy. After treatment is initiated, patients should be followed up every 4 months until disease stabilization. Patients that achieve stabilization on first line therapy, should continue first line therapy for maintenance therapy.

POSITION STATEMENT:

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

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) of the subcutaneous formulation of tocilizumab 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 tocilizumab (Actemra) or tocilizumab-bavi (Tofidence).

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

Table 1

Disease State	Step 1		Step 2 (Directed to ONE step 1 agent)	Step 3a (Directed to TWO step 1 agents)	Step 3b (Directed to TWO agents from step 1 and/or step 2)	Step 3c (Directed to THREE step 1 agents)
	Step 1a	Step 1b (Directed to ONE TNF inhibitor) NOTE: Please see Step 1a for preferred TNF inhibitors				
Rheumatoid Disorders						
Ankylosing Spondylitis (AS)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx, Enbrel, Hadlima, Humira	Oral: Rinvoq, Xeljanz, Xeljanz XR	N/A	SQ: Cimzia, Simponi, Taltz	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Nonradiographic Axial Spondyloarthritis (nr-axSpA)	SQ: Cimzia, Cosentyx	Oral: Rinvoq	N/A	SQ: Taltz	N/A	N/A

Polyarticular Juvenile Idiopathic Arthritis (PJIA)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Enbrel, Hadlima, Humira	Oral: Xeljanz	SQ: **Actemra** (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira is a required Step 1 agent)	N/A	SQ: Orencia	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Psoriatic Arthritis (PsA)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx, Enbrel, Humira, Hadlima, Skyrizi, Stelara, Tremfya Oral: Otezla	Oral: Rinvoq, Xeljanz, Xeljanz XR	N/A	SQ: Cimzia, Orencia, Simponi, Taltz	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Rheumatoid Arthritis	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Enbrel, Hadlima, Humira	Oral: Rinvoq, Xeljanz, Xeljanz XR	SQ: **Actemra** (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira is a required Step 1 agent)	Oral: Olumiant SQ: Cimzia, Kevzara, Kineret, Orencia, Simponi	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Dermatological Disorders						
Hidradenitis Suppurativa (HS)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx, Hadlima, Humira	N/A	N/A	N/A	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Psoriasis (PS)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx,	N/A	N/A	SQ: Cimzia	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**,

	Enbrel, Hadlima, Humira, Skyrizi, Stelara, Tremfya Oral: Otezla					Bimzelx, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Siliq, Taltz, Yuflyma**, Yusimry** Oral: Sotyktu
Inflammatory Bowel Disease						
Crohn's Disease	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira, Skyrizi, Stelara	Oral: Rinvoq	N/A	SQ: Cimzia (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira are required Step 1 agents)	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Ulcerative Colitis	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira, Stelara	Oral: Rinvoq, Xeljanz, Xeljanz XR	SQ: Simponi (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira is a required Step 1 agent)	N/A	Zeposia (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira, Rinvoq, Stelara, OR Xeljanz/Xeljanz XR are required Step agents)	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Entyvio, Hulio**, Hyrimoz**, Idacio**, Omvoh, Yuflyma**, Yusimry** Oral: Velsipity
Other						
Uveitis	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira	N/A	N/A	N/A	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Indications Without Prerequisite Biologic Immunomodulators						
Alopecia Areata (AA) Atopic Dermatitis	N/A	N/A	N/A	N/A	N/A	N/A

Deficiency of IL-1 Receptor Antagonist (DIRA) Enthesitis Related Arthritis (ERA) Giant Cell Arteritis (GCA) Neonatal-Onset Multisystem Inflammatory Disease (NOMID) Polymyalgia Rheumatica (PMR) Systemic Juvenile Idiopathic Arthritis (SJIA) Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD)						

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

****Note**: Amjevita (one of: 10 mg/0.2 mL, 20 mg/0.4 mL, 40 mg/0.8 mL), Hadlima, and Humira are required Step 1 agents

Note: Branded generic available for Cyltezo, Hulio, Hyrimoz, and Idacio and are included as a target at same step level in this program

SUBCUTANEOUS ACTEMRA (PHARMACY BENEFIT)

Initiation of subcutaneous tocilizumab (Actemra) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "7"):

1. **ONE** of the following ("a", "b", or "c"):
    a. Information has been provided that indicates the member has been treated with subcutaneous tocilizumab (starting on samples is not approvable) within the past 90 days
    b. The prescriber states the member has been treated with subcutaneous tocilizumab (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 tocilizumab will be used for the treatment of an indication listed in Table 2, and **ALL** of the indication-specific criteria are met
        ii. **EITHER** of the following 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 tocilizumab
            II. The prescriber has provided information in support of using subcutaneous tocilizumab for the member's age
2. The prescriber is a specialist in the area of the member's diagnosis (e.g., rheumatologist for JIA, PsA, RA; pulmonologist, radiologist, pathologist, rheumatologist for SSc-ILD) or has consulted with a specialist in the area of the member's diagnosis

3. Member does **NOT** have any FDA labeled contraindications to subcutaneous tocilizumab
4. Member has been tested for latent tuberculosis (TB) **AND**, if positive, the member has begun therapy for latent TB
5. Member will **NOT** be using subcutaneous tocilizumab in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), 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. If subcutaneous tocilizumab is requested for a diagnosis of systemic sclerosis associated interstitial lung disease, the request is for the Actemra syringe (NOTE: Actemra ACTpen is not approvable for SSc-ILD)
7. **ANY** of the following ("a". "b", or "c"):
    a. The dosage does not exceed 162 mg SQ every week
        - QL: 162 mg/0.9 mL pen - 4 pens (3.6 mL)/28 days
        - QL: 162 mg/0.9 mL syringe - 4 syringes (3.6 mL)/28 days
    b. The requested quantity (dose) exceeds the program quantity limit but does **NOT** exceed the maximum FDA labeled dose **OR** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit
    c. The requested quantity (dose) exceeds the program quantity limit and exceeds the maximum FDA labeled dose **AND** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the prescriber has provided information in support of therapy with a higher dose for the requested indication (submitted copy required, e.g., clinical trials, phase III studies, guidelines required

