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Subject: Tocilizumab (Actemra®) Injection and 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. 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. The subcutaneous formulation is now FDA-approved for the treatment of RA, PJIA, SJIA, 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

severe, steroid-refractory immune checkpoint inhibitor-related inflammatory arthritis.

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 recommend a treat-to-target approach in therapy, regardless of disease activity. ACR guidelines categorize therapy for those with early RA (disease duration <6 months) or established RA (disease duration ≥6 months) as follows:

- In general, MTX is the preferred initial DMARD therapy for most patients with RA with active disease.
- For early RA patients, the ACR recommends the following:
    - Naïve to therapy: DMARDs, methotrexate (MTX) preferred, as initial, monotherapy therapy unless contraindicated. Other DMARD monotherapy options include sulfasalazine, hydroxychloroquine, and leflunomide.
    - Moderate or high disease activity despite DMARD monotherapy: treatment with combination DMARDs or a TNF-inhibitor (e.g., adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab) or a non-TNF inhibitor (abatacept, rituximab, or tocilizumab [excludes anakinra]), with or without MTX.
    - Moderate or high disease activity despite the previous DMARD or biologic therapy: addition of low-dose glucocorticoid (≤10 mg/day of prednisone or equivalent) to bridge therapy until therapeutic effects of DMARD is reached. ACR also recommends short-term (<3 months) with lowest dose of glucocorticoids for flares.
- For established RA patients, the ACR recommends the following:
    - Low disease activity and is DMARD naïve: DMARD monotherapy, MTX preferred, is recommended over a TNF-inhibitor.
    - Moderate or high disease and is DMARD naïve: DMARD monotherapy, MTX preferred, is recommended over double or triple DMARD therapy and tofacitinib.
    - Moderate-high disease activity despite DMARD monotherapy: combination DMARD therapy OR the addition of TNF inhibitor, non-TNF biologic, or tofacitinib with or without MTX is recommended rather than continuing DMARD monotherapy. Combination biologic therapy and MTX is recommended over biologic monotherapy.
    - Moderate or high disease despite TNF-inhibitor and not on DMARD: addition of one or two DMARD, rather than TNF-inhibitor monotherapy

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.[26-28] 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.[27,28] 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. The ACR defines SJIA as arthritis in ≥1 joint for at least 6 weeks' duration in a child less than 16 years of age with or preceded by a fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least 3 days and accompanied by one or more of the following: evanescent erythematous rash, generalized lymphadenopathy, hepatomegaly or splenomegaly, and serositis. 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 treatment depends on the presence of active systemic features and physician global assessment score (MD global) and active joint count (AJC):

- Active systemic features and varying degrees of synovitis:
  - Initial therapy: anakinra, glucocorticoids (oral or IV) monotherapy, or NSAID monotherapy
  - Continued disease activity despite initial therapy:
    - 1 month of anakinra: canakinumab, tocilizumab, MTX, leflunomide, or TNF inhibitor
    - 2 weeks of glucocorticoids (GC): anakinra, canakinumab, tocilizumab, MTX, or leflunomide
    - 1 month of NSAIDs: GC monotherapy, anakinra, canakinumab, or tocilizumab
- Without active systemic features and varying degrees of synovitis:
  - Initial therapy: MTX, leflunomide, NSAID monotherapy, or intra-articular GC
  - Continued disease activity despite initial therapy:
    - 3 months of MTX or leflunomide: abatacept, anakinra, TNF inhibitor, or tocilizumab
    - 1 month of NSAIDs: anakinra, MTX, or leflunomide
    - Following initial intra-articular GC joint injection: anakinra, MTX, or leflunomide
  - Continued disease activity despite second line therapy:
    - 1 month of anakinra: abatacept, MTX, leflunomide, TNF inhibitor, or tocilizumab
    - 3 months of MTX or leflunomide: abatacept, anakinra, TNF inhibitor, or tocilizumab

OTHER DISORDERS

Giant Cell Arteritis (GCA)

Giant cell arteritis (GCA), also known as Horton disease, cranial arteritis, and temporal arteritis, 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. Due to the risk of

vision loss, treatment should begin as soon as possible. High-dose systemic glucocorticoids are the mainstay of therapy for GCA. Indications for the addition of a glucocorticoid-sparing agents includes presence of significant premorbid disease, emergence of significant glucocorticoid-related side effects during treatment, or a relapsing course necessitating protracted glucocorticoid use. Methotrexate or tocilizumab are recommended options for glucocorticoid sparing agents.

