Reference number(s)
2423-A

STANDARD MEDICARE PART B MANAGEMENT

ACTEMRA (tocilizumab)

POLICY

I. 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.

A. FDA-Approved Indications
1. Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs
2. Adult patients with giant cell arteritis
3. Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis
4. Patients 2 years of age and older with active systemic juvenile idiopathic arthritis
5. Adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) for slowing the rate of decline in pulmonary function
6. 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)
7. 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)

B. Compendial Uses
1. Rheumatoid arthritis with no previous treatment failure
2. Unicentric Castleman disease
3. Multicentric Castleman disease
4. Immunotherapy-related inflammatory arthritis
5. Acute graft versus host disease
6. Cytokine release syndrome (other than severe or life-threatening CAR T-cell induced CRS)
7. Thyroid eye disease

Note: The criteria outlined in this policy is only applicable to coverage in the outpatient setting. Hospitalized members receiving Actemra for the 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 enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for systemic sclerosis-associated interstitial lung disease: For initial requests: Results of a chest high-resolution computed tomography (HRCT) study.

III. CRITERIA FOR INITIAL APPROVAL

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

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

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

D. **Systemic sclerosis-associated interstitial lung disease (SSc-ILD)**
Authorization of 12 months may be granted for treatment of sclerosis-associated interstitial lung disease when the diagnosis was confirmed by a high-resolution computed tomography (HRCT) study of the chest.

E. **Unicentric Castleman disease**
Authorization of 12 months may be granted for treatment of unicentric Castleman disease when all of the following criteria are met:
1. The member is HIV-negative.
2. The member is human herpesvirus-8-negative.
3. The requested medication will be used as a single agent.
4. The disease has progressed following treatment of relapsed/refractory disease.

F. Multicentric Castleman disease
Authorization of 12 months may be granted for treatment of multicentric Castleman disease when both of the following criteria are met:
1. The requested medication will be used as a single agent.
2. The disease has progressed following treatment of relapsed/refractory or progressive disease.

G. Cytokine release syndrome
1. Authorization of 1 month may be granted for treatment of chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome (CRS).
2. Authorization of 1 month may be granted for treatment of cytokine release syndrome in members with refractory CRS related to blinatumomab therapy.

H. **Immunotherapy-related inflammatory arthritis**
Authorization of 12 months may be granted for treatment of refractory or severe immunotherapy-related inflammatory arthritis that has not responded to systemic corticosteroids.

I. Acute graft versus host disease
Authorization of 12 months may be granted for treatment of acute graft versus host disease when either of the following criteria is met:
1. Member has experienced an inadequate response to systemic corticosteroids.
2. Member has an intolerance or contraindication to corticosteroids