Policy Number	**RX501.115**
Policy Effective Date	**12/15/2025**

Tocilizumab and Associated Biosimilar(s)

Table of Contents

Related Policies (if applicable)
RX502.061: Oncology Medications

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical

journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: This medical policy does NOT address oncologic indications. This medical policy IS NOT TO BE USED for oncologic indications. Refer to RX502.061 Oncology Medications for oncologic indications.

NOTE 2: The criteria outlined in this policy addresses coverage in the outpatient setting. Hospitalized members receiving tocilizumab (Actemra) and its biosimilars for the treatment of coronavirus disease 2019 (COVID-19) will be managed according to the member's inpatient benefit.

NOTE 3: Tocilizumab (Actemra®) and its biosimilars may be self-administered. Refer to the applicable pharmacy benefit plan when self-administered.

Intravenous administration of tocilizumab (Actemra® and the biosimilars tocilizumab-bavi [Tofidence], tocilizumab-anoh [Avtozma], and tocilizumab-aazg [Tyenne]) **may be considered medically necessary** when administered intravenously (IV) for the following indications:

- Treatment of adults with moderately to severely active rheumatoid arthritis (RA);
- Treatment of individuals 2 years of age and older with active systemic juvenile idiopathic arthritis (SJIA);
- Treatment of individuals 2 years of age and older with active polyarticular juvenile idiopathic arthritis (PJIA);
- Treatment of adults with giant cell arteritis (GCA).

NOTE 4: For rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis, tocilizumab may be used alone or in combination with methotrexate (MTX). In rheumatoid arthritis, other non-biologic disease-modifying antirheumatic drugs (DMARDs) may be used.

Intravenous administration of tocilizumab (Actemra® and the biosimilars tocilizumab-bavi [Tofidence], tocilizumab-anoh (Avtozma), and tocilizumab-aazg [Tyenne]) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration indications.

Policy Guidelines

None.

Description

Tocilizumab
Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody. It binds specifically to both soluble and membrane-bound IL-6 receptors and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pro-inflammatory cytokine and has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis. (2)

Rheumatoid Arthritis
Rheumatoid arthritis (RA) is an autoimmune and inflammatory disease in which the immune system attacks healthy cells by mistake, causing inflammation or painful swelling in affected parts of the body. RA mainly attacks the joints in the hands, wrists and knees, and usually attacks many joints at the same time. The lining of the joint becomes inflamed, causing damage to joint tissue, which in turn causes long-lasting or chronic pain, unsteadiness and deformity of the affected joints. RA can also affect other tissues in the body and cause problems in organs such as the lungs, heart and eyes. (5)

Polyarticular Juvenile Idiopathic Arthritis (pJIA)
Polyarticular juvenile idiopathic arthritis (formerly called polyarticular-onset juvenile RA is a subset of juvenile idiopathic arthritis (JIA) that is defined by the presence of more than four affected joints during the first six months of illness. This disease, which comprises 20 to 30 percent of patients with JIA, is included in the group termed "childhood polyarthritis." Polyarticular JIA is more frequent in females than males. There is a bimodal distribution of the age at onset. The first peak is between the ages of two and five years, and the second is between 10 and 14 years. This age distribution suggests that two or more distinct diseases may be included in this classification. In children less than 10 years of age, polyarticular JIA often begins similarly to oligoarticular disease, with one or two joints affected. The development of the disease is often indolent until an intercurrent infection precipitates a dramatic increase in symptoms. The disease then becomes relentlessly progressive, spreading to involve five or more joints within the first six months after disease onset. Joint involvement is symmetric, with the knees, wrists, and ankles most frequently affected. There are typically periods of apparent response to therapy followed by relapses with an increasing number of involved joints. Polyarticular JIA may go unrecognized at first because of its initial indolent course. This failure to recognize the initial symptoms may make it appear that the disease had a sudden onset and rapid progression. In older children and adolescents, these patients usually have a relatively rapid onset of inflammation in multiple joints, including involvement of the many small joints of the hands and feet, within two to three months of disease onset. Pain in the small joints is a

common manifestation of polyarticular JIA and initially may be out of proportion to the degree of inflammation and stiffness. The joints of the fingers, wrists, elbows, hips, knees, and ankles are most commonly affected. (6)

Systemic Juvenile Idiopathic Arthritis (SJIA) (7)

Formerly called Still's disease or systemic juvenile RA, systemic juvenile idiopathic arthritis (SJIA) is classified as a category of JIA that includes patients characterized by daily fever, rash and arthritis. It is termed "adult-onset Still's disease" when it begins in patients over the age of 16 years. SJIA accounts for approximately 10 to 20 percent of all cases of JIA. It typically affects both sexes equally and may present in children as young as one year of age or younger. Patients with SJIA fall into the category of systemic arthritis according to the 2004 International League of Associations for Rheumatology (ILAR) proposed classification of the childhood arthritides. Children with this illness comprise between 10 and 20 percent of all cases of JIA. However, data suggest that this illness is a unique condition similar to the autoinflammatory family of diseases, with distinct manifestations and treatment response patterns that distinguish it from the other diseases categorized as JIA. This form of JIA is very distinctive but may be difficult to diagnose for the following reasons:

- Arthritis, although necessary to establish a definitive diagnosis, may not be evident early in the course of the disease.
- The systemic disease features, such as fever and rash, may not be present in their typical forms initially, even though these features are also necessary to establish a definitive diagnosis.
- There are currently no specific diagnostic tests for this disorder.
- Affected children are often quite ill with high, spiking fevers; rashes; markedly elevated white blood cell (WBC) counts; anemia; highly elevated acute phase reactants; and often lymphadenopathy, hepatosplenomegaly, or pericarditis. Most such children are initially thought to have an infection or a malignancy, and the correct diagnosis is only suspected after there has been no response to antibiotic therapy and malignancy has been excluded.

Some children who present with fever, rash, and diffuse joint pain may in fact have an infection, leukemia, or other serious condition that requires different treatment. Thus, it is essential that clinicians thoroughly exclude other conditions before making this diagnosis since there is no diagnostic test for SJIA.

Giant Cell Arteritis

Giant cell arteritis (GCA) is a type of vasculitis or arteritis, the main feature of this group of diseases is inflammation of blood vessels. Vessels most often involved are the arteries of the scalp and head, especially the arteries over the temples, which is why another term for GCA is "temporal arteritis." Giant cell arteritis may overlap with polymyalgia rheumatica (pain and stiffness in the neck, shoulder, and hip). GCA occurs only in older adults, those over age of 50, and can cause swelling and thickening of the arteries located on each side of the head called the temporal artery. A new, persisting headache is a common symptom of GCA. Symptoms of GCA promptly improve with corticosteroids. If GCA affects blood flow to the eye, loss of vision can occur. Prompt detection and treatment of GCA can prevent loss of vision. (8)

Regulatory Status (1-4, 9)

The U.S. Food and Drug Administration (FDA) approved Actemra® (tocilizumab) on:

- January 11, 2010 for the treatment of moderately to severely active RA.
- April 17, 2011 for the treatment of SJIA.
- April 30, 2013 for children with PJIA.
- October 22, 2013 for a new subcutaneous formulation of Actemra for use in adult patients with moderately to severely active RA.
- May 22, 2017 for a subcutaneous formulation for giant cell arteritis.
- August 31, 2017 for the treatment of chimeric antigen receptor (CAR) T-cell-induced cytokine release syndrome (CRS).
- May 14, 2018 for a subcutaneous formulation for use in active PJIA.
- September 13, 2018 for a subcutaneous formulation for use in active SJIA.
- November 26, 2018 for the ACTpen (a single-dose, prefilled autoinjector for Actemra).
- February 28, 2022 for intravenous administration of Actemra in the treatment of adult patients with giant cell arteritis.
- December 21, 2022 for the treatment of hospitalized adults with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

In addition, the FDA approved the following biosimilars to tocilizumab:

- Tofidence (tocilizumab-bavi) was FDA approved on September 29, 2023, for the treatment of moderately to severely active RA, treatment of SJIA and for the treatment of PJIA.
- Tyenne (tocilizumab-aazg) was FDA approved on March 5, 2024, for the treatment of rheumatoid arthritis, giant cell arthritis, PJIA, and SJIA.
- Avtozma (tocilizumab-anoh) was FDA approved on January 24, 2025, for the treatment of rheumatoid arthritis, giant cell arthritis, polyarticular PJIA and SJIA.

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for Actemra® (tocilizumab) and each biosimilar.

Rheumatoid Arthritis (1-4)

Intravenous Administration

The efficacy and safety of intravenously administered tocilizumab was assessed in five randomized, double-blind, multicenter studies in patients greater than 18 years with active rheumatoid arthritis (RA) diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 8 tender and 6 swollen joints at baseline. Tocilizumab was given intravenously every 4 weeks as monotherapy (Study I), in combination with methotrexate (MTX) (Studies II and III) or other disease-modifying anti-rheumatic drugs (DMARDs) (Study IV)

in patients with an inadequate response to those drugs, or in combination with MTX in patients with an inadequate response to tumor necrosing factor (TNF) antagonists (Study V).

Study I (NCT00109408) evaluated patients with moderate to severe active RA who had not been treated with MTX within 24 weeks prior to randomization, or who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response. In this study, 67% of patients were MTX-naïve, and over 40% of patients had RA less than 2 years. Patients received tocilizumab 8 mg per kg monotherapy or MTX alone (dose titrated over 8 weeks from 7.5 mg to a maximum of 20 mg weekly). The primary endpoint was the proportion of tocilizumab patients who achieved an ACR 20 response at week 24.