Approval duration: 12 months

Table 2

Indications and Specific Criteria	
Indication	**Specific Criteria**
Moderately to severely active rheumatoid arthritis (RA)	**BOTH** of the following: 1. **ONE** of the following: a. The member has tried and had an inadequate response to maximally tolerated methotrexate (e.g., titrated to 25 mg weekly) for at least 3 months

	OR b. The member has tried and had an inadequate response to another conventional agent (i.e., hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA for at least 3 months **OR** c. 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** d. 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** e. 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 2. **ANY** of the following: a. The member has tried and had an inadequate response to Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only], Hadlima (adalimumab-bwwd), **OR** Humira (adalimumab) for at least 3 months **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 Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only], Hadlima (adalimumab-bwwd), **OR** Humira (adalimumab) **OR** c. The member has an FDA labeled contraindication to **ALL** of the following: • Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] • Enbrel (etanercept)

	• Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Xeljanz/Xeljanz XR (tofacitinib) d. The prescriber has provided information indicating why **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 • Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] • Enbrel (etanercept) • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Xeljanz/Xeljanz XR (tofacitinib)
Giant cell arteritis (GCA)	**ONE** of the following: 1. The member has tried and had an inadequate response to systemic corticosteroids (e.g., prednisone, methylprednisolone) used in the treatment of GCA for at least 7 to 10 days **OR** 2. The member has an intolerance or hypersensitivity to systemic corticosteroids used in the treatment of GCA **OR** 3. The member has an FDA labeled contraindication to **ALL** systemic corticosteroids **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 GCA
Active systemic juvenile idiopathic arthritis (SJIA)	Diagnosis only
Moderately to severely active	**BOTH** of the following:

polyarticular juvenile idiopathic arthritis (PJIA)	1. **ONE** of the following: a. 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** b. The member has an intolerance or hypersensitivity to **ONE** of the conventional agents used in the treatment of PJIA **OR** c. The member has an FDA labeled contraindication to **ALL** of the conventional agents used in the treatment of PJIA **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 PJIA **AND** 2. **ANY** of the following: a. The member has tried and had an inadequate response to Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only], Hadlima (adalimumab-bwwd), **OR** Humira (adalimumab) for at least 3 months **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 Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only], Hadlima (adalimumab-bwwd), **OR** Humira (adalimumab) **OR** c. The member has an FDA labeled contraindication to **ALL** of the following: • Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] • Enbrel (etanercept) • Hadlima (adalimumab-bwwd)

	• Humira (adalimumab) • Xeljanz/Xeljanz XR (tofacitinib) **OR** d. The prescriber has provided information indicating why **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 • Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] • Enbrel (etanercept) • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Xeljanz/Xeljanz XR (tofacitinib)
Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD)	The patient's diagnosis has been confirmed on high-resolution computed tomography (HRCT) or chest radiography scans
Other indications	The member has another FDA labeled indication or an indication supported in DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a

Continuation of subcutaneous tocilizumab (Actemra) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "7"):

1. An authorization or reauthorization for subcutaneous tocilizumab has been previously approved by Florida Blue
2. Member has had clinical benefit with subcutaneous tocilizumab therapy
3. The prescriber is a specialist in the area of the member's diagnosis (e.g., rheumatologist for JIA, PsA, RA; pulmonologist, radiologist, pathologist, rheumatologist for SSc-ILD) or has consulted with a specialist in the area of the member's diagnosis
4. Member does **NOT** have any FDA labeled contraindications to subcutaneous tocilizumab
5. Member will **NOT** be using subcutaneous tocilizumab in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), 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. If subcutaneous tocilizumab is requested for a diagnosis of systemic sclerosis associated interstitial lung disease, the request is for the Actemra syringe (NOTE: Actemra ACTpen is not approvable for SSc-ILD)
7. **ANY** of the following ("a". "b", or "c"):
    a. The dosage does not exceed 162 mg SQ every week
        - QL: 162 mg/0.9 mL pen - 4 pens (3.6 mL)/28 days
        - QL: 162 mg/0.9 mL syringe - 4 syringes (3.6 mL)/28 days
    b. The requested quantity (dose) exceeds the program quantity limit but does **NOT** exceed the maximum FDA labeled dose **OR** the maximum compendia-supported dose (i.e. DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit
    c. The requested quantity (dose) exceeds the program quantity limit and exceeds the maximum FDA labeled dose **AND** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the prescriber has provided information in support of therapy with a higher dose for the requested indication (submitted copy required, e.g., clinical trials, phase III studies, guidelines required)

Approval duration: 12 months

INTRAVENOUS ACTEMRA AND TOFIDENCE (MEDICAL BENEFIT)

Initiation of intravenous (IV) tocilizumab (Actemra) or IV tocilizumab-bavi (Tofidence) **meets the definition of medical necessity** when **ALL** of the following are met ("1" and "5"):

1. The requested IV tocilizumab product will be used for the treatment of an indication listed in Table 3 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 JIA, PsA, RA) or has consulted with a specialist in the area of the member's diagnosis
3. Member does **NOT** have any FDA labeled contraindications to the requested IV tocilizumab product
4. Member has been tested for latent tuberculosis (TB) **AND**, if positive, the member has begun therapy for latent TB [this requirement does not apply for the treatment of COVID-19]
5. Member will **NOT** be using the requested IV tocilizumab product in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), 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: 12 months (except for CRS, COVID-19, and immune checkpoint inhibitor-related inflammatory arthritis which are approved for 1 month, and acute GVHD which is approved for 6 months)

