Reference number(s)
2423-A

Standard Medicare Part B Management Actemra and Biosimilars

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Actemra	tocilizumab
Avtozma	tocilizumab-anoh
Tofidence	tocilizumab-bavi
Tyenne	tocilizumab-aazg
tocilizumab-aazg (unbranded Tyenne)	tocilizumab-aazg
tocilizumab-anoh (unbranded Avtozma)	tocilizumab-anoh

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met, and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1-6]

- Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs
- Adult patients with giant cell arteritis
- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis
- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis
- Adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) for slowing the rate of decline in pulmonary function

- Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS)
- Hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)

Compendial Uses[7,8]

- Rheumatoid arthritis with no previous treatment failure
- Unicentric Castleman disease
- Multicentric Castleman disease
- Immune checkpoint inhibitor-related toxicity
- Acute graft versus host disease
- Cytokine release syndrome (other than severe or life-threatening CAR T-cell induced CRS)
- Thyroid eye disease
- Polymyalgia rheumatica
- Noninfectious uveitis
- Chronic active antibody-mediated rejection (CAAMR) in renal transplant patients

Note: The criteria outlined in this policy is only applicable to coverage in the outpatient setting. Hospitalized members receiving treatment of COVID-19 will be managed according to the member's inpatient benefit.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Coverage Criteria

Rheumatoid arthritis[1-7]

Authorization of 12 months may be granted for treatment of rheumatoid arthritis.

Juvenile idiopathic arthritis[1-6]

Authorization of 12 months may be granted for treatment of polyarticular or systemic juvenile idiopathic arthritis.

Giant cell arteritis[1-6]

Authorization of 12 months may be granted for treatment of giant cell arteritis.

Systemic sclerosis associated interstitial lung disease (SSc-ILD)[1-4,6]

Authorization of 12 months may be granted for treatment of sclerosis-associated interstitial lung disease.

Unicentric Castleman disease[8]

Authorization of 12 months may be granted for treatment of unicentric Castleman disease.

Multicentric Castleman disease[8]

Authorization of 12 months may be granted for treatment of multicentric Castleman disease.

Cytokine release syndrome[1,8]

Authorization of 1 month may be granted for prophylaxis or treatment of cytokine release syndrome (CRS).

Immunotherapy-related inflammatory arthritis[8]

Authorization of 12 months may be granted for treatment of moderate or severe immune checkpoint inhibitor-related inflammatory arthritis.

Immune checkpoint inhibitor-related toxicity[8]

Authorization of 6 months may be granted for treatment of immune checkpoint inhibitor-related toxicity.

Acute graft versus host disease[8]

Authorization of 12 months may be granted for treatment of acute graft versus host disease.

Thyroid Eye Disease[7]

Authorization of 12 months may be granted for treatment of active Graves' orbitopathy.

Polymyalgia rheumatica (PMR)[8]

Authorization of 12 months may be granted for treatment of polymyalgia rheumatica (PMR).

Noninfectious uveitis[7,12]

Authorization of 12 months may be granted for treatment of noninfectious uveitis.

Chronic active antibody-mediated rejection (CAAMR) in renal transplant patients[7,13]

Authorization of 12 months may be granted for treatment of chronic active antibody-mediated rejection in renal transplant patients.

Continuation of Therapy

Cytokine release syndrome, acute graft versus host disease, and immune checkpoint inhibitor-related toxicity (excluding inflammatory arthritis)

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

All other indications

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with a tocilizumab product.

Authorization for 12 months may be granted when all of the following criteria are met:

- The member is currently receiving therapy with a tocilizumab product.
- The requested medication is being used to treat an indication listed in the coverage criteria.
- The member is receiving benefit from therapy.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Actemra and its biosimilars.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Hematopoietic cell transplantation
- NCCN Guideline: Management of immunotherapy-related toxicities
- NCCN Guideline: B-cell lymphomas
- The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy
- American Academy of Ophthalmology Guideline: Noninfectious uveitis

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Actemra and its biosimilars are covered in addition to the following:

- Rheumatoid arthritis with no previous treatment failure
- Unicentric Castleman disease
- Multicentric Castleman disease