Study II (NCT00106535) was a 104-week study with an optional 156-week extension phase that evaluated patients with moderate to severe active RA who had an inadequate clinical response to MTX. Patients received tocilizumab 8 mg per kg, tocilizumab 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). Upon completion of 52-weeks, patients received open-label treatment with tocilizumab 8 mg per kg through 104 weeks or they had the option to continue their double-blind treatment if they maintained a greater than 70% improvement in swollen/tender joint count. Two pre-specified interim analyses at week 24 and week 52 were conducted. The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response. At weeks 52 and 104, the primary endpoints were change from baseline in modified total Sharp-Genant score and the area under the curve (AUC) of the change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) score.

Study III (NCT00106548) evaluated patients with moderate to severe active RA who had an inadequate clinical response to MTX. Patients received tocilizumab 8 mg per kg, tocilizumab 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Study IV (NCT00106574) evaluated patients who had an inadequate response to their existing therapy, including one or more DMARDs. Patients received tocilizumab 8 mg per kg or placebo every four weeks, in combination with the stable DMARDs. The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Study V (NCT00106522) evaluated patients with moderate to severe active RA who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy was discontinued prior to randomization. Patients received tocilizumab 8 mg per kg, tocilizumab 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Clinical Response

The percentages of intravenous tocilizumab-treated patients achieving ACR 20, 50 and 70 responses are shown in Table 2a and 2b. In all intravenous studies, patients treated with 8 mg

per kg tocilizumab had higher ACR 20, ACR 50, and ACR 70 response rates versus MTX- or placebo-treated patients at week 24.

During the 24-week controlled portions of Studies I to V, patients treated with tocilizumab at a dose of 4 mg per kg in patients with inadequate response to DMARDs or TNF antagonist therapy had lower response rates compared to patients treated with tocilizumab 8 mg per kg.

Table 2a. Clinical Response at Weeks 24 and 52 in Active and Placebo Controlled Trials of Intravenous Tocilizumab (Percent of Patients)

	Study I		**Study II**			**Study III**		
Response rate	MTX N = 284	Toc 8 mg/kg N = 286 (95% CI)[a]	PBO + MTX N = 393	Toc 4 mg/kg + MTX N = 399 (95% CI)[a]	Toc 8 mg/kg + MTX N = 398 (95% CI)[a]	PBO + MTX N = 204	Toc 4 mg/kg + MTX N = 213 (95% CI)[a]	Toc 8 mg/kg + MTX N = 205 (95% CI)[a]
ACR 20								
Week 24	53%	70% (0.11, 0.27)	27%	51% (0.17, 0.29)	56% (0.23, 0.35)	27%	48% (0.15, 0.32)	59% (0.23, 0.41)
Week 52	N/A	N/A	25%	47% (0.15, 0.28)	56% (0.25, 0.38)	N/A	N/A	N/A
ACR 50								
Week 24	34%	44% (0.04, 0.20)	10%	25% (0.09, 0.20)	32% (0.16, 0.28)	11%	32% (0.13, 0.29)	44% (0.25, 0.41)
Week 52	N/A	N/A	10%	29% (0.14, 0.25)	36% (0.21, 0.32)	N/A	N/A	N/A
ACR 70								
Week 24	15%	28% (0.07, 0.22)	2%	11% (0.03, 0.13)	13% (0.05, 0.15)	2%	12% (0.04, 0.18)	22% (0.12, 0.27)
Week 52	N/A	N/A	4%	16% (0.08, 0.17)	20% (0.12, 0.21)	N/A	N/A	N/A
Major Clinical								

Responses[b]								
Week 52	N/A	N/A	1%	4% (0.01, 0.06)	7% (0.03, 0.09)	N/A	N/A	N/A

ACR: American College of Rheumatology; N/A: not applicable; Toc: tocilizumab; PBO: placebo; MTX: methotrexate; DMARDs: disease-modifying anti-rheumatic drugs.

[a] CI: 95% confidence interval of the weighted difference to placebo adjusted for site (and disease duration for Study I only).

[b] Major clinical response is defined as achieving an ACR 70 response for a continuous 24-week period.

Table 2b. Clinical Response at Weeks 24 and 52 in Active and Placebo Controlled Trials of Intravenous Tocilizumab (Percent of Patients)

	Study IV		**Study IV**		
Response rate	PBO + DMARDs N = 413	Toc 8 mg/kg + DMARDS N = 803 (95% CI)[a]	PBO + MTX N = 158	Toc 4 mg/kg + MTX N = 161 (95% CI)[a]	Toc 8 mg/kg + MTX N = 170 (95% CI)[a]
ACR 20					
Week 24	24%	61% (0.30, 0.40)	10%	30% (0.15, 0.36)	50% (0.36, 0.56)
Week 52	N/A	N/A	N/A	N/A	N/A
ACR 50					
Week 24	9%	38% (0.23, 0.33)	4%	17% (0.05, 0.25)	29% (0.21, 0.41)
Week 52	N/A	N/A	N/A	N/A	N/A
ACR 70					
Week 24	3%	21% (0.13, 0.21)	1%	5% (-0.06, 0.14)	12% (0.03, 0.22)
Week 52	N/A	N/A	N/A	N/A	N/A
Major Clinical Responses[b]					
Week 52	N/A	N/A	N/A	N/A	N/A

ACR: American College of Rheumatology; N/A: not applicable; Toc: tocilizumab; PBO: placebo; MTX: methotrexate; DMARDs: disease-modifying anti-rheumatic drugs.