Table 3

Indications and Specific Criteria		
Indication	**Specific Criteria**	**Maximum Allowable Dose***
Moderately to severely active rheumatoid arthritis (RA)	**ONE** of the following: 1. The member has tried and had an inadequate response to maximally tolerated methotrexate (e.g., titrated to 25 mg weekly) for at least 3 months **OR** 2. The member has tried and had an inadequate response to another conventional agent (i.e., hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA for at least 3 months **OR** 3. The member has an intolerance or hypersensitivity to **ONE** of the following conventional agents (i.e., maximally tolerated methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** 4. The member has an FDA labeled contraindication to **ALL** of the following conventional agents (i.e., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** 5. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of RA	8 mg/kg (maximum of 800 mg) every 4 weeks
Giant cell arteritis (GCA)	**ONE** of the following: 1. The member has tried and had an inadequate response to systemic	6 mg/kg (maximum of 600 mg) every 4 weeks

	corticosteroids (e.g., prednisone, methylprednisolone) used in the treatment of GCA for at least 7 to 10 days **OR** 2. The member has an intolerance or hypersensitivity to systemic corticosteroids used in the treatment of GCA **OR** 3. The member has an FDA labeled contraindication to **ALL** systemic corticosteroids **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 GCA	
Cytokine release syndrome (CRS)	When **BOTH** of the following are met ("1" and "2"): 1. **EITHER** of the following ("a" or "b"): a. Member is experiencing CRS symptoms (e.g., fever, vascular leak, hypotension, pulmonary edema, coagulopathy, organ failure) **OR** b. Tocilizumab is being ordered proactively in anticipation of possible CRS **AND** 2. The member has received **EITHER** of the following in the previous 30 days, **OR** will be receiving **EITHER** of the following in the next 30 days (if tocilizumab is being ordered proactively): a. CAR T-cell therapy b. Blinatumomab (Blincyto) therapy	Less than 30 kg: • 12 mg/kg • No more than 4 total doses given at least 8 hours apart 30 kg or above: • 8 mg/kg (not to exceed 800 mg) • No more than 4 total doses given at least 8 hours apart

Immune checkpoint inhibitor-related adverse effects	When **ALL** of the following are met ("1", "2", and "3"): 1. Member has been receiving treatment with an immune checkpoint inhibitor (e.g., ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, darvalumab) **AND** 2. Member has **ANY** of the following immunotherapy-related adverse effects: a. Moderate or severe inflammatory arthritis b. Giant cell arteritis c. Polymyalgia rheumatica **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 b. Member has been unable to taper off systemic steroids after at least 2 weeks of treatment	4 mg/kg X 1 dose. May repeated one additional 4 mg/kg dose if the member does not have adequate improvement in symptoms.
Active systemic juvenile idiopathic arthritis (SJIA)	Diagnosis only	Less than 30 kg: • 12 mg/kg every 2 weeks 30 kg or above: • 8 mg/k every 2 weeks
Moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA)	**ONE** of the following: 1. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., methotrexate, leflunomide) used in the treatment of PJIA for at least 3 months **OR**	Less than 30 kg: • 10 mg/kg every 4 weeks 30 kg or above: • 8 mg/k every 4 weeks

	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	
Unicentric Castleman's disease (CD)	When **ALL** of the following are met ("1", "2", "3", and "4"): 1. Used as monotherapy for treatment of CD **AND** 2. Member's disease is relapsed or refractory **AND** 3. Member is HIV-negative **AND** 4. Member is human herpesvirus-8-negative	12 mg/kg every 2 weeks
Multicentric Castleman's disease (CD)	When **ALL** of the following are met ("1", "2, and 3"): 1. Used as monotherapy for treatment of CD **AND** 2. Members disease is relapsed or refractory **AND** 3. Member has had an inadequate therapeutic response to at least **TWO** prior treatments	12 mg/kg every 2 weeks
Neuromyelitis optica spectrum disorder (NMOSD)	When **BOTH** of the following are met ("1" and "2"):	8 mg/kg (maximum of 800 mg) every 4 weeks

	1. Member has a history of at least 1 relapse in the previous year **AND** Tocilizumab will not be used concurrently with an alternative biologic agent for the treatment of NMOSD (e.g., eculizumab, inebilizumab, rituximab, satralizumab)	
Acute graft-versus-host disease (GVHD)	**ALL** of the following ("1" to "3"): 1. The member has previously received an allogeneic HSCT **AND** 2. Tocilizumab will be used as additional therapy in conjunction with systemic corticosteroids **AND** 3. The member has steroid-refractory disease	8 mg/kg (maximum of 800 mg) every 2 weeks
Coronavirus disease 2019 (COVID-19) treatment	**ALL** of the following ("1" to "4"): 1. Member is hospitalized **AND** 2. Member is 2 years of age or older **AND** 3. Member is receiving systemic corticosteroids **AND** 4. Member requires supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)	Less than 30 kg: • 12 mg/kg X 1 dose 30 kg or above: • 8 mg/kg X 1 dose (maximum of 800 mg) May repeat one additional dose at least 8 hours after the first dose if clinical signs or symptoms worsen or do not improve.
Orphan Indications (non-FDA approved)		
Systemic sclerosis	When **BOTH** of the following are met ("1"and "2"): 1. Member has severe disease with diffuse skin involvement, interstitial lung disease,	12 mg/kg every 2 weeks

	myocarditis, and/or inflammatory myopathy or arthritis **AND** 2. Member is refractory to systemic immunosuppressive therapy with methotrexate, mycophenolate, or cyclophosphamide, OR has intolerable adverse effects with or a contraindication to immunosuppressive therapy	
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 for the requested indication (submitted copy required; e.g., clinical trials, phase III studies, guidelines required)		

Continuation of intravenous (IV) tocilizumab (Actemra) or IV tocilizumab-bavi (Tofidence) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "6"):

1. An authorization or reauthorization for either IV tocilizumab or IV tocilizumab-bavi has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of a condition in Table 3 (except for CRS, acute GVHD, COVID-19, and immune checkpoint inhibitor-related inflammatory arthritis – see initiation criteria), **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 JIA, PsA, RA) or has consulted with a specialist in the area of the member's diagnosis
3. Member does **NOT** have any FDA labeled contraindications to the requested IV tocilizumab product
4. Member has had clinical benefit with the requested IV tocilizumab product
5. Member will **NOT** be using the requested IV tocilizumab product in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Rinvoq (upadacitinib), Opzelura (ruxolitinib), 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 does not exceed the following based on the specific indication and member weight:
        - RA and NMOSD: 8 mg/kg IV (max of 800 mg) every 4 weeks
        - GCA: 6 mg/kg IV (max of 600 mg) every 4 weeks
        - SJIA/SJRA:
            - Less than 30 kg: 12 mg/kg IV every 2 weeks
            - 30 kg or above: 8 mg/kg IV every 2 weeks
        - JIA:
            - Less than 30 kg: 10 mg/kg IV every 4 weeks
            - 30 kg or above: 8 mg/kg IV every 4 weeks
        - Castleman's Disease and systemic sclerosis: 12 mg/kg IV every 2 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 for the requested indication (submitted copy required; e.g., clinical trials, phase III studies, guidelines required)