- Immune checkpoint inhibitor-related toxicity
- Acute graft versus host disease
- Cytokine release syndrome (other than severe or life-threatening CAR T-cell induced CRS)
- Polymyalgia rheumatica
- Noninfectious uveitis
- Chronic active antibody-mediated rejection (CAAMR) in renal transplant patients

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using tocilizumab to treat rheumatoid arthritis with no previous treatment failure can be found in the FUNCTION trial (Burmester et al). In the randomized FUNCTION trial in methotrexate-naive patients with early rheumatoid arthritis (N=1162), a significantly greater proportion of patients receiving tocilizumab 8 mg/kg with methotrexate compared with methotrexate alone achieved remission evaluated with a Disease Activity Score using 28 joints and erythrocyte sedimentation rate (DAS28-ESR) of less than 2.6 at week 24 (45% vs 15%). Tocilizumab 8 mg/kg plus methotrexate was also associated with a significant sustained DAS28-ESR response rate at week 52 compared with methotrexate alone (49% vs 20%), as well as an American College of Rheumatology (ACR) criteria improvement of 20% (ACR20), 50% (ACR50), and 70% (ACR70), and significantly greater inhibition of joint damage. Tocilizumab 8 mg/kg alone was significantly better than methotrexate alone for DAS28-ESR remission at weeks 24 and 52, but there was no significant difference between the 2 treatments for any of the ACR responses. After 2 years in the FUNCTION trial, DAS28-ESR remission was reported in 47.6% of patients in the tocilizumab 8 mg/kg plus methotrexate group and 43.5% in the tocilizumab 8 mg/kg monotherapy group compared with 16% in the methotrexate monotherapy group. More patients in the tocilizumab 8 mg/kg plus methotrexate group and the tocilizumab 8 mg/kg monotherapy group compared with the methotrexate monotherapy group achieved ACR20 (65.2% and 61.6% vs 25.4%), ACR50 (57.6% and 53.1% vs 22%), and ACR70 (46.6% and 39.4% vs 17.4%); the mean change from baseline to 2 years in vander Heijde-modified total Sharp score (vdH mTSS) was 0.19 and 0.62 versus 1.88.

Support for using tocilizumab to treat unicentric and multicentric Castleman disease can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using tocilizumab to treat immunotherapy-related inflammatory arthritis can be found in the National Comprehensive Cancer Network's guideline for management of immunotherapy-related toxicities. The NCCN Guideline indicates tocilizumab should be considered as additional disease modifying antirheumatic therapy for the management of moderate or severe immunotherapy-related inflammatory arthritis if no improvement was noted after holding immunotherapy and treating with oral corticosteroids or if the provider was unable to taper corticosteroids.

Support for using tocilizumab to treat acute graft versus host disease can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline

for hematopoietic cell transplantation supports the use of tocilizumab for acute graft-versus-host disease as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options.

Support for using tocilizumab to treat cytokine release syndrome can be found in the National Comprehensive Cancer Network's guideline for the management of immunotherapy-related toxicities. The NCCN Guideline supports the adding of tocilizumab for the management of the following immunotherapy-related conditions:

- Prolonged (more than three days) G1 cytokine release syndrome (CRS) in patients with significant symptoms, comorbidities, and/or in elderly patients
- CRS symptoms that persist for more than 24 hours in patients who have been treated with axicabtagene ciloleucel or brexucabtagene autoleucel
- G1 CRS that develops less than 72 hours after infusion in patients who have been treated with lisocabtagene maraleucel
- G2-G4 CRS
- G1-G4 neurotoxicity as additional single-dose therapy if concurrent CRS

Support for using tocilizumab for prophylaxis of cytokine release syndrome can be found in the National Comprehensive Cancer Network's guideline for the management of immunotherapy-related toxicities. The NCCN Guideline supports the use of tocilizumab as prophylactic use to reduce the risk of Cytokine Release Syndrome when administering teclistamab-cqyv.

Support for using tocilizumab to treat cytokine release syndrome can be found in the National Comprehensive Cancer Network's guideline for acute lymphoblastic leukemia. The NCCN Guideline for acute lymphoblastic leukemia indicates tocilizumab can be considered as supportive care for patients with severe cytokine release syndrome related to blinatumomab therapy.