[a] CI: 95% confidence interval of the weighted difference to placebo adjusted for site (and disease duration for Study I only).

[b] Major clinical response is defined as achieving an ACR 70 response for a continuous 24-week period.

In study II, a greater proportion of patients treated with 4 mg per kg and 8 mg per kg tocilizumab + MTX achieved a low level of disease activity as measured by a disease activity score-28 for RA with erythrocyte sedimentation rate (DAS 28-ESR) less than 2.6 compared with placebo + MTX treated patients at week 52. The proportion of tocilizumab-treated patients achieving DAS 28-ESR less than 2.6, and the number of residual active joints in these responders in Study II are shown in Table 3.

Table 3. Proportion of Patients with DAS28-ESR Less Than 2.6 with Number of Residual Active Joints in Trials of Intravenous Tocilizumab

Study II			
	Placebo + MTX **N = 393**	**Tocilizumab 4 mg/kg + MTX** **N = 399**	**Tocilizumab 8 mg/kg + MTX** **N = 398**
DAS28-ESR less than 2.6			
Proportion of responders at week 52 (n[a]) 95% confidence interval	3% (12)	18% (70) 0.10, 0.19	32% (127) 0.24, 0.34
Of responders, proportion with 0 active joints (n[a])	33% (4)	27% (19)	21% (27)
Of responders, proportion with 1 active joint (n[a])	8% (1)	19% (13)	13% (16)
Of responders, proportion with 2 active joint (n[a])	25% (3)	13% (9)	20% (25)
Of responders, proportion with 3 or more active joint (n[a])	33% (4)	41% (29)	47% (59)

DAS28-ESR: disease activity score-28 for rheumatoid arthritis with erythrocyte sedimentation rate.
MTX: methotrexate.
[a] n denotes numerator of all the percentage. Denominator is the intent-to-treat population. Not all patients received DAS28 assessments at week 52.

The results of the components of the ACR response criteria for Studies III and V are shown in Table 4. Similar results to Study III were observed in Studies I, II and IV.

Table 4a. Components of ACR Response at Week 24 in Trials of Intravenous Tocilizumab

	Study III					
	Tocilizumab 4 mg/kg + MTX **N = 213**		**Tocilizumab 8 mg/kg + MTX** **N = 205**		**Placebo + MTX** **N = 204**	
Component (mean)	Base line	Week 24[a]	Base line	Week 24[a]	Base line	Week 24
Number of	33	19 -7.0	32	14.5 -9.6	33	25

tender joints (0-68)		(-10.0, -4.1)		(-12.6, -6.7)		
Number of swollen joints (0-66)	20	10 -4.2 (-6.1, -2.3)	19.5	8 -6.2 (-8.1, -4.2)	21	15
Pain[b]	61	33 -11.0 (-17.0, -5.0)	60	30 -15.8 (-21.7, -9.9)	57	43
Patient global assessment[b]	66	34 -10.9 (-17.1, -4.8)	65	31 -14.9 (-20.9, -8.9)	64	45
Physician global assessment[b]	64	26 -5.6 (-10.5, -0.8)	64	23 -9.0 (-13.8, -4.2)	64	32
Disability index (HAQ)[c]	1.64	1.01 -0.18 (-0.34, -0.02)	1.55	0.96 -0.21 (-0.37, -0.05)	1.55	1.21
CRP (mg per dL)	2.79	1.17 -1.30 (-2.0, -0.59)	2.61	0.25 -2.156 (-2.86, -1.46)	2.36	1.89

MTX: methotrexate; CRP: C-reactive protein.

[a] Data shown is mean at week 24, difference in adjusted mean change from baseline compared with placebo + MTX at week 24 and 95% confidence interval for that difference.

[b] Visual analog scale: 0 = best, 100 = worst.