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

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

FDA-approved:

Actemra

Tocilizumab is indicated for the treatment of the following conditions:

- Rheumatoid arthritis (RA) in adult patients with moderately to severely active disease who have had an inadequate response to one or more DMARDs (both the IV and SQ routes are FDA-approved)
- Giant cell arteritis (GCA) in adult patients (both the IV and SQ routes are FDA-approved)
- Systemic sclerosis-associated interstitial lung disease (SSc-ILD) for slowing the rate of decline in pulmonary function in adult patients (only the SQ route is FDA-approved)
- Polyarticular juvenile idiopathic arthritis (PJIA) in persons 2 years of age or older with active disease (both the IV and SQ routes are FDA-approved)
- Systemic juvenile idiopathic arthritis (SJIA) in persons 2 years of age or older with active disease (both the IV and SQ routes are FDA-approved)

- Chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients 2 years of age and older (only the IV route is FDA-approved)
- Hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO (only the IV route is FDA-approved)

For the treatment of RA, GCA, PJIA, and SJIA, tocilizumab can be administered as an IV infusion drip over 1 hour or a subcutaneous injection. When administered intravenously, it should not be administered as an IV bolus or push. Initially, the subcutaneous injection should be administered under the guidance of a healthcare practitioner. After proper training, a member may self-inject tocilizumab or the member's caregiver may administer tocilizumab if the healthcare practitioner determines that it is appropriate.

For RA, GCA, SSc-ILD, PJIA and SJIA, therapy should not be initiated in persons with an absolute neutrophil count (ANC) less than 2000 per mm^3, platelet count less than 100,000 mm^3, or an ALT/AST greater than 1.5 times the upper limit of normal (ULN). For COVID-19, therapy should not be initiated in persons with an ANC less than 1000 per mm^3, platelet count below 50,000 mm^3, or ALT or AST greater than 10 times ULN. The recommended dosage, based on indication, is identified in Table 4.

Table 4

FDA-approved indications and dosing			
Indication	**Dose**		
GCA	IV infusion	6 mg/kg (up to a max of 600 mg) every 4 weeks in combination with a tapering course of glucocorticoids. Actemra can be used alone following discontinuation of glucocorticoids.	
	SQ injection	162 mg given once every week in combination with a tapering course of glucocorticoids. Every other week dosing may be prescribed based on clinical considerations. Actemra can be used alone following discontinuation of glucocorticoids. When transitioning from intravenous therapy to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled intravenous dose.	
SSc-ILD	SQ injection	162 mg given once every week. Subcutaneous administration with the prefilled ACTPen autoinjector has not been studied in SSc-ILD.	
RA	IV infusion	4 mg/kg every 4 weeks initially, followed by an increase to 8 mg/kg every 4 weeks based on clinical response. The dose should not exceed 800 mg per infusion.	
	SQ injection	Less than 100 kg	162 mg SQ every other week, followed by an increase to weekly based on clinical response
		At or above 100 kg	162 mg SQ every week
COVID-19	IV infusion	8 mg/kg (not to exceed 800 mg). If clinical signs or symptoms worsen or do not improve after the first dose, one additional	

		infusion may be administered at least 8 hours after the initial infusion.	
CRS	IV infusion	Less than 30 kg	12 mg/kg IV X 1 dose. If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses may be administered. The interval between consecutive doses should be at least 8 hours.
		30 kg or more	8 mg/kg (not to exceed 800 mg) IV X 1 dose. If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses may be administered. The interval between consecutive doses should be at least 8 hours.
PJIA	IV infusion	Less than 30 kg	10 mg/kg IV every 4 weeks
		At or above 30 kg	8 mg/kg IV every 4 weeks
	SQ injection	Less than 30 kg	162 mg once every 3 weeks
		At or above 30 kg	162 mg once every 2 weeks
SJIA	IV infusion	Less than 30 kg	12 mg/kg IV every 2 weeks
		At or above 30 kg	8 mg/kg IV every 2 weeks
	SQ injection	Less than 30 kg	162 mg once every 2 weeks
		At or above 30 kg	162 mg once every week
GCA, giant cell arteritis; RA, rheumatoid arthritis; CRS, cytokine release syndrome; COVID-19, Coronavirus disease 2019; PJIA, polyarticular juvenile idiopathic arthritis; SJIA, systemic juvenile idiopathic arthritis			

Dosage Adjustments: Table 5 reviews recommended dose modifications for laboratory abnormalities associated with treatment of RA, SSc-ILD, and GCA. Dose reduction of tocilizumab has not been studied in SJIA and PJIA populations. Dose interruptions are recommended for liver enzyme abnormalities, low neutrophil counts, and low platelet counts in persons with SJIA and PJIA at levels similar to what is outline for persons with RA.