Support for using tocilizumab to treat thyroid eye disease can be found in the 2021 European Group on Grave's orbitopathy (EUGOGO) clinical practice guidelines. Tocilizumab can be used as second-line treatment for patients with moderate to severe and active Graves' orbitopathy (GO) unresponsive to first-line therapy. In patients with glucocorticoid-resistant disease, tocilizumab should be considered as treatment may rapidly resolve inflammatory signs. Methylprednisolone intravenous (IV) in combination with oral mycophenolate sodium (or mofetil) is first-line treatment.

Support for using tocilizumab to treat polymyalgia rheumatica can be found in the National Comprehensive Cancer Network's guideline for guideline for management of immunotherapy-related toxicities. The NCCN Guideline indicates tocilizumab should be considered as additional disease modifying antirheumatic therapy for the management of polymyalgia rheumatica if unable to taper prednisone or no improvement in symptoms.

Support for using tocilizumab to treat noninfectious uveitis can be found in the American Academy of Ophthalmology guidelines. Tocilizumab can be considered for noninfectious uveitis including different uveitis entities and anatomic locations (Grade C recommendation; evidence level 4). Therapies should be individualized with consideration of cause of uveitis, patient history, comorbidities, and patient preference.

Support for using tocilizumab to treat chronic active antibody-mediated rejection (CAAMR) in renal transplant patients can be found in the trial conducted by Khairallah P, et al. Kidney transplant recipients from Columbia University Irving Medical Center who had been prescribed tocilizumab for the treatment of CAAMR and followed for at least 3 months between August 2013 through December 2019. Tocilizumab was initiated for the treatment of CAAMR at the discretion of the treating provider, at a dose of 8 mg/kg every 4 weeks until the provider discontinued the treatment. Patients received tocilizumab for the treatment of CAAMR at a median of 3.2 [IQR 1.7, 6.4] years after transplantation. Patients were on tocilizumab for a median of 11.2 months (IQR 5.8, 20.8) prior to the end of the study period. Half the patients (19/38) underwent a kidney biopsy following tocilizumab initiation. There was a significant improvement in interstitial inflammation (score 1[0,1 to 0,1], p = 0.03). Mean eGFR 3 months prior to tocilizumab initiation was 41 ± 17 ml/min/1.73 m2. eGFR had decreased to 34±16 ml/min/1.73 m^2 at the time of tocilizumab initiation. Following treatment with tocilizumab, eGFR remained stable at 34 ± 15 ml/min/1.73 m2 at 3 months and improved to 36 ± 15 ml/min/1.73 m^2 by 6 months following treatment. The rate of decline in eGFR prior to tocilizumab initiation was -2.6 ml/min/1.73 m^2 (SE = 0.7, p = 0.0006) per month. The difference between slopes before and after initiation of treatment was 2.6 ml/min/1.73 m^2 (SE = 0.8, p = 0.002) per month for up to 6 months following tocilizumab initiation. In conclusion, we found that treatment of patients with chronic AMR refractory to other therapies with tocilizumab was associated with a decrease in the rate of eGFR decline and a decrease in interstitial inflammation and stabilization in other histologic features of CAAMR.

Support for using tocilizumab to treat immunotherapy-related toxicity can be found in the National Comprehensive Cancer Network's guideline for management of immunotherapy-related toxicities. The NCCN Guideline indicates that tocilizumab should be considered as additional corticosteroid-sparing immunosuppression for management of the following immunotherapy-related toxicities: G2 elevated alanine transaminase/aspartate transaminase (ALT/AST) if liver enzymes suggest worsening or no improvement after 3-7 days of prednisone, G3 or G4 elevated ALT/AST if no improvement after 1-2 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 1-2 days of prednisone/methylprednisolone and hemophagocytic lymphohistiocytosis (HLH)-like syndrome if no response to corticosteroids after 5 days. Tocilizumab should also be considered as additional therapy for management of moderate (G2) pneumonitis if no improvement after 48-72 hours of corticosteroids or severe (G3-4) pneumonitis if no improvement after 48 hours.

References

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