Medical Policy Bulletin
Title:
Tocilizumab (Actemra®) & Related Biosimilars for Intravenous Infusion & Subcutaneous Injection
Policy #:
MA08.045o

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

In the absence of coverage criteria from applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals, or other Medicare coverage documents, this policy uses internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, and/or regulatory status.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

MEDICALLY NECESSARY

INITIAL THERAPY
Tocilizumab products are considered medically necessary and, therefore, covered for the following indications when, for each individual indication, all of the associated criteria are met:

Castleman Disease (CD)

- In one of the following conditions, as a single agent:
  - Multicentric CD: Subsequent therapy for multicentric CD that has progressed following treatment of relapsed/refractory or progressive disease
    - May use as a substitute for siltuximab (Sylvant) if there is a shortage of siltuximab or it is not available
  - Unicentric CD: Second-line therapy for individuals with relapsed/refractory or progressive unresectable disease who are human immunodeficiency virus–negative and human herpesvirus-8–negative
- Active or latent tuberculosis (TB) has been ruled out
- Tocilizumab products are administered by intravenous infusion

Coronavirus disease 2019 (COVID-19)

- In individuals 2 years of age or older who are hospitalized with coronavirus disease 2019 (COVID-19)

- In conjunction with systemic corticosteroids and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)
- Active or latent TB has been ruled out
- Tocilizumab products are administered by intravenous infusion

Cytokine release syndrome (CRS) caused by chimeric antigen receptor (CAR) T-cell therapy (e.g., axicabtagene ciloleucel [Yescarta], brexucabtagene autoleucel [Tecartus], lisocabtagene maraleucel [Breyanzi], tisagenlecleucel [Kymriah])

- In individuals 2 years of age or older
- When used alone or in combination with corticosteroids
- When used for the following grades, per National Cancer Institute's Common Terminology criteria for Adverse Events (CTCAE v5.0) Grading System*:
    - CRS Grades 2–4
    - CRS symptoms that persist for more than 24 hours in individuals treated with axicabtagene ciloleucel (Yescarta) or brexucabtagene autoleucel (Tecartus)
    - For prolonged (>3 days) Grade 1 CRS in individuals with significant symptoms, comorbidities, and/or in elderly individuals
    - Grade 1 CRS that develops less than 72 hours after infusion in those treated with lisocabtagene maraleucel (Breyanzi)
- Active or latent TB has been ruled out
- When used up to a maximum of four doses
- Tocilizumab products are administered by intravenous infusion

Cytokine release syndrome (CRS), caused by blinatumomab (Blincyto) therapy in individuals with acute lymphoblastic leukemia

- In individuals 2 years of age or older
- Active or latent TB has been ruled out
- When used up to a maximum of four doses

Giant cell arteritis (GCA)

- In individuals 18 years of age or older
- Documented diagnosis of active GCA demonstrated by signs and symptoms associated with GCA (e.g., new-onset localized headache, scalp tenderness, ischemia-related vision loss, unexplained mouth or jaw pain upon mastication, or shoulder and/or hip girdle pain associated with inflammatory morning stiffness) AND one of the following:
    - Acute-phase reactant elevation (e.g., C-reactive protein ≥1 mg/L or erythrocyte sedimentation rate ≥30 mm/h)
    - Temporal artery biopsy or cross-sectional imaging
- There is documentation of inadequate response, intolerance, or contraindication to systemic corticosteroids
- Active or latent TB has been ruled out
- Tocilizumab products are administered by intravenous infusion or subcutaneous injection

Graft-versus-host disease (GVHD), acute, after hematopoietic cell transplantation

- In conjunction with systemic corticosteroids and/or immunosuppressive agent following no response (steroid-refractory disease) to first-line therapy options
- Active or latent TB has been ruled out
- Tocilizumab products are administered by intravenous infusion

Immunotherapy-related toxicities caused by immune checkpoint inhibitors (e.g., ipilimumab [Yervoy], nivolumab [Opdivo], pembrolizumab [Keytruda])

- There is documentation of one of the following:
    - Moderate to severe inflammatory arthritis if no improvement after holding immunotherapy and treating with oral corticosteroids or if unable to taper corticosteroids
    - Polymyalgia rheumatica if unable to taper prednisone or no improvement in symptoms
    - Giant cell arteritis (urgent referral to rheumatology even in mild cases)
    - G2 elevated alanine transaminase/aspartate transaminase (ALT/AST) if liver enzymes suggest worsening or no improvement after 3 to 7 days of prednisone
    - G3 or G4 elevated ALT/AST if no improvement after 1 to 2 days of prednisone/methylprednisolone

    - G2 elevated alkaline phosphatase (predominant) with or without bilirubin/AST/ALT elevations if alkaline phosphatase worsens or does not improve within 3 days after initiating corticosteroids
    - G3 or G4 elevated alkaline phosphatase (predominant) with or without bilirubin/AST/ALT elevations if no improvement after 1 to 2 days of prednisone/methylprednisolone
- Active or latent TB has been ruled out

Immunotherapy-related toxicities caused by CD3-based lymphocyte engager therapies

- Prophylactic therapy to reduce the risk of progression to severe or refractory Cytokine Release Syndrome (CRS) when administering teclistamab-cqyv (Tecvayli)
- Active or latent TB has been ruled out
- Tocilizumab products are administered by intravenous infusion

Neurotoxicity caused by CAR T-cell therapy (e.g., axicabtagene ciloleucel [Yescarta], lisocabtagene maraleucel [Breyanzi], tisagenlecleucel [Kymriah])