[c] HAQ: Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Table 4b. Components of ACR Response at Week 24 in Trials of Intravenous Tocilizumab

	Study V					
	Tocilizumab 4 mg/kg + MTX N = 161		**Tocilizumab 8 mg/kg + MTX N = 170**		**Placebo + MTX N = 158**	
Component (mean)	Base line	Week 24[a]	Base line	Week 24[a]	Base line	Week 24
Number of tender joints (0-68)	31	21 -10.8 (-14.6, -7.1)	32	17 -15.1 (-18.8, -11.4)	30	30
Number of swollen joints (0-66)	19.5	13 -6.2 (-9.0, -3.5)	19	11 -7.2 (-9.9, -4.5)	19	18
Pain[b]	63.5	43 -12.4 (-22.1, -2.1)	65	33 -23.9 (-33.7, -14.1)	64	48
Patient global	70	46 -10.0	70	36 -17.4	71	51

assessment[b]		(-20.3, 0.3)		(-27.8, -7.0)		
Physician global assessment[b]	66.5	39 -10.5 (-18.6, -2.5)	66	28 -18.2 (-26.3, -10.0)	67.5	43
Disability index (HAQ)[c]	1.67	1.39 -0.25 (-0.42, -0.09)	1.75	1.34 -0.34 (-0.51, -0.17)	1.70	1.58
CRP (mg per dL)	3.11	1.77 -1.34 (-2.5, -0.15)	2.80	0.28 -2.52 (-3.72, -1.32)	3.705	3.06

MTX: methotrexate; CRP: C-reactive protein.

[a] Data shown is mean at week 24, difference in adjusted mean change from baseline compared with placebo + MTX at week 24 and 95% confidence interval for that difference.

[b] Visual analog scale: 0 = best, 100 = worst.

[c] HAQ: Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Radiographic Response

In Study II, structural joint damage was assessed radiographically and expressed as change in total Sharp-Genant score and its components, the erosion score and joint space narrowing score. Radiographs of hands/wrists and forefeet were obtained at baseline, 24 weeks, 52 weeks, and 104 weeks and scored by readers unaware of treatments group and visit number. The results from baseline to week 52 are shown in Table 5. Tocilizumab 4 mg per kg slowed (less than 75% inhibition compared to the control group) and tocilizumab 8 mg per kg inhibited (at least 75% inhibition compared to the control group) the progression of structural damage compared to placebo plus MTX at week 52.

Table 5. Mean Radiographic Change from Baseline to Week 52 in Study II

	Placebo + MTX N = 294	**Tocilizumab 4 mg/kg + MTX N = 343**	**Tocilizumab 8 mg/kg + MTX N = 353**
Week 52[a]			
Total Sharp-Genant Score, Mean (SD)	1.17 (3.14)	0.33 (1.30)	0.25 (0.98)
Adjusted Mean Difference[b] (95% CI)		-0.83 (-1.13, -0.52)	-0.90 (-1.20, -0.59)
Erosion Score, Mean (SD)	0.76 (2.14)	0.20 (0.83)	0.15 (0.77)
Adjusted Mean Difference[b] (95% CI)		-0.55 (-0.76, -0.34)	-0.60 (-0.80, -0.39)
Joint Space Narrowing Score, Mean (SD)	0.41 (1.71)	0.13 (0.72)	0.10 (0.49)
Adjusted Mean		-0.28	-0.30

Difference[b] (95% CI)		(-0.44, -0.11)	(-0.46, -0.14)

MTX: methotrexate; SD: standard deviation; CI: confidence interval.

[a] Week 52 analysis employs linearly extrapolated data for patients after escape, withdrawal, or loss to follow up.

[b] Difference between the adjusted means (tocilizumab + MTX - Placebo + MTX).

The mean change from baseline to week 104 in Total Sharp-Genant Score for the tocilizumab 4 mg per kg groups was 0.47 (SD = 1.47) and for the 8 mg per kg groups was 0.34 (SD = 1.24). By the week 104, most patients in the control (placebo + MTX) group had crossed over to active treatment, and results are therefore not included for comparison. Patients in the active groups may have crossed over to the alternate active dose group, and results are reported per original randomized dose group.

In the placebo group, 66% of patients experienced no radiographic progression (Total Sharp-Genant Score change ≤ 0) at week 52 compared to 78% and 83% in the tocilizumab 4 mg per kg and 8 mg per kg, respectively. Following 104 weeks of treatment, 75% and 83% of patients initially randomized to tocilizumab 4 mg per kg and 8 mg per kg, respectively, experienced no progression of structural damage compared to 66% of placebo treated patients.

Health Related Outcomes

In Study II, physical function and disability were assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI). Both dosing groups of tocilizumab demonstrated a greater improvement compared to the placebo group in the AUC of change from baseline in the HAQ-DI through week 52. The mean change from baseline to week 52 in HAQ-DI was 0.6, 0.5, and 0.4 for tocilizumab 8 mg per kg, tocilizumab 4 mg per kg, and placebo treatment groups, respectively. Sixty-three percent (63%) and sixty percent (60%) of patients in the tocilizumab 8 mg per kg and tocilizumab 4 mg per kg treatment groups, respectively, achieved a clinically relevant improvement in HAQ-DI (change from baseline of ≥ 0.3 units) at week 52 compared to 53% in the placebo treatment group.