Table 5

Dose Modifications		
Laboratory Abnormality	**Lab Value**	**Recommendation**
Liver enzymes	Greater than 1 to 3x ULN	Dose modify concomitant DMARDs or immunomodulatory agents if appropriate. For persistent increases in this range

		• IV: reduce tocilizumab dose to 4 mg/kg or interrupt tocilizumab until ALT or AST have normalized • SQ: reduce injection frequency to every other week or hold dosing until ALT/AST have normalized. Resume every other week and increase frequency to every week as clinically appropriate
	Greater than 3 to 5x ULN (confirmed by repeat testing)	Interrupt tocilizumab dosing until less than 3x ULN and follow recommendations above for greater than 1 to 3x ULN. For persistent increases greater than 3x ULN, discontinue tocilizumab.
	Greater than 5x ULN	Discontinue tocilizumab.
Low ANC	Greater than 1000	Maintain dose.
	500-1000	Interrupt tocilizumab dosing. When ANC greater than 1000 cells per mm3: • IV: resume tocilizumab at 4 mg/kg and increase to 8 mg/kg as clinically appropriate • SQ: resume at every other week and increase frequency to every week as clinically appropriate
	Less than 500	Discontinue tocilizumab.
Low platelet count		Interrupt tocilizumab dosing. When platelet count is greater than 100,000 cells per mm3: • IV: resume tocilizumab at 4 mg/ kg and increase to 8 mg/kg as clinically appropriate • SQ: resume at every other week and increase frequency to every week as clinically appropriate.
	Less than 50,000	Discontinue tocilizumab.
ULN, upper limit of normal; DMARD, disease modifying anti-rheumatic drug; ANC, absolute neutrophil count		

Tofidence

Tocilizumab-bavi is indicated for the treatment of the following conditions:

- Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs)
- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis
- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis

Refer to Actemra for dosing recommendations and dosing modifications.

Drug Availability:

Tocilizumab (Actemra) is supplied in the following strengths:

IV Formulation

- 80 mg/4 mL as a single-use vial
- 200 mg/10 mL as a single-use vial
- 400 mg/20 mL as a single-use vial

SQ Formulation

- 162 mg single-use ACTPen autoinjector
- 162 mg single-use prefilled glass syringe

Must be refrigerated at 36°F to 46°F (2ºC to 8ºC). Do not freeze. Protect the vials, syringes, and autoinjectors from light by storage in the original package until time of use, and keep syringes and autoinjectors dry. Once removed from the refrigerator, the prefilled syringe and autoinjector can be stored up to 2 weeks at or below 86°F (30°C). The prefilled syringe and autoinjector must always be kept in the carton.

Tocilizumab-bavi (Tofidence) is supplied in the following strengths:

- 80 mg/4 mL as a single-use vial
- 200 mg/10 mL as a single-use vial
- 400 mg/20 mL as a single-use vial

Must be refrigerated at 36°F to 46°F (2ºC to 8ºC). Do not freeze. Protect the vials from light by storage in the original package until time of use.

PRECAUTIONS:

Boxed Warning

- WARNING: RISK OF SERIOUS INFECTIONS

  Patients treated with tocilizumab 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.

If a serious infection develops, interrupt Actemra/Tofidence until the infection is controlled.

Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients, except those with COVID-19, should be tested for latent tuberculosis before Actemra/Tofidence use and during therapy. Treatment for latent infection should be initiated prior to Actemra/Tofidence use.
- Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
- Bacterial, viral and other infections due to opportunistic pathogens.

The risks and benefits of treatment with Actemra/Tofidence 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 Actemra/Tofidence, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Contraindication

- Do not administer to persons with a history of hypersensitivity to tocilizumab products.

Precautions/Warnings

- **Gastrointestinal perforation:** use with caution in persons who may be at an increased risk.
- **Hepatotoxicity**: monitor patients for signs and symptoms of hepatic injury. Modify or discontinue tocilizumab if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop.
- **Laboratory monitoring:** recommended due to potential consequences of treatment-related changes in neutrophils, platelets, lipids, and liver function tests.
- **Live vaccines:** do not administer with tocilizumab.

BILLING/CODING INFORMATION:

HCPCS Coding:

J3262	Injection, tocilizumab, 1 mg [for intravenous Actemra]
J3590	Unclassified biologics [for subcutaneous Actemra ONLY]
M0249	Intravenous infusion, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, includes infusion and post administration monitoring, first dose
M0250	Intravenous infusion, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive

	mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, includes infusion and post administration monitoring, second dose
Q0249	Injection, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, 1 mg
Q5133	Injection, tocilizumab-bavi (Tofidence), biosimilar, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity for J3262 and Q5133:

B10.89	Other human herpesvirus infection
D47.Z2	Castleman disease
D89.810	Acute graft-versus-host disease
D89.812	Acute on chronic graft-versus-host disease
D89.832	Cytokine release syndrome, grade 2
D89.833	Cytokine release syndrome, grade 3
D89.834	Cytokine release syndrome, grade 4
D89.839	Cytokine release syndrome, grade unspecified
G36.0	Neuromyelitis optica [Devic]
G92.00	Immune effector cell-associated neurotoxicity syndrome, grade unspecified
G92.01	Immune effector cell-associated neurotoxicity syndrome, grade 1
G92.02	Immune effector cell-associated neurotoxicity syndrome, grade 2
G92.03	Immune effector cell-associated neurotoxicity syndrome, grade 3
G92.04	Immune effector cell-associated neurotoxicity syndrome, grade 4
M05.00 – M05.09	Felty's syndrome
M05.10 – M05.19	Rheumatoid lung disease with rheumatoid arthritis
M05.20 – M05.29	Rheumatoid vasculitis with rheumatoid arthritis
M05.30 – M05.39	Rheumatoid heart disease with rheumatoid arthritis
M05.40 – M05.49	Rheumatoid myopathy with rheumatoid arthritis
M05.50 – M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis
M05.60 – M05.69	Rheumatoid arthritis with involvement of other organs and systems
M05.70 – M05.7A	Rheumatoid arthritis with rheumatoid factor without organ or systems involvement
M05.80 – M05.8A	Other rheumatoid arthritis with rheumatoid factor
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.00 – M06.0A	Rheumatoid arthritis without rheumatoid factor
M06.20 – M06.29	Rheumatoid bursitis
M06.30 – M06.39	Rheumatoid nodule
M06.4	Inflammatory polyarthropathy [for immunotherapy-related inflammatory arthritis ONLY]
M06.80 – M06.8A	Other specified rheumatoid arthritis
M06.9	Rheumatoid arthritis, unspecified
M08.09	Unspecified juvenile rheumatoid, multiple sites
M08.20 – M08.2A	Juvenile rheumatoid arthritis with systemic onset