- Grade* 1–4 neurotoxicity as additional single-dose therapy if individual has concurrent CRS
- When used up to a maximum of four doses
- Active or latent TB has been ruled out
- Tocilizumab products are administered by intravenous infusion

Polyarticular juvenile idiopathic arthritis (PJIA), active

- In individuals 2 years of age or older
- Active or latent TB has been ruled out
- When used alone or in combination with methotrexate
- There is documentation of inadequate response, intolerance, or contraindication to non-biologic DMARDs (e.g., methotrexate)
- Tocilizumab products are administered by intravenous infusion or subcutaneous injection

Rheumatoid arthritis

- Moderately to severely active disease
- In individuals 18 years of age or older
- Active or latent TB has been ruled out
- When used alone or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs)
- There is documentation of inadequate response, intolerance, or contraindication to a 3-month trial of one or more DMARDs
- Tocilizumab products are administered by intravenous infusion or subcutaneous injection

Systemic juvenile idiopathic arthritis (SJIA), active

- In individuals 2 years of age or older
- Active or latent TB has been ruled out
- When used alone or in combination with methotrexate
- There is documentation of inadequate response, intolerance, or contraindication to nonsteroidal anti-inflammatory drugs (NSAIDS), corticosteroids, or DMARDs (e.g., leflunomide, methotrexate)
- Tocilizumab products are administered by intravenous infusion or subcutaneous injection

Systemic Sclerosis–Associated Interstitial Lung Disease (SSa-ILD)

- In individuals 18 years of age or older
- Documented diagnosis of active diffuse cutaneous systemic sclerosis (SSc) and meets both of the following criteria:
    - Modified Rodnan skin score (mRSS) 10 or greater
    - Acute-phase reactant elevation (e.g., C-reactive protein ≥6 mg/L, erythrocyte sedimentation rate ≥28 mm/h, or platelet count ≥330 × 10^9/L)
- Documented diagnosis of interstitial lung disease (ILD) through pulmonary function testing, chest radiograph, or echocardiography
- There is documentation of inadequate response, intolerance, or contraindication to a 3-month trial of one or more DMARDs (e.g., mycophenolate mofetil, cyclophosphamide, azathioprine)
- Active or latent TB has been ruled out

- Tocilizumab products are administered by subcutaneous injection

*See Guidelines Section for Grading Tables for CRS and neurotoxicity.

CONTINUATION THERAPY

Tocilizumab products are considered medically necessary and, therefore, covered for continuation therapy (after the timeframes indicated below) when there is documentation of a positive clinical response or stabilization to therapy (e.g., improvement in total active [swollen and tender] joint count from baseline, improvement in symptoms [e.g., pain, stiffness, inflammation, fever, fatigue, non-productive cough] from baseline).

- Castleman disease: 6 weeks or greater
- RA: 24 weeks or greater
- PJIA: 16 weeks or greater
- GCA: 12 weeks or greater
- SJIA: 12 weeks or greater
- SSa-ILD: 48 weeks or greater

EXPERIMENTAL/INVESTIGATIONAL

All other uses for tocilizumab products for intravenous infusion or subcutaneous injection are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

Guidelines

This policy is consistent with Medicare's coverage determination. The Company's payment methodology may differ from Medicare.

BENEFIT APPLICATION

Subject to the applicable Evidence of Coverage, tocilizumab (Actemra) and related biosimilars are covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria listed in this medical policy are met.

Certain drugs are available through either the member's medical benefit (Part B benefit) or pharmacy benefit (Part D benefit), depending on how the drug is prescribed, dispensed, or administered. This medical policy only addresses instances when tocilizumab (Actemra) and related biosimilars are covered under a member's medical benefit (Part B benefit). It does not address instances when tocilizumab (Actemra) and related biosimilars are covered under a member's pharmacy benefit (Part D benefit).

CONSIDERATION FOR ADMINISTRATION

Tocilizumab (Actemra) and related biosimilars have not been studied, and their use should be avoided in combination with biological disease-modifying antirheumatic drugs (DMARDs) such as tumor necrosis factor (TNF) antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies, and selective co-stimulation modulators, due to the increased possibility of immunosuppression and increased risk of infection.

MODIFIED RODNAN SKIN SCORE

The modified Rodnan skin score is a method to assess the skin thickness of different areas of the body in individuals

with scleroderma. The modified Rodnan skin score is obtained by clinical palpation of 17 different body areas (fingers, hands, forearms, upper arms, face, chest, abdomen, thighs, lower legs, and feet) and subjective averaging of the thickness of each specific site: 0 = normal (A); 1 = mild (B); 2 = moderate (C); and 3 = severe (D). The maximum total score is 51.

THE NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE v5.0) GRADING SYSTEM*

Cytokine release syndrome (CRS)	
Grade 1	Fever with or without constitutional symptoms
Grade 2	Hypotension responding to fluids; hypoxia responding to <40% O_2
Grade 3	Hypotension managed with one pressor; hypoxia requiring ≥40% O_2
Grade 4	Life-threatening consequences; requiring ventilator support or vasopressor-refractory shock
Grade 5	Death

CAR T-cell-related Neurotoxicity*

Grade 1	Mild impact on activities of daily living (ADLs)
Grade 2	Moderate impact on ADLs
Grade 3	Severe impact on ADLs; seizure; signs of elevated intracranial pressure (e.g., papilledema, Cushing's triad, hypertension, bradycardia)
Grade 4	Critical condition and/or obtunded and cannot perform assessment of tasks; repetitive seizures without return to baseline or life-threatening seizures (non-convulsive or convulsive)

*Sources:

- National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology - Management of Immunotherapy-Related Toxicities.* V.1.2021. 02/01/2021.
- National Institutes of Health. Common Terminology criteria for Adverse Events (CTCAE v5.0) Grading System.