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.

POSITION STATEMENT:

Site of Care: If intravenous tocilizumab (Actemra) 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.

Note: The preferred and non-preferred, self-administered products for certain indications are as follows:

Table 1

Disease State	Step 1 (Preferred)	Step 2 (Non-preferred directed to ONE step 1 agent)	Step 3a (Non-preferred directed to TWO step 1 agents)	Step 3b (Non-preferred directed to TWO agents from step 1 and/or step 2)	Step 3c (Non-preferred directed to THREE step 1 agents)
Rheumatoid Disorders					
Ankylosing Spondylitis (AS)	SQ: Cosentyx, Enbrel, Humira	N/A	SQ: Cimzia, Simponi, Taltz	N/A	N/A
Nonradiographic Axial Spondyloarthritis	SQ: Cimzia, Cosentyx	N/A	SQ: Taltz	N/A	N/A

(nr-axSpA)					
Polyarticular Juvenile Idiopathic Arthritis (PJIA)	SQ: Enbrel, Humira Oral: Xeljanz	SQ: **Actemra** (Humira is required Step 1 agent)	N/A	SQ: Orencia	N/A
Psoriatic Arthritis (PsA)	SQ: Cosentyx, Enbrel, Humira, Stelara, Tremfya Oral: Otezla, Xeljanz, Xeljanz XR	N/A	SQ: Cimzia, Orencia, Simponi, Taltz	N/A	N/A
Rheumatoid Arthritis	SQ: Enbrel, Humira, Oral: Rinvoq, Xeljanz, Xeljanz XR	SQ: **Actemra** (Humira is required Step 1 agent)	Oral: Olumiant SQ: Cimzia, Kevzara, Kineret, Orencia, Simponi	N/A	N/A
Dermatological Disorders					
Hidradenitis Suppurativa (HS)	SQ: Humira	N/A	N/A	N/A	N/A
Psoriasis (PS)	SQ: Cosentyx, Enbrel, Humira, Skyrizi, Stelara, Tremfya Oral: Otezla	N/A	SQ: Cimzia, Ilumya, Siliq	N/A	SQ: Taltz
Inflammator the prescribery Bowel Disease					
Crohn's Disease	SQ: Humira, Stelara	SQ: Cimzia (Humira is required Step 1 agent)	N/A	N/A	N/A
Ulcerative Colitis	SQ: Humira, Stelara	SQ: Simponi, Stelara Oral: Xeljanz, Xeljanz XR	N/A	N/A	N/A
Other					
Uveitis	SQ: Humira	N/A	N/A	N/A	N/A
Indications Without Preferred Agents Required					
Giant Cell Arteritis (GCA) Neonatal-Onset Multisystem Inflammatory Disease (NOMID) Systemic Juvenile Idiopathic Arthritis (SJIA)	N/A	N/A	N/A	N/A	N/A

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

SUBCUTANEOUS ACTEMRA (PHARMACY BENEFIT)

Initiation of subcutaneous tocilizumab (Actemra) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "6"):

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 ("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) 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 or Otezla

6. **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 autoinjector - 4 autoinjectors (3.6 mL)/28 days
- QL: 162 mg/0.9 mL syringe - 4 syringes (3.6 mL)/28 days

b. The requested quantity (dose) is greater than program's 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) is greater that the program's quantity limit and greater than 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, AHFS, or NCCN compendium recommended use 1 or 2a for the treatment of RA 2. **ANY** of the following: a. The member has tried and had an inadequate response to 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), FDA labeled contraindication, or hypersensitivity to Humira (adalimumab) **OR** c. The prescriber has provided information indicating why Humira (adalimumab) is not clinically appropriate for the member, AND the prescriber has provided a complete list of previously tried agents for the requested indication

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** **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, AHFS, or NCCN compendium recommended use 1 or 2a for the treatment of GCA
Active systemic juvenile idiopathic arthritis (SJIA)	**ONE** of the following: 1. The member has tried and had an inadequate response to NSAIDs (e.g., ibuprofen, celecoxib) used in the treatment of SJIA for at least 1 month **OR** 2. The member has an intolerance or hypersensitivity to NSAIDs used in the treatment of SJIA **OR** 3. The member has an FDA labeled contraindication to **ALL** NSAIDs used in the treatment of SJIA **OR** 4. The member has tried and had an inadequate response to another conventional agent (i.e., methotrexate, leflunomide, systemic corticosteroids) used in the treatment of SJIA for at least 3-months **OR** 5. The member has an intolerance or hypersensitivity to **ONE** of the conventional agents used in the treatment of SJIA **OR** 6. The member has FDA labeled contraindication to **ALL** of the conventional agents used in the treatment of SJIA **OR** 7. 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, AHFS, or NCCN compendium recommended use