M08.3	Juvenile rheumatoid polyarthritis (seronegative)
M08.89	Other juvenile arthritis, multiple sites
M31.5	Giant cell arteritis with polymyalgia rheumatica
M31.6	Other giant cell arteritis
M34.0 – M34.9	Systemic sclerosis [scleroderma]
R59.0 – R59.9	Enlarged lymph nodes
T80.82XA	Complication of immune effector cellular therapy, initial encounter
T80.82XS	Complication of immune effector cellular therapy, subsequent encounter
U07.1	COVID-19

ICD-10 Diagnosis Codes That Support Medical Necessity for J3590 (for Actemra SC ONLY):

M05.00 – M05.09	Felty's syndrome
M05.10 – M05.19	Rheumatoid lung disease with rheumatoid arthritis
M05.20 – M05.29	Rheumatoid vasculitis with rheumatoid arthritis
M05.30 – M05.39	Rheumatoid heart disease with rheumatoid arthritis
M05.40 – M05.49	Rheumatoid myopathy with rheumatoid arthritis
M05.50 – M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis
M05.60 – M05.69	Rheumatoid arthritis with involvement of other organs and systems
M05.70 – M05.7A	Rheumatoid arthritis with rheumatoid factor without organ or systems involvement
M05.80 – M05.8A	Other rheumatoid arthritis with rheumatoid factor
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.00 – M06.0A	Rheumatoid arthritis without rheumatoid factor
M06.20 – M06.29	Rheumatoid bursitis
M06.30 – M06.39	Rheumatoid nodule
M06.80 – M06.8A	Other specified rheumatoid arthritis
M06.9	Rheumatoid arthritis, unspecified
M08.09	Unspecified juvenile rheumatoid, multiple sites
M08.20 – M08.2A	Juvenile rheumatoid arthritis with systemic onset
M08.3	Juvenile rheumatoid polyarthritis (seronegative)
M08.89	Other juvenile arthritis, multiple sites
M31.5	Giant cell arteritis with polymyalgia rheumatica
M31.6	Other giant cell arteritis
M34.81	Systemic sclerosis with lung involvement

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date. The Site of Care Policy for Select Specialty Medications does not apply to Medicare Advantage members.

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

DEFINITIONS:

B cells: lymphocytes that play a large role in the humoral immune response (as opposed to the cell-mediated immune response, which is governed by T cells). The principal functions of B cells are to make antibodies against antigens, perform the role of antigen-presenting cells (APCs) and eventually develop into memory B cells after activation by antigen interaction. B cells are an essential component of the adaptive immune system.

Cytokines: any of a number of substances that are secreted by specific cells of the immune system which carry signals locally between cells, and thus have an effect on other cells.

DMARDs: An acronym for disease-modifying antirheumatic drugs. These are drugs that modify the rheumatic disease processes, and slow or inhibit structural damage to cartilage and bone. These drugs are unlike symptomatic treatments such as NSAIDs that do not alter disease progression. DMARDs can be further subcategorized. With the release of biologic agents (e.g., anti-TNF drugs), DMARDs were divided into either: (1) conventional, traditional, synthetic, or non-biological DMARDs; or as (2) biological DMARDs. However, with the release of newer targeted non-biologic drugs and biosimilars, DMARDs are now best categorized as: (1) conventional synthetic DMARDs (csDMARD) (e.g., MTX, sulfasalazine), (2) targeted synthetic DMARDs (tsDMARD) (e.g., tofacitinib, apremilast), and (3) biological DMARDs (bDMARD), which can be either a biosimilar DMARD (bsDMARD) or biological originator DMARD (boDMARD).

Fibroblast: a type of cell that synthesizes the extracellular matrix and collagen, the structural framework (stroma) for animal tissues, and plays a critical role in wound healing.

Interleukin-6 (IL-6): a protein that in humans is encoded by the IL6 gene. It acts as both a pro-inflammatory and anti-inflammatory cytokine. It is secreted by T cells and macrophages to stimulate immune response to trauma, especially burns or other tissue damage leading to inflammation.

Lymphocyte: a type of white blood cell in the vertebrate immune system.

Macrophages: white blood cells within tissues, produced by the division of monocytes.

Monocyte: a type of white blood cell, part of the human body's immune system.

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.

T cells or T lymphocytes: belong to a group of white blood cells known as lymphocytes and play a central role in cell-mediated immunity.

RELATED GUIDELINES:

Abatacept (Orencia), 09-J0000-67
Adalimumab (Humira), 09-J0000-46
Anakinra (Kineret), 09-J0000-45
Baricitinib (Olumiant), 09-J3000-10
Certolizumab Pegol (Cimzia), 09-J0000-77
Etanercept (Enbrel), 09-J0000-38
Golimumab (Simponi, Simponi Aria), 09-J1000-11
Infliximab Products [infliximab (Remicade), infliximab-dyyb (Inflectra), and infliximab-abda (Renflexis)], 09-J0000-39
Sarilumab (Kevzara), 09-J2000-87
Tofacitinib (Xeljanz, Xeljanz XR) Oral Solution, Tablet and Extended-Release Tablet, 09-J1000-86
Upadacitinib (Rinvoq), 09-J3000-51

OTHER:

Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy
Abrilada (adalimumab-afzb)
Actemra (tocilizumab)
Adalimumab
Adbry (tralokinumab-ldrm)
Amjevita (adalimumab-atto)
Arcalyst (rilonacept)
Avsola (infliximab-axxq)
Benlysta (belimumab)
Bimzelx (bimekizumab-bkzx)
Cimzia (certolizumab)
Cinqair (reslizumab)
Cosentyx (secukinumab)
Cyltezo (adalimumab-adbm)
Dupixent (dupilumab)
Enbrel (etanercept)
Entyvio (vedolizumab)
Fasenra (benralizumab)
Hadlima (adalimumab-bwwd)
Hulio (adalimumab-fkjp)
Humira (adalimumab)
Hyrimoz (adalimumab-adaz)
Idacio (adalimumab-aacf)

Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)
Nucala (mepolizumab)
Omvoh (mirikizumab-mrkz)
Orencia (abatacept)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Siliq (brodalumab)
Simponi (golimumab)
Simponi Aria (golimumab)
Skyrizi (risankizumab-rzaa)
Stelara (ustekinumab)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence ((tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tysabri (natalizumab)
Wezlana (ustekinumab-auub)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zymfentra (infliximab-dyyb)

Table 6: Conventional Synthetic DMARDs

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

Table 7: Grading of Severity of Rheumatoid Arthritis

Severity	Criteria

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

REFERENCES:

1. Abdallah H, Hsu JC, Lu P, et al. Pharmacokinetic and Pharmacodynamic Analysis of Subcutaneous Tocilizumab in Patients with Rheumatoid Arthritis From 2 Randomized, Controlled Trials: SUMMACTA and BREVACTA. J Clin Pharmacol. 2017 Apr;57(4):459-468. doi: 10.1002/jcph.826. Epub 2016 Nov 17.
2. Actemra (tocilizumab) [package insert]. Genetech, Inc. South San Francisco (CA): December 2022.
3. An MM, Zou Z, Shen H, Zhang JD, Cao YB, Jiang YY. The addition of tocilizumab to DMARD therapy for rheumatoid arthritis: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol. Jan 2010;66(1):49-59.
4. Bansback N, Phibbs CS, Sun H, et al; CSP 551 RACAT Investigators.Triple Therapy Versus Biologic Therapy for Active Rheumatoid Arthritis: A Cost-Effectiveness Analysis. Ann Intern Med. 2017 Jul 4;167(1):8-16.
5. Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Rese 2011;63(4):465-82.
6. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018 Jun 10;36(17):1714-1768.
7. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood. 2016 Jun 30;127(26):3321-30.
8. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2023. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 10/24/23.
9. De Benedetti F, Brunner HI, Ruperto N, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Eng J Med 2012; 367:2385-95.

10. FDA Orphan Drug Designations and Approvals [Internet]. Washington, D.C. [cited2023 Oct 24]. Available fromFDA.gob: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/.
11. Fernández-Codina A, Walker KM, Pope JE. Treatment Algorithms for Systemic Sclerosis According to Experts. Arthritis Rheum. 2018 Nov;70(11):1820-1828.
12. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2021 Jul;73(7):924-939.
13. Graudal N, Hubeck-Graudal T, Tarp S, et al. Effect of combination therapy on joint destruction in rheumatoid arthritis: a network meta-analysis of randomized controlled trials. PLoS One. 2014 Sep 22;9(9):e106408.
14. Grupp SA, Buechner J, Bittencourt H, et al. Analysis of a global registration trial of the efficacy and safety of CTL019 in pediatric and young adults with relapsed/refractory acute lymphoblastic leukemia (ALL). Blood. 2016;128(suppl): abstract 221.
15. Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2019 Jul 3. pii: annrheumdis-2019-215672. [Epub ahead of print]
16. Karlsson JA, Neovius M, Nilsson JA, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in early rheumatoid arthritis: 2-year quality-of-life results of the randomised, controlled, SWEFOT trial. Ann Rheum Dis. 2013 Dec;72(12):1927-33.
17. Khanna D, Lescoat A, Roofeh D, et al. Systemic Sclerosis-Associated Interstitial Lung Disease: How to Incorporate Two Food and Drug Administration-Approved Therapies in Clinical Practice. Arthritis Rheumatol. 2022;74(1):13-27.
18. Kim ST, Tayar J, Trinh VA, et al. Successful treatment of arthritis induced by checkpoint inhibitors with tocilizumab: A case series. Ann Rheum Dis. 2017 Dec;76(12):2061-2064.
19. Krause ML, Amin A, and Makol A. Use of DMARDs and biologics during pregnancy and lactation in rheumatoid arthritis: what the rheumatologist needs to know. Ther Adv Musculoskelet Dis. 2014 Oct; 6(5): 169–184.
20. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014 Jul 10;124(2):188-95.
21. Maritsi DN, Onoufriou M, Vartzelis G, et al. Complete clinical remission with tocilizumab in two infants with systemic juvenile idiopathic arthritis: a case series. Scand J Rheumatol. 2017 Jan;46(1):75-76.
22. Matsuyama M, Suzuki T, Tsuboi H, et al. Anti-interleukin-6 receptor antibody (tocilizumab) treatment of multicentric Castleman's disease. Intern Med. 2007;46(11):771-774.
23. Maz M, Chung SA, Abril A, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. Arthritis Care Res (Hoboken). 2021 Aug;73(8):1071-1087.
24. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 10/24/23.
25. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 10/24/23.
26. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Acute Lymphoblastic Leukemia. Version 3.2023 – October 09, 2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed 10/26/23.
27. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. B-Cell Lymphomas. Version 6.2023 – October 10, 2023. Available at http://www.nccn.org/professionals/physician_gls/PDF/b-cell.pdf. Accessed 10/26/23.

28. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Hematopoietic Cell Transplantation (HCT). Version 3.2023 - October 9, 2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf. Accessed 10/26/23.
29. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related-Toxicities. Version 3.2023 - October 11, 2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed 10/26/23.
30. Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19(1):12-19.
31. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. Ann Rheum Dis. Oct 2009;68(10):1580-1584.
32. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis. Arthritis Care Res (Hoboken). 2022 Apr;74(4):521-537. Epub 2022 Mar 1.
33. Peper SM, Lew R, Mikuls T, et al. Rheumatoid Arthritis Treatment After Methotrexate: The Durability of Triple Therapy Versus Etanercept. Arthritis Care Res (Hoboken). 2017 Oct;69(10):1467-1472.
34. Rahimi R, Nikfar S, Rezaie A, et al. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. Reprod. Toxicol; 2008:25,271–275.
35. Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Rheumatol. 2019 Jun;71(6):846-863. Epub 2019 Apr 25.
36. Scott DL, Ibrahim F, Farewell V, et al. Tumour necrosis factor inhibitors versus combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis: TACIT non-inferiority randomised controlled trial. BMJ. 2015 Mar 13;350:h1046.
37. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. Mar 22, 2008; 371(9617):987-997.
38. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020 Jun;79(6):685-699. Epub 2020 Jan 22.
39. Stroud CRG, Hegde A, Cherry C, et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. Journal of Oncology Pharmacy Practice. 5 Dec 2017.
40. Tofidence (tocilizumab-bavi) [package insert]. Biogen MA Inc. Cambridge, MA: September 2023.
41. Update of EULAR Recommendations for the Treatment of Systemic Sclerosis. Ann Rheum Dis. 2017; 76:1327-1339.
42. van Vollenhoven RF, Geborek P, Forslind K, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2-year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet. 2012 May 5;379(9827):1712-20.