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Tocilizumab (Actemra) was approved by the FDA on January 8, 2010, for treatment of adults with moderately to severely active rheumatoid arthritis, after at least one tumor necrosis factor antagonist has been tried and failed. On October 11, 2012, based on the safety and efficacy outcomes from further Phase III and postmarketing studies, the FDA expanded the approval for the treatment of adult individuals with moderately to severely active RA who have had an inadequate response to one or more DMARDs. Supplemental approvals for tocilizumab (Actemra) have since been issued by the FDA. The FDA has issued subsequent approvals for biosimilar products.

PEDIATRIC USE
The safety and effectiveness of tocilizumab (Actemra) and related biosimilars in pediatric individuals with conditions other than polyarticular juvenile idiopathic arthritis (pJIA), systemic juvenile idiopathic arthritis (Still disease) (SJIA) or cytokine-release syndrome (CRS) have not been established. The safety and effectiveness in pediatric individuals below the age of 2 have not been established in pJIA, SJIA, or CRS.

Description

Tocilizumab (Actemra) for intravenous infusion is a humanized monoclonal antibody that inhibits the interleukin-6 receptor that binds specifically to both the soluble and membrane-bound interleukin-6 receptors, thereby blocking the inflammatory response.

ACTIVE RHEUMATOID ARTHRITIS (RA)

RA is a chronic inflammatory autoimmune disorder that involves inflammation of the synovial joints and can result in erosion of cartilage and bone. The American College of Rheumatology's guidelines for the treatment of RA

recommend that newly diagnosed individuals with RA begin treatment with disease-modifying antirheumatic drugs (DMARDs). DMARDs slow down disease progression, and some act with mild chemotherapeutic action, causing immunosuppression. Furthermore, DMARDs can be subdivided into the traditional small-molecular-mass, chemically synthesized nonbiologic DMARDs (such as, but not limited to, methotrexate, sulfasalazine, azathioprine, leflunomide, hydroxychloroquine sulfate, and cyclosporine) and the newer biologic DMARDs. Examples of biologic DMARDs include, but are not limited to, etanercept (Enbrel), adalimumab (Humira), anakinra (Kineret), abatacept (Orencia), rituximab (Rituxan), and infliximab (Remicade).

TOCILIZUMAB (ACTEMRA) FOR INTRAVEOUS INFUSION
Tocilizumab (Actemra) for intravenous infusion was approved by the US Food and Drug Administration (FDA) on January 8, 2010, for the treatment of adult individuals with moderately to severely active RA who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies. In phase II and phase III clinical trials, tocilizumab (Actemra), when used in combination with methotrexate or alone, has been shown to be effective in reducing the signs and symptoms of RA in individuals who had an inadequate response to TNF antagonists. On October 11, 2012, based on the safety and efficacy outcomes from further phase III and postmarketing studies, the FDA expanded the approval for the treatment of adult individuals with moderately to severely active RA who have had an inadequate response to one or more DMARDs. These studies showed a statistically significant greater percentage of individuals achieving ACR20 at Week 24 with the use of tocilizumab (Actemra®) for intravenous infusion plus a DMARD when compared to the placebo plus a DMARD.

Tocilizumab (Actemra) for intravenous infusion is administered by intravenous infusion in adults once every 4 weeks over 60 minutes.

TOCILIZUMAB (ACTEMRA) FOR SUBCUTANEOUS INJECTION
The safety and efficacy of tocilizumab (Actemra) for subcutaneous injection was assessed in two randomized, double-blind, controlled, multicenter studies in individuals with active RA. Study SC-I was a noninferiority study that compared the efficacy and safety of tocilizumab (Actemra) 162 mg administered every week subcutaneously to 8 mg per kg intravenously every 4 weeks. Study SC-II was a placebo-controlled superiority study that evaluated the safety and efficacy of tocilizumab (Actemra) 162 mg administered every other week subcutaneously to placebo. Both studies were performed in adults with moderate to severe active RA diagnosed according to ACR criteria who had at least four tender and four swollen joints at baseline (SC-I) or at least eight tender and six swollen joints at baseline (SC-II), and an inadequate response to their existing DMARD therapy. All individuals in both SC studies received background nonbiologic DMARD(s). The primary endpoint in both studies was the proportion of individuals who achieved an ACR20 response at Week 24. SC-I demonstrated noninferiority of subcutaneous route compared to intravenous route (n=1262; 69% vs 73.4%); SC-II, a greater portion of individuals treated with tocilizumab (Actemra) for subcutaneous injection ACR20 compared to placebo-treated individuals (n=656; 61% vs 32%).

Tocilizumab (Actemra) for subcutaneous injection is administered every other week or weekly, based on weight.

CORONAVIRUS DISEASE 2019 (COVID-19)
Tocilizumab (Actemra) for intravenous infusion was approved by the FDA on December 21, 2022, for the treatment of hospitalized individuals 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).