	1 or 2a for the treatment of SJIA
Moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA)	**BOTH** of the following: 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 AHFS, or NCCN compendium recommended use 1 or 2a for the treatment of PJIA **AND** 2. **ANY** of the following: a. The member has tried and had an inadequate response to adalimumab (Humira) for at least 3 months b. The member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration), FDA labeled contraindication, or hypersensitivity to adalimumab (Humira) c. The prescriber has provided information indicating why adalimumab (Humira) is not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried agents for the requested indication
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 "6"):

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) 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 or Otezla
6. **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 autoinjector - 4 autoinjectors (3.6 mL)/28 days
        - QL: 162 mg/0.9 mL syringe - 4 syringes (3.6 mL)/28 days
    b. The requested quantity (dose) is greater than program's 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) is greater that the program's quantity limit and greater than 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 (MEDICAL BENEFIT)

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

1. Intravenous tocilizumab 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 IV 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 IV tocilizumab in combination with another biologic immunomodulator agent or Otezla

Approval duration: 12 months (except for CRS 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	**ONE** of the following: 1. The member has tried and had an	8 mg/kg (maximum of 800 mg) every 4 weeks

arthritis (RA)	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, AHFS, or NCCN compendium recommended use 1 or 2a for the treatment of RA	
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 labeled contraindication to **ALL** systemic corticosteroids	8 mg/kg (maximum of 800 mg) every 4 weeks

	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, AHFS, or NCCN compendium recommended use 1 or 2a for the treatment of GCA	
Cytokine release syndrome (CRS)	When **BOTH** of the following are met ("1" and "2"): 1. Member is experiencing CRS symptoms (e.g., fever, vascular leak, hypotension, pulmonary edema, coagulopathy, organ failure) 2. The member has received **EITHER** of the following in the previous 30 days: 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 inflammatory arthritis	When **ALL** of the following are met ("1", "2", "3" and "4"): 1. Member has been receiving treatment with an immune checkpoint inhibitor (e.g., ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, darvalumab) **AND** 2. Member has severe joint symptoms that are limiting their activities of daily living **AND** 3. Member has had an inadequate response to , intolerable adverse effects with, or a contraindication to an adequate trial of systemic corticosteroid treatment (defined as at least 1 mg/kg/day of methylprednisolone or equivalent for 2 weeks or more) [the specific adverse effects and/or contraindications must be provided] **AND** 4. Member's immune checkpoint inhibitor therapy will be either permanently	4 mg/kg X 1 dose. May repeated one additional 4 mg/kg dose if the member does not have adequate improvement in symptoms.

	discontinued or held during treatment with tocilizumab	
Active systemic juvenile idiopathic arthritis (SJIA)	**ONE** of the following: 1. The member has tried and had an inadequate response to NSAIDs (e.g., ibuprofen, celecoxib) used in the treatment of SJIA for at least 1-month **OR** 2. The member has an intolerance or hypersensitivity to NSAIDs used in the treatment of SJIA **OR** 3. The member has an FDA labeled contraindication to **ALL** NSAIDs used in the treatment of SJIA **OR** 4. The member has tried and had an inadequate response to another conventional agent (i.e., methotrexate, leflunomide, systemic corticosteroids) used in the treatment of SJIA for at least 3-months **OR** 5. The member has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of SJIA **OR** 6. The member has an FDA labeled contraindication to **ALL** of the conventional agents used in the treatment of SJIA **OR** 7. 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, AHFS, or NCCN compendium recommended use 1 or 2a for the treatment of SJIA	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	Less than 30 kg: • 10 mg/kg every 4 weeks

	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, AHFS, or NCCN compendium recommended use 1 or 2a for the treatment of PJIA	30 kg or above: • 8 mg/k every 4 weeks
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)	1. When **ALL** of the following are met ("1", "2, and 3"): 2. Used as monotherapy for treatment of CD **AND** 3. Members disease is relapsed or refractory **AND** 4. 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"): 1. Member has a history of at least 1 relapse in the previous year 2. Tocilizumab will not be used concurrently	8 mg/kg (maximum of 800 mg) every 4 weeks