Other Health-Related Outcomes

General health status was assessed by the Short Form Health Survey (SF-36) in Studies I – V. Patients receiving tocilizumab demonstrated greater improvement from baseline compared to placebo in the Physical Component Summary (PCS), Mental Component Summary (MCS), and in all 8 domains of the SF-36

Cardiovascular Outcomes

Study WA25204 (NCT01331837) was a randomized, open-label (sponsor-blinded), 2-arm parallel-group, multi-center, non-inferiority, cardiovascular (CV) outcomes trial in patients with a diagnosis of moderate to severe RA. This CV safety study was designed to exclude a moderate increase in CV risk in patients treated with tocilizumab compared with a TNF inhibitor standard of care (etanercept).

The study included 3,080 seropositive RA patients with active disease and an inadequate response to non-biologic disease-modifying anti-rheumatic drugs who were aged ≥50 years with at least one additional CV risk factor beyond RA. Patients were randomized 1:1 to IV tocilizumab 8 mg/kg Q4W or SC etanercept 50 mg QW and followed for an average of 3.2 years. The primary endpoint was the comparison of the time-to-first occurrence of any component of a composite of major adverse CV events (MACE; non-fatal myocardial infarction, non-fatal stroke, or CV death), with the final intent-to-treat analysis based on a total of 161 confirmed CV events (83/1538 [5.4%] for tocilizumab; 78/1542 [5.1%] for etanercept) reviewed by an independent and blinded adjudication committee.

Non-inferiority of tocilizumab to etanercept for CV risk was determined by excluding >80% relative increase in the risk of MACE. The estimated hazard ratio (HR) for the risk of MACE comparing tocilizumab to etanercept was 1.05; 95% CI (0.77, 1.43).

Polyarticular Juvenile Idiopathic Arthritis (1-4)

Intravenous Administration

The efficacy of tocilizumab was assessed in a three-part study, WA19977 (NCT00988221), including an open-label extension in children 2 to 17 years of age with active polyarticular juvenile idiopathic arthritis (PJIA), who had an inadequate response to MTX or inability to tolerate MTX. Patients had at least 6 months of active disease (mean disease duration of 4.2 ± 3.7 years), with at least five joints with active arthritis (swollen or limitation of movement accompanied by pain and/or tenderness) and/or at least 3 active joints having limitation of motion (mean, 20 ± 14 active joints). The patients treated had subtypes of JIA that at disease onset included Rheumatoid Factor Positive or Negative Polyarticular JIA, or Extended Oligoarticular JIA. Treatment with a stable dose of MTX was permitted but was not required during the study. Concurrent use of disease modifying antirheumatic drugs (DMARDs), other than MTX, or other biologics (e.g., TNF antagonists or T cell costimulation modulator) were not permitted in the study.

Part I consisted of a 16-week active tocilizumab treatment lead-in period (n=188) followed by Part II, a 24-week randomized double-blind placebo-controlled withdrawal period, followed by Part III, a 64-week open-label period. Eligible patients weighing at or above 30 kg received tocilizumab at 8 mg/kg intravenously once every four weeks. Patients weighing less than 30 kg were randomized 1:1 to receive either tocilizumab 8 mg/kg or 10 mg/kg intravenously every four weeks. At the conclusion of the open-label Part I, 91% of patients taking background MTX in addition to tocilizumab and 83% of patients on tocilizumab monotherapy achieved an ACR 30 response at week 16 compared to baseline and entered the blinded withdrawal period (Part II) of the study. The proportions of patients with JIA ACR 50/70 responses in Part I were 84.0%, and 64%, respectively for patients taking background MTX in addition to tocilizumab and 80% and 55% respectively for patients on tocilizumab monotherapy.

In Part II, patients (ITT, n=163) were randomized to tocilizumab (same dose received in Part I) or placebo in a 1:1 ratio that was stratified by concurrent MTX use and concurrent corticosteroid

use. Each patient continued in Part II of the study until week 40 or until the patient satisfied JIA ACR 30 flare criteria (relative to week 16) and qualified for escape.

The primary endpoint was the proportion of patients with a JIA ACR 30 flare at week 40 relative to week 16. JIA ACR 30 flare was defined as 3 or more of the 6 core outcome variables worsening by at least 30% with no more than 1 of the remaining variables improving by more than 30% relative to week 16.

Tocilizumab treated patients experienced significantly fewer disease flares compared to placebo-treated patients (26% [21/82] versus 48% [39/81]; adjusted difference in proportions -21%, 95% CI: -35%, -8%).

During the withdrawal phase (Part II), more patients treated with tocilizumab showed JIA ACR 30/50/70 responses at week 40 compared to patients withdrawn to placebo.