The efficacy of tocilizumab (Actemra) for the treatment of COVID-19 was based on RECOVERY, a randomized, controlled, open-label study in 4116 hospitalized adult individuals with severe COVID-19–related pneumonia. The results are supported by three other randomized, double-blind, placebo-controlled studies: EMPACTA, COVACTA, REMDACTA. In RECOVERY trial, individuals were randomly assigned to receive standard of care or IV tocilizumab. At baseline, the majority of individuals were on supplemental oxygen, 45% required low-flow oxygen, 41% required noninvasive ventilation or high-flow oxygen, and 14% required invasive mechanical ventilation. At baseline, 82% of individuals were receiving systemic corticosteroids. The primary efficacy endpoint of the trial was time to death through day 28. The study showed tocilizumab (Actemra) improved survival and clinical outcomes at 28 days. The mortality rate was 31% in those who received tocilizumab (Actemra), compared with 35% in those who received standard of care. Reduction in mortality was observed in a larger proportion of individuals receiving systemic corticosteroids compared with those not receiving a systemic corticosteroid at randomization; however, the authors reported that this may have been a chance finding. Those who received tocilizumab (Actemra) were also more likely to be discharged from the hospital within 28 days and less likely to require invasive mechanical ventilation.

A meta-analysis of the EMPACTA, COVACTA, REMDACTA, and RECOVERY studies evaluated the risk difference through Day 28, estimated by the Kaplan-Meier method, in the subgroup of individuals receiving baseline corticosteroids (note: RECOVERY trial represented 78.8% of the total sample size). The combined risk difference showed that tocilizumab (Actemra) treatment (n=2261) resulted in a 4.61% absolute reduction in the risk of death at Day 28 compared to standard of care.

CYTOKINE RELEASE SYNDROME (CRS)

Cytokine release syndrome (CRS) occurs when immune-based chemotherapy or introduction of immune cells, such as chimeric antigen receptor (CAR) T cells, cause an abnormally large activation of the cells involved in the immune system (e.g., lymphocytes or myeloid cells) which then release inflammatory cytokines. Symptoms of CRS may develop within minutes, hours, or days after the infusion. Symptoms range from mild to severe or life-threatening and may include fever, hypotension, mental status changes, tachycardia; worsening of respiratory distress, including pulmonary infiltrates, increasing oxygen requirements, or need for mechanical ventilation; organ toxicity; and seizures. The severity of CRS is defined in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v5.0) grading system, where a score of one is non–life-threatening (e.g., fever, nausea) and a score of five is death.

TOCILIZUMAB (ACTEMRA) FOR INTRAVEOUS INFUSION
Tocilizumab (Actemra) for intravenous infusion was approved by the FDA on August 30, 2017, for the treatment of CAR T-cell– induced severe or life-threatening CRS in adults and pediatric individuals 2 years of age and older.

The efficacy of tocilizumab (Actemra) for severe or life-threatening CRS was reviewed in a retrospective analysis of pooled outcome data from clinical trials of CAR T-cell therapies for hematological malignancies. Forty-five individuals received tocilizumab (Actemra) 8 mg/kg (12 mg/kg for individuals <30 kg) with or without additional high-dose corticosteroids. The analysis only reviewed the first episode of CRS in each patient. The median time from start of CRS to first dose of tocilizumab was 4 days (range, 0–18 days). Resolution of CRS was defined as lack of fever and off vasopressors for at least 24 hours. Individuals were considered responders if CRS resolved within 14 days of the first dose of tocilizumab, no more than two doses of tocilizumab were needed, and no drugs other than tocilizumab and corticosteroids were used for treatment. The results of this review concluded that 31 individuals (69%) achieved a clinical response to the first CRS episode.

Tocilizumab (Actemra) for intravenous infusion is administered by intravenous infusion in individuals 2 years of age and older over 60 minutes. A maximum dose of 800 mg per infusion is recommended. A maximum of four doses administered at least 8 hours apart may be prescribed, if necessary. Tocilizumab (Actemra) for intravenous infusion may be administered alone or in combination with corticosteroids.

GIANT CELL ARTERITIS (GCA)

Giant cell arteritis (GCA; also known as Horton disease, cranial arteritis, and temporal arteritis) is the most common of the systemic vasculitides and is categorized as a vasculitis of large- and medium-sized vessels because it can involve the aorta and great vessels. GCA typically occurs in adults 50 to 80 years of age. Signs and symptoms include new-onset headache, abrupt onset of visual disturbances, especially transient monocular visual loss, jaw claudication, and high erythrocyte sedimentation rate (ESR) and/or high serum C-reactive protein (CRP). In the United States, the lifetime risk of developing GCA has been estimated at approximately 1% in women and 0.5% in men. Treatment of GCA includes a corticosteroid taper, tocilizumab (Actemra), or methotrexate.

TOCILIZUMAB (ACTEMRA) FOR INTRAVEOUS INFUSION
The efficacy of tocilizumab (Actemra) for intravenous infusion is based on pharmacokinetic exposure and extrapolation to the efficacy established for tocilizumab (Actemra) for subcutaneous injection in individuals with GCA.
TOCILIZUMAB (ACTEMRA) FOR SUBCUTANEOUS INJECTION
The safety and efficacy of tocilizumab (Actemra) for subcutaneous injection was assessed by Stone et al. (2017) in a randomized, double-blind, multicenter study in 251 individuals 50 years of age or older with active, new-onset, or relapsing GCA and were randomly assigned to one of four treatment arms. Two subcutaneous doses of tocilizumab (Actemra) (162 mg every week and 162 mg every other week) in combination with a 26-week prednisone taper were compared to two different placebo-control groups (prednisone-taper regimen over 26 weeks and 52 weeks) randomized 2:1:1:1. The study consisted of a 52-week blinded period, followed by a 104-week open-label extension. The primary efficacy endpoint was the proportion of individuals achieving sustained remission from Week 12 through Week 52 (sustained remission was defined by a patient attaining a sustained [1] absence of GCA signs and symptoms from Week 12 through Week 52, [2] normalization of ESR [to <30 mm/hr without an elevation to ≥30 mm/hr attributable to GCA] from Week 12 through Week 52, [3] normalization of CRP [to <1 mg/dL, with an absence of successive elevations to ≥1 mg/dL] from Week 12 through Week 52, and [4] successful adherence to the