	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 2. Tocilizumab will be used as additional therapy in conjunction with systemic corticosteroids 3. The member has steroid-refractory disease	8 mg/kg (maximum of 800 mg) every 2 weeks
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, 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	12 mg/kg every 2 weeks
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) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "6"):

1. An authorization or reauthorization for IV tocilizumab 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, 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 IV tocilizumab
4. Member has had clinical benefit with IV tocilizumab therapy
5. Member will **NOT** be using IV tocilizumab in combination with another biologic immunomodulator agent or Otezla
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: 8 mg/kg IV (max of 800 mg) every 4 weeks
      - GCA and NMOSD: 8 mg/kg IV (max of 800 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: 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 (only the SQ route is FDA-approved, IV route is used off-label)
- 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)

For the treatment of RA, 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.

Therapy should not be initiated in persons with an absolute neutrophil count (ANC) less than 2000, platelet count less than 100,000, or an ALT/AST greater than 1.5 times the upper limit of normal (ULN). The recommended dosage, based on indication, is identified in Table 4. Tocilizumab may be used alone or in combination with methotrexate; in RA, other DMARDs may be used.

Table 4

FDA-approved indications and dosing			
Indication	**Dose**		
GCA	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.	
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
CRS	Less than 30 kg	12 mg/kg IV (not to exceed 800 mg) 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 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; 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 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		

Drug Availability: tocilizumab 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 prefilled glass syringe

PRECAUTIONS:

Boxed Warning

- Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in persons receiving tocilizumab.
- If a serious infection develops, interrupt tocilizumab until the infection is controlled.
- Perform test for latent TB; if positive, start treatment for TB prior to starting tocilizumab.
- Monitor all individuals administered tocilizumab for active TB during treatment, even if initial latent TB test is negative.

Contraindication

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

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 formulation]
J3590	Unclassified biologics [for subcutaneous formulation]

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

D36.0	Benign neoplasm of lymph nodes
D47.Z2	Castleman disease
D89.810	Acute graft-versus-host disease
D89.812	Acute on chronic graft-versus-host disease
D89.831 – D89.839	Cytokine release syndrome
G36.0	Neuromyelitis optica [Devic]
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

ICD-10 Diagnoses Codes That Support Medical Necessity for J3590:

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

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) Tablets, 09-J1000-86

OTHER:

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): June 2019.
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 [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at: www.clinicalpharmacilogy-ip.com. Accessed 9/29/20.
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. ClinicalTrials.gov. A Study to Evaluate Pharmacokinetics and Safety of Tocilizumab (RoActemra/Actemra) in Participants Less Than 2 Years Old With Active Systemic Juvenile Idiopathic Arthritis (sJIA). ClinicalTrials.gov Identifier: NCT01455701. Available at: https://clinicaltrials.gov/ct2/show/NCT01455701.
11. FDA Orphan Drug Designations and Approvals [Internet]. Washington, D.C. [cited 2020 Sep 29]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/.
12. Graudal N, Hubeck-Graudal T, Tarp S, et al. Effect of combination therapy on joint destruction in rheumatoid arthritis: a network meta-analysis of randomized controlled trials. PLoS One. 2014 Sep 22;9(9):e106408.

13. 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.
14. 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]
15. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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.
21. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 9/29/20.
22. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 9/29/20.
23. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Version 2.2020. Hematopoietic Cell Transplantation (HCT): Pre-Transplant Recipient Evaluation and Management of Graft-Versus-Host Disease. Available at https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf. Accessed 8/20/20.
24. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Version 1.2020. Management of Immunotherapy-Related-Toxicities. Available at https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed 9/29/20.
25. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Version 4.2020. B-Cell Lymphomas. Available at http://www.nccn.org/professionals/physician_gls/PDF/b-cell.pdf. Accessed 9/29/20.
26. 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.
27. 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.
28. 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.
29. 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.

30. 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.
31. 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.
32. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2016 Jan;68(1):1-25
33. 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.
34. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017 Jun;76(6):960-977.
35. 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.
36. 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.
37. 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.
38. Wingerchuck DM, Banwell B, Bennett JL et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015; 85 (2): 177-89.
39. 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 10/14/20.

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.