Systemic Juvenile Idiopathic Arthritis (1-4)

Intravenous Administration

The efficacy of tocilizumab for the treatment of active SJIA was assessed in WA18221 (NCT00642460), a 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study. Patients treated with or without MTX, were randomized (tocilizumab:placebo = 2:1) to one of two treatment groups: 75 patients received tocilizumab infusions every two weeks at either 8 mg per kg for patients at or above 30 kg or 12 mg per kg for patients less than 30 kg and 37 were randomized to receive placebo infusions every two weeks. Corticosteroid tapering could occur from week six for patients who achieved a JIA ACR 70 response. After 12 weeks or at the time of escape, due to disease worsening, patients were treated with tocilizumab in the open-label extension phase at weight appropriate dosing.

The primary endpoint was the proportion of patients with at least 30% improvement in JIA ACR core set (JIA ACR 30 response) at week 12 and absence of fever (no temperature at or above 37.5°C in the preceding 7 days). JIA ACR (American College of Rheumatology) responses are defined as the percentage improvement (e.g., 30%, 50%, 70%) in 3 of any 6 core outcome variables compared to baseline, with worsening in no more than 1 of the remaining variables by 30% or more. Core outcome variables consist of physician global assessment, parent per patient global assessment, number of joints with active arthritis, number of joints with limitation of movement, erythrocyte sedimentation rate (ESR), and functional ability (childhood health assessment questionnaire-CHAQ). Primary endpoint results and JIA ACR response rates at week 12 are shown in Table 6.

Table 6. Efficacy Findings at Week 12

	Tocilizumab N=75	**Placebo N=37**
Primary Endpoint: JIA ACR 30 Response + Absence of Fever		
Responders	85%	24%
Weighted Difference	62	-

(95% CI)	(45, 78)	
JIA ACR Response Rates at Week 12		
JIA ACR 30		
Responders Weighted difference[a] (95% CI)[b]	91% 67 (51, 83)	24% -
JIA ACR 50		
Responders Weighted difference[a] (95% CI)[b]	85% 74 (58, 90)	11% -
JIA ACR 70		
Responders Weighted difference[a] (95% CI)[b]	71% 63 (46, 80)	8% -

ACR: American College of Rheumatology; JIA: Juvenile Idiopathic Arthritis; CI: Confidence interval.
[a] The weighted difference is the difference between the tocilizumab and Placebo response rates, adjusted for the stratification factors (weight, disease duration, background oral corticosteroid dose and background methotrexate use).
[b] CI: confidence interval of the weighted difference.

The treatment effect of tocilizumab was consistent across all components of the JIA ACR response core variables. JIA ACR scores and absence of fever responses in the open label extension were consistent with the controlled portion of the study (data available through 44 weeks).

Systemic Features
Of patients with fever or rash at baseline, those treated with tocilizumab had fewer systemic features; 35 out of 41 (85%) became fever free (no temperature recording at or above 37.5°C in the preceding 14 days) compared to 5 out of 24 (21%) of placebo-treated patients, and 14 out of 22 (64%) became free of rash compared to 2 out of 18 (11%) of placebo-treated patients. Responses were consistent in the open label extension (data available through 44 weeks).

Corticosteroid Tapering
Of the patients receiving oral corticosteroids at baseline, 8 out of 31 (26%) placebo and 48 out of 70 (69%), tocilizumab patients achieved a JIA ACR 70 response at week 6 or 8 enabling corticosteroid dose reduction. Seventeen (24%) tocilizumab patients versus 1 (3%) placebo patient were able to reduce the dose of corticosteroid by at least 20% without experiencing a subsequent JIA ACR 30 flare or occurrence of systemic symptoms to week 12. In the open label portion of the study, by week 44, there were 44 out of 103 (43%) tocilizumab patients off oral corticosteroids. Of these 44 patients 50% were off corticosteroids 18 weeks or more.

Health Related Outcomes
Physical function and disability were assessed using the Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI). Seventy-seven percent (58 out of 75) of patients in the tocilizumab treatment group achieved a minimal clinically important improvement in CHAQ-DI (change from baseline of ≥ 0.13 units) at week 12 compared to 19% (7 out of 37) in the placebo treatment group.

Giant Cell Arteritis (1-4)

Intravenous Administration

Intravenously administered tocilizumab in patients with GCA was assessed in WP41152 (NCT03923738), an open-label PK-PD (Pharmacokinetics-Pharmacodynamics) and safety study to determine the appropriate intravenous dose of tocilizumab that achieved comparable PK-PD profiles to the tocilizumab-SC (subcutaneous) regimen.

At enrollment, all patients (n=24) were in remission on intravenous tocilizumab (tocilizumab-IV). In Period 1, all patients received open-label tocilizumab-IV 7 mg/kg every 4 weeks for 20 weeks. Patients who completed Period 1 and remained in remission (n=22) were eligible to enter Period 2 and received open-label tocilizumab-IV 6 mg/kg every 4 weeks for 20 weeks.

The efficacy of intravenous tocilizumab 6 mg/kg in adult patients with GCA is based on pharmacokinetic exposure and extrapolation to the efficacy established for subcutaneous tocilizumab in patients with GCA.