prednisone taper defined by not more than 100 mg of excess prednisone from Week 12 through Week 52.] Tocilizumab (Actemra) 162 mg weekly and 162 mg every other week both showed superiority in achieving sustained remission from Week 12 through Week 52 (56% and 53%, respectively) compared with placebo group (14%) that underwent 26-week prednisone taper (P<0.001) (primary outcome) and 18% of those in the placebo group that underwent the 52-week taper (secondary outcome, P<0.001).

Tocilizumab (Actemra) for subcutaneous injection is administered every other week or weekly, based on clinical considerations.

POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS

Tocilizumab (Actemra) for intravenous infusion was approved by the FDA on April 29, 2013, for the treatment of individuals ages 2 years and older with active polyarticular juvenile idiopathic arthritis (pJIA). PJIA is a subset of juvenile idiopathic arthritis (JIA) and comprises 20% to 30% of all individuals with JIA.

TOCILIZUMAB (ACTEMRA) FOR INTRAVEOUS INFUSION

Tocilizumab (Actemra) for intravenous infusion was approved by the FDA on April 29, 2013, for the treatment of individuals ages 2 years and older with active PJIA. PJIA is a subset of JIA and comprises 20% to 30% of all individuals with JIA. The diagnosis of PJIA is made when five or more joints are affected in the first 6 months after disease onset. Management of PJIA may include medications such as corticosteroids or NSAIDs, or DMARDs, including immunomodulators or biologic agents.

Tocilizumab (Actemra) for intravenous infusion was investigated in a three-part trial of 188 individuals with active PJIA, ages 2 to 17 years of age, who had inadequate clinical response to methotrexate or were intolerant to methotrexate. Part I was a 16-week, open-label trial of tocilizumab (Actemra), followed by Part II, which was a 24-week randomized double-blind placebo-controlled withdrawal period. Finally, Part III was a 64-week open-label extension. In Part I, response to treatment was defined as at least a 30% improvement in the American College of Rheumatology's (ACR) JIA efficacy variables. After 16 weeks of therapy, 91% and 83% of individuals, respectively, achieved an ACR 30 response compared to baseline, while receiving concomitant methotrexate or on tocilizumab (Actemra) for intravenous infusion monotherapy. ACR 50/70 responses were 84% and 64%, respectively, for individuals receiving concomitant methotrexate, and 80% and 55%, respectively, for individuals on tocilizumab (Actemra) for intravenous infusion monotherapy. Those who achieved an ACR 30 response (n=163) entered Part II of the study, in which individuals were randomly assigned to tocilizumab (Actemra) for intravenous infusion or placebo (1:1 ratio). The results of this study reported that those receiving tocilizumab (Actemra) for intravenous infusion experienced significantly fewer disease flares compared to placebo-treated individuals (26% vs 48%). Also, more individuals treated with tocilizumab (Actemra) for intravenous infusion showed ACR 30/50/70 responses at Week 40 compared to individuals withdrawn to placebo.

Tocilizumab (Actemra) for intravenous infusion is administered by intravenous infusion in individuals 2 years of age and older once every 4 weeks over 60 minutes, and may be administered alone or in combination with methotrexate.

TOCILIZUMAB (ACTEMRA) FOR SUBCUTANEOUS INJECTION

The efficacy of tocilizumab (Actemra) for subcutaneous injection in children 2 to 17 years of age is based on pharmacokinetic exposure and extrapolation of the established efficacy of intravenous tocilizumab (Actemra) in polyarticular JIA individuals and subcutaneous tocilizumab (Actemra) in individuals with RA. The study included individuals with an inadequate response or inability to tolerate methotrexate. Tocilizumab (Actemra) for subcutaneous injection is administered every other week or every 3 weeks, based on weight.

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA)

Active SJIA, also known as Still disease, is a rare, potentially life-threatening disease in children that causes severe inflammation throughout the body. The occurrence of fever spikes; rash; swelling and inflammation of the lymph nodes, liver, and spleen; and high white blood cell and platelet counts differentiate SJIA from other juvenile idiopathic forms of arthritis. The prevalence of JIA is estimated to be 1 to 2 per 1000 children, and SJIA affects about 10% of all juvenile idiopathic arthritis individuals.

TOCILIZUMAB (ACTEMRA) FOR INTRAVEOUS INFUSION

Tocilizumab (Actemra) for intravenous infusion was approved by the FDA on April 15, 2011, for the treatment of individuals ages 2 years and older with active SJIA, also known as Still disease. Tocilizumab (Actemra) for intravenous infusion was used in an international, multicenter controlled trial of 112 individuals with SJIA, ages 2 to 17 years of age, who had inadequate clinical response to NSAIDs or corticosteroids or methotrexate due to toxicity or

lack of efficacy. Eighty-five percent of those who received tocilizumab (Actemra) for intravenous infusion responded to treatment, compared to 24 percent of individuals who received the placebo. Response was defined as at least a 30% improvement in the American College of Rheumatology's JIA efficacy variables, as well as the absence of fever in the preceding 7 days. However, among those who received tocilizumab (Actemra®), there were three cases of macrophage-activation syndrome, a potentially fatal complication of childhood systemic inflammatory disorders.