43. van den Hoogen F, Khanna D, Fransen J, et al. Classification Criteria for Systemic Sclerosis: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis Rheum. 2013 Nov;65(11):2737–2747.

44. Villiger PM, Adler S, Kuchen S, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2016 May 7;387(10031):1921-7. doi: 10.1016/S0140-6736(16)00560-2. Epub 2016 Mar 4.

45. Wingerchuck DM, Banwell B, Bennett JL et al. International Consensus Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorders. Neurology. 2015; 85 (2): 177-89.

46. Zhang C, Zhang M, Qiu W, et al; TANGO Study Investigators. Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial. Lancet Neurol. 2020 May;19(5):391-401.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Committee on 11/08/23.

GUIDELINE UPDATE INFORMATION:

05/15/10	New Medical Coverage Guideline.
01/01/11	Revision to guideline; consisting of updating coding.
07/15/11	Review and revision to guideline; consisting of adding new indication of SJIA, updating dosing, coding and references.
07/15/12	Review and revision to guideline; consisting of reformatting position statement, dosage and administration, precautions and references.
01/15/13	Revision to guideline; consisting of modifying coverage criteria for rheumatoid arthritis.
09/15/13	Review and revision to guideline; consisting of revising description, position statement, dosage administration, and precautions; updating program exceptions and references.
01/01/14	Revision to guideline; consisting of updating position statement and adding new formulation.
04/15/14	Revision to guideline; consisting of revising position statement.
09/15/14	Review and revision to guideline; consisting of updating position statement and references.
09/15/15	Review and revision to guideline; consisting of updating description section, position statement, billing/coding, related guidelines, and references.
11/01/15	Revision: ICD-9 Codes deleted.
09/15/16	Review and revision to guideline consisting of updating description section, position statement, billing/coding, related guidelines, and references.
10/01/16	Revision: ICD-10 code updates.
05/15/17	Revision to guideline consisting of clarifying language in the description section and position statement.
07/15/17	Revision to guideline consisting of updating the position statement, dosage/administration section, coding/billing, and references to include a new FDA-approved indication of giant cell arteritis (GCA).

10/15/17	Review and revision to guideline consisting of updating description, position statement, dosage/administration, coding/billing, definitions, related guidelines, and references.
01/01/18	Revision to guideline consisting of updating the preferred self-administered biologic products according to indication for use. Tofacitinib (Xeljanz, Xeljanz XR) added as prerequisite therapy for rheumatoid arthritis when tocilizumab is used as self-administered subcutaneous therapy.
05/15/18	Revision to guideline consisting of updating the position statement, dosage/administration, and coding/billing.
07/01/18	Revision to guideline consisting of the position statement.
07/15/18	Revision to guideline consisting of updating the description section, position statement, dosage/administration, coding/billing, and references based on FDA approval of SQ administration for PJIA and new NCCN guideline for management of immunotherapy-related toxicities.
10/15/18	Review and revision to guideline consisting of updating the position statement, description, dosage/administration, related guidelines, and references.
10/15/19	Review and revision to guideline consisting of updating the position statement, precautions, and references.
11/11/19	Revision to guideline consisting of adding a reference to the Site of Care Policy for Select Specialty Medications and updating the Program Exceptions.
01/01/20	Revision to guideline consisting of updating the position statement due to changes in preferred and non-preferred products.
07/01/20	Revision to guideline consisting of updating the description and position statement.
01/01/21	Review and revision to guideline consisting of updating the position statement and references.
03/15/21	Revision to guideline consisting of updating Table 1 in the position statement.
08/15/21	Revision to guideline consisting of updating the consisting of updating the description section, position statement, dosage/administration, coding/billing, other section, and references.
10/01/21	Revision: Addition of HCPCS codes M0249, M0250, and Q0249. Addition of ICD-10 code range G92.00 – G92.05.
11/15/21	Revision to guideline consisting of updating the position statement.
01/01/22	Review and revision to guideline consisting of updating the description, position statement, and references.
02/15/22	Update to Table 1 in Position Statement.
03/15/22	Revision to guideline consisting of updating the position statement and other section.
04/15/22	Revision to guideline consisting of updating the description section, position statement, dosage/administration section, and references.
05/15/22	Update to Table 1 in Position Statement.
07/15/22	Update to Table 1 in Position Statement.
09/15/22	Update to Table 1 in Position Statement.

01/01/23	Review and revision to guideline consisting of updating the position statement, other section, and references. New drugs were added to the list of drugs that are not permitted for use in combination.
03/15/23	Revision to guideline consisting of updating the description section, position statement, dosage/administration, precautions, and references based on the FDA approval of IV Actemra for the treatment of certain hospitalized adults with COVID-19.
04/15/23	Revision to guideline consisting of updating the description section, position statement, and references related to SSc-ILD. The conventional agent prerequisites were removed for SSc-ILD.
07/01/23	Revision to guideline consisting of updating the position statement and other section. Amjevita and Hadlima added as Step 1a agents. Humira biosimilar products added to list of Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.
01/01/24	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, other section, and references. Added tocilizumab-bavi (Tofidence) IV infusion to guideline, the first biosimilar to Actemra IV. It is covered at parity with IV Actemra with the same indications and criteria. Tofidence is included in the Site of Care Program. For SJIA indication, removed NSAIDs step requirement. Amjevita low concentration [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] clarified as the preferred prerequisite product. Updated the immune checkpoint inhibitor-related adverse effects criteria. Update to Table 1 in Position Statement. New drugs were added to the list of drugs that are not permitted for use in combination.
04/01/24	Revision: Added HCPCS code Q5133.