Summary of Evidence

Based on the clinical studies provided to the U.S. Food and Drug Administration, tocilizumab and biosimilars may be considered medically necessary for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs); treatment of individuals 2 years of age and older with active systemic juvenile idiopathic arthritis (SJIA); treatment of individuals 2 years of age and older with active polyarticular juvenile idiopathic arthritis (PJIA) and treatment of adults with giant cell arteritis.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	C9399, J3262, J3490, J3590, Q5133, Q5135, Q5156

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Labels

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/15/2025	Document updated with literature review. The following changes were made to the Coverage section: 1) Added medically necessary language for

	biosimilar tocilizumab-anoh (Avtozma); 2) Tocilizumab-anoh (Avtozma) added to the existing experimental, investigational and/or unproven statement, 3) Added "non-Food and Drug Administration" to the experimental, investigational and/or unproven statement, and 4) Note 5 removed: "Tocilizumab (Actemra® and the biosimilars tocilizumab-bavi [Tofidence™], and tocilizumab-aazg [Tyenne®]) shall not be used concurrently with other biologics used to treat the indications above. Please refer to the Description Section for a list of biological DMARDs." Document title changed from Tocilizumab. References 1-4 added; others removed.
08/01/2024	Document updated with literature review. The following changes were made to the Coverage section: 1) Added medically necessary language for biosimilars tocilizumab-bavi (Tofidence) and tocilizumab-aazg (Tyenne); 2) Clarified "moderately to severely active RA" - removed criteria for inadequate response to one or more DMARDs; 3) Tocilizumab-bavi (Tofidence) and tocilizumab-aazg (Tyenne) added to the existing EIU statement for all other indications, including use of tocilizumab in the outpatient setting for COVID-19. Reference 7, 13 and 14 added; others updated/removed. Document title changed from Tocilizumab.
12/01/2023	Document updated with literature review. The following changes were made to the Coverage section: 1) Removed information concerning Tocilizumab therapy administered for specific patients with the SARS-CoV-2 (COVID-19) virus provided under an Emergency Use Authorization (EUA) from NOTE 4; 2) Replaced NOTE 2 with the criteria outlined in this policy addresses coverage in the outpatient setting. Hospitalized members receiving tocilizumab (Actemra) for the treatment of coronavirus disease 2019 (COVID-19) will be managed according to the member's inpatient benefit and renumbered NOTEs; 3 Added "including use of tocilizumab in the outpatient setting for COVID-19" to the following statement: Intravenous administration of Actemra (tocilizumab) is considered experimental, investigational and/or unproven for all other indications, including use of tocilizumab in the outpatient setting for COVID-19. Reference number 6 added, other references updated.
05/01/2023	Document updated with literature review. The following changes were made to Coverage: 1) Added the following indication "treatment of adult patients with giant cell arteritis" to the statement: Actemra® (tocilizumab) may be considered medically necessary when administered intravenously (IV) for the following U.S. Food and Drug Administration (FDA) labeled indications; 2) Added "Intravenous administration of" to the following statement: Intravenous administration of Actemra® (tocilizumab) may be considered medically necessary for the following off-label indication; 3) Added "Intravenous administration of" to the following statement: Intravenous administration of Actemra (tocilizumab) is considered experimental, investigational and/or unproven for all other indications; 4) Added NOTE 3: Tocilizumab (Actemra) shall not be used concurrently with other biologics

	used to treat the indications above. Please refer to the Description Section for a list of biological disease-modifying antirheumatic drugs (DMARDs). Reference number 4 added, other references updated.
08/01/2021	Document updated with literature review. The following changes were made to Coverage: 1) Removed indication for cytokine release syndrome; 2) Added NOTE 1: This medical policy does NOT address oncologic indications. This medical policy IS NOT TO BE USED for oncologic indications. Refer to RX502.061 Oncology Medications for oncologic indications; 3) Clarified NOTE 2, by adding non-biologic to the following statement: In rheumatoid arthritis, other non-biologic DMARDs may be used; 4) Added the following off label indication: Actemra® (tocilizumab) may be considered medically necessary for the following off-labeled indication: Treatment of adult patients with rheumatoid arthritis (moderate to severe), with no previous treatment failure. The following references were added: 6-10.
07/01/2021	Document updated. The following change was made to Coverage: Added "NOTE 2: Tocilizumab therapy administered for specific patients with the SARS-CoV-2 (COVID-19) virus provided under an Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration (FDA) during a public health emergency is NOT addressed by this policy".
10/01/2020	New medical document originating from RX501.051. Tocilizumab (Actemra®) may be considered medically necessary when administered intravenously (IV) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs); treatment of patients 2 years of age and older with active systemic juvenile idiopathic arthritis (sJIA); treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (pJIA); and adult and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome. Actemra is considered experimental, investigational and/or unproven for all other indications.