Tocilizumab (Actemra) for intravenous infusion is administered by intravenous infusion in individuals 2 years of age and older once every 2 weeks over 60 minutes, and may be administered alone or in combination with methotrexate.

TOCILIZUMAB (ACTEMRA) FOR SUBCUTANEOUS INJECTION

The efficacy of subcutaneous tocilizumab (Actemra) in children 2 to 17 years of age is based on pharmacokinetic exposure and extrapolation of the established efficacy of intravenous tocilizumab (Actemra) in systemic JIA individuals. Tocilizumab (Actemra) for subcutaneous injection is administered every other week or weekly, based on weight.

SYSTEMIC SCLEROSIS–ASSOCIATED INTERSTITIAL LUNG DISEASE

Systemic scleroderma (SSc) is a disease characterized by rapid growth of fibrous (connective) tissue that leads to scarring of skin and internal organs. Interstitial lung disease (ILD) is a frequent complication of SSc that is often progressive and has a poor prognosis, compared to individuals without pulmonary involvement. Diffuse cutaneous SSc, a subtype of SSc, is characterized by extensive skin involvement and extension of skin sclerosis proximal to the elbows and is a risk factor for developing ILD early in the course of SSc. Individuals with limited cutaneous SSc, in which skin sclerosis is generally restricted to the hands, distal extremities, and, to a lesser extent, the face and neck, are less likely to develop ILD early in the course of disease, but may develop ILD as a late manifestation. Individuals with SSc who have early development of ILD typically have a higher modified Rodnan skin score (mRSS) and serum creatine phosphokinase (CPK) levels, hypothyroidism, renal, and cardiac involvement. SSc-associated ILD is usually suspected when an individual with known SSc develops dyspnea, cough, auscultatory crackles, or abnormalities on pulmonary function testing or the chest radiograph. Treatment includes immunomodulators, such as mycophenolate mofetil, tocilizumab, cyclophosphamide, azathioprine, and agents that treat pulmonary arterial hypertension.

TOCILIZUMAB (ACTEMRA) FOR SUBCUTANEOUS INJECTION

Tocilizumab (Actemra) for subcutaneous injection was approved by the FDA on March 4, 2021, indicated for slowing the rate of decline in pulmonary function in 210 adults with SSc-associated interstitial lung disease. The safety and efficacy of tocilizumab (Actemra) was assessed in a phase III multicenter, randomized, double-blind, placebo-controlled study of adults with diffuse cutaneous SSc for 60 months or less and a mRSS of 10 to 35 at screening. Participants were randomly assigned (1:1) to receive subcutaneous tocilizumab 162 mg or placebo weekly for 48 weeks. The primary endpoint resulted in no significant difference between tocilizumab and placebo for change in mean baseline mRSS from baseline to week 48 (P=0.10), although those treated with tocilizumab had a numerically greater reduction in skin sclerosis after 48 weeks. However, the change from baseline in FVC% (forced vital capacity measured as a percentage of predicted normal values) at week 48 favored tocilizumab versus placebo in the overall population and in the subset of patients with diagnosed interstitial lung disease, and suggests stabilization of lung function, per the researchers.

Tocilizumab (Actemra) for subcutaneous injection is administered every week.

SAFETY

Tocilizumab (Actemra) should be interrupted if an individual develops a serious infection or an opportunistic infection or sepsis, until the infection is controlled. Other safety concerns that require monitoring during tocilizumab (Actemra) are elevated liver enzymes, elevated low-density lipoproteins or bad cholesterol, hypertension, and gastrointestinal perforations.

OFF-LABEL INDICATIONS

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company’s off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)

N/A

ICD - 10 Procedure Code Number(s)

N/A

ICD - 10 Diagnosis Code Number(s)

Report the most appropriate diagnosis code in support of medically necessary criteria as listed in the policy.

HCPCS Level II Code Number(s)

J3262	Injection, tocilizumab, 1 mg
M0237	Intravenous infusion, tocilizumab-anoh, for hospitalized adult patients with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ecmo) only, includes infusion and post administration monitoring, first dose
M0238	Intravenous infusion, tocilizumab-anoh, for hospitalized adult patients with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ecmo) only, includes infusion and post administration monitoring, second dose
M0249	Intravenous infusion, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, includes infusion and post administration monitoring, first dose
M0250	Intravenous infusion, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, includes infusion and post administration monitoring, second dose
Q0237	Injection, tocilizumab-anoh, for hospitalized adult patients with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ecmo) only, 1 mg
Q0249	Injection, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, 1 mg
Q5133	Injection, tocilizumab-bavi (Tofidence), biosimilar, 1 mg

Q5135	Injection, tocilizumab-aazg (tyenne), biosimilar, 1 mg
Q5156	Injection, tocilizumab-anoh (avtozma), biosimilar, 1 mg

Revenue Code Number(s)

N/A

Policy History

Revisions From MA08.045o:

03/20/2026	This version of the policy will become effective 03/20/2026. This policy has been updated to communicate the coverage criteria, in alignment with US Food and Drug Administration (FDA) and National Comprehensive Cancer Network (NCCN). The following criteria for COVID-19 has been revised to include pediatrics: • In individuals 2 years of age or older who are hospitalized with coronavirus disease 2019 (COVID-19) The following HCPCS codes have been added to this policy, retro-effective 06/24/2021: • M0249 Intravenous infusion, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, includes infusion and post administration monitoring, first dose • M0250 Intravenous infusion, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, includes infusion and post administration monitoring, second dose • Q0249 Injection, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) only, 1 mg

Revisions From MA08.045n:

12/15/2025	This version of the policy will become effective 12/15/2025. The following HCPCS codes have been added to this policy, retro-effective 01/24/2025: • M0237 Intravenous infusion, tocilizumab-anoh, for hospitalized adult patients with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ecmo) only, includes infusion and post administration monitoring, first dose • M0238 Intravenous infusion, tocilizumab-anoh, for hospitalized adult patients with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ecmo) only, includes infusion and post administration monitoring, second dose • Q0237 Injection, tocilizumab-anoh, for hospitalized adult patients with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ecmo) only, 1 mg

	The following NOC codes have been replaced in this policy to represent tocilizumab-anoh (Avtozma): REMOVED: • C9399 Unclassified drugs or biologics • J3590 Unclassified biologics REPLACED WITH: Q5156 Injection, tocilizumab-anoh (avtozma), biosimilar, 1 mg

Revisions From MA08.045m:

09/16/2025	This version of the policy will become effective 09/16/2025. This policy was updated to communicate the coverage position for the newly added biosimilar agent (tocilizumab-anoh [Avtozma]). Additionally, the management of Castleman disease was revised to allow use as a substitute for siltuximab (Sylvant) if there is a shortage of siltuximab or it is not available and immunotherapy-related toxicities was revised to include lymphocyte engager-related toxicities, in alignment with the National Comprehensive Cancer Network (NCCN) compendium. The following NOC codes have been added to this policy to represent tocilizumab-anoh (Avtozma): • C9399 Unclassified drugs or biologics • J3590 Unclassified biologics All of the ICD-10 CM codes have been removed from this policy, since they are informational. Report the most appropriate diagnosis code in support of medically necessary criteria as listed in the policy.

Revisions From MA08.045l:

12/16/2024	This version of the policy will become effective 12/16/2024. This policy has been updated to communicate the coverage criteria, in alignment with US Food and Drug Administration (FDA) and National Comprehensive Cancer Network (NCCN). Cytokine release syndrome (CRS) caused by Blincyto was added. Immunotherapy-related toxicities were expanded to additional corticosteroid-sparing immunosuppresion. The policy title was expanded to include related biosimilars. The following ICD-10 CM codes have been **added** to this policy as medically necessary: • C91.00 Acute lymphoblastic leukemia not having achieved remission • C91.01 Acute lymphoblastic leukemia, in remission • C91.02 Acute lymphoblastic leukemia, in relapse • R74.01 Elevation of levels of liver transaminase levels The following HCPCS codes have been **added** to this policy as medically necessary: • Q5135 Injection, tocilizumab-aazg (tyenne), biosimilar, 1 mg

Revisions From MA08.045k:

05/07/2024	This version of the policy will become effective 05/07/2024. The following HCPCS code has been **added to** this policy: Q5133 Injection, tocilizumab-bavi (tofidence), biosimilar, 1 mg

Revisions From MA08.045j:

11/13/2023	This version of the policy will become effective 11/13/2023.

	This policy has been updated to communicate the coverage criteria, in alignment with US Food and Drug Administration (FDA) and National Comprehensive Cancer Network (NCCN). Coronavirus disease 2019 (COVID-19) indication was added. Cytokine release syndrome (CRS) caused by Blincyto was removed. Immunotherapy-related Toxicities were expanded to inflammatory arthritis, polymyalgia rheumatica, and giant cell arteritis . Additionally, Continuation Therapy was added as a policy criterion. The following ICD-10 CM codes have been **added** to this policy: M35.3 Polymyalgia rheumatica U07.1 COVID-19

Revisions From MA08.045i:

07/18/2022	This version of the policy will become effective 07/18/2022. This policy has been updated to communicate the coverage criteria revisions for tocilizumab (Actemra) for intravenous infusion, for use in Cytokine release syndrome, Inflammatory arthritis caused by Immune Checkpoint Inhibitors, and Neurotoxicity caused by chimeric antigen receptor (CAR) T cell therapy, which are in alignment with US Food and Drug Administration (FDA) and National Comprehensive Cancer Network (NCCN). The following ICD-10 CM codes have been **added** to this policy: G92.01 Immune effector cell-associated neurotoxicity syndrome, grade 1 G92.02 Immune effector cell-associated neurotoxicity syndrome, grade 2 G92.03 Immune effector cell-associated neurotoxicity syndrome, grade 3 G92.04 Immune effector cell-associated neurotoxicity syndrome, grade 4 M06.4 Inflammatory polyarthropathy T80.82XA Complication of immune effector cellular therapy, initial encounter T80.82XD Complication of immune effector cellular therapy, subsequent encounter T80.89XA Other complications following infusion, transfusion and therapeutic injection, initial encounter T80.89XD Other complications following infusion, transfusion and therapeutic injection, subsequent encounter The following ICD CM codes have been **deleted** from this policy, due to specificity/laterality: M05.019, M05.029, M05.039, M05.049, M05.059, M05.069, M05.079, M05.119, M05.129, M05.139, M05.149, M05.159, M05.169, M05.179, M05.219, M05.229, M05.239, M05.249, M05.259, M05.269, M05.279, M05.319, M05.329, M05.339, M05.349, M05.359, M05.369, M05.379, M05.419, M05.429, M05.439, M05.449, M05.459, M05.469, M05.479, M05.519, M05.529, M05.539, M05.549, M05.559, M05.569, M05.579, M05.619, M05.629, M05.639, M05.649, M05.659, M05.669, M05.679, M05.719, M05.729, M05.739, M05.749, M05.759, M05.769, M05.779, M05.819, M05.829, M05.839, M05.849, M05.859, M05.869, M05.879, M06.019, M06.029, M06.039, M06.049, M06.059, M06.069, M06.079, M06.819, M06.829, M06.839, M06.849, M06.859, M06.869, M06.879, M08.219, M08.229, M08.239, M08.249, M08.259, M08.26,9 M08.279.

Revisions From MA08.045h:

07/01/2021	This version of the policy will become effective 07/01/2021. This policy has been updated to communicate the coverage criteria of tocilizumab (Actemra) for intravenous infusion and/or subcutaneous injections for giant cell arteritis and systemic sclerosis-associated interstitial lung disease. The coverage criteria for the following indications were revised:

	• Cytokine release syndrome (CRS) caused by chimeric antigen receptor (CAR) T cell therapy • Inflammatory arthritis, severe, immunotherapy-related, caused by Immune Checkpoint Inhibitors The following HCPCS codes have been **added**: M31.5 Giant cell arteritis with polymyalgia rheumatica M31.6 Other giant cell arteritis M34.81 Systemic sclerosis with lung involvement The following HCPCS codes have been **deleted**: M06.1 Adult-onset Still's disease M08.40 - M08.48 Pauciarticular juvenile rheumatoid arthritis

Revisions From MA08.045g:

10/01/2020	This policy has been identified for the ICD-10 CM code update, effective 10/01/2020. The following ICD-10 CM codes have been **added** to this policy: D89.831 Cytokine release syndrome, grade 1 D89.832 Cytokine release syndrome, grade 2 D89.833 Cytokine release syndrome, grade 3 D89.834 Cytokine release syndrome, grade 4 M05.7A Rheumatoid arthritis with rheumatoid factor of other specified site without organ or systems involvement M05.8A Other rheumatoid arthritis with rheumatoid factor of other specified site M06.0A Rheumatoid arthritis without rheumatoid factor, other specified site M06.8A Other specified rheumatoid arthritis, other specified site M08.2A Juvenile rheumatoid arthritis with systemic onset, other specified site

Revisions From MA08.045f:

06/08/2020	This version of the policy will become effective 06/08/2020. This policy was updated with the following changes: The addition of two indications, according to National Comprehensive Cancer Network (NCCN): • Cytokine release syndrome (CRS), caused by blinatumomab (Blincyto®) therapy in individuals with acute lymphoblastic leukemia • Graft-versus-host disease (GVHD), acute, after hematopoietic cell transplantation. ICD-10 Diagnosis code: D89.810 Acute graft-versus-host disease • The addition of coverage criteria for Polyarticular juvenile idiopathic arthritis (PJIA) regarding prior use or consideration of non-biologic disease-modifying anti-rheumatic drugs (DMARDs) (e.g., methotrexate), according to US Food and Drug Administration (FDA) and Ringold et al 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis. The addition of coverage criteria for previous consideration/use of DMARDs (e.g., leflunomide, methotrexate) for systemic juvenile idiopathic arthritis (Still's disease), according to Ringold et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Per Novitas Solutions, Inc. Article (A53127) For Self-Administered Drug Exclusion List, a Billing Requirement was added to this policy regarding the Coding Modifier: JA Intravenous administration.

Revisions From MA08.045e:

04/22/2019	This policy has undergone a routine review and the medical necessity criteria have been revised to reflect the United States Food and Drug Administration (FDA) labeling and National Comprehensive Cancer Network (NCCN). The coverage criteria for Castleman's Disease and Neurotoxicity caused by chimeric antigen receptor (CAR) T cell therapy have been added to this policy. The coverage criteria have been revised for Cytokine release syndrome caused by chimeric antigen receptor (CAR) T cell therapy.

Revisions From MA08.045d:

12/19/2018	This policy has been reissued in accordance with the Company's annual review process.
11/15/2017	This policy has been updated to communicate the Company's coverage criteria for tocilizumab (Actemra®) for the treatment of cytokine release syndrome (CRS).

Revisions From MA08.045c:

06/21/2017	This policy has been reissued in accordance with the Company's annual review process.
12/28/2016	This policy was updated to include criterion that active or latent tuberculosis (TB) has been ruled out prior to administration of this drug. Also, the Risk Evaluation and Mitigation Strategy (REMS) program has been eliminated by the FDA. Extensive coding additions and deletions have been made.

Revisions From MA08.045b:

10/01/2015	The following ICD-10 narrative has been **revised** in this policy: M08.88: **FROM:** Other juvenile arthritis, vertebrae **TO:** Other juvenile arthritis, other specified site The following ICD-9 codes have been **removed** from this policy, since ICD-10 codes are effective 10/01/15: 714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33, 720.0

Revisions From MA08.045a:

07/01/2015	This policy has been reviewed and reissued to communicate the Company’s continuing position on tocilizumab (Actemra®) for intravenous infusion.

Revisions From MA08.045:

01/01/2015	This is a new policy.

Version Effective Date:
03/20/2026
Version Issued Date:
03/20/2026
Version Reissued Date:
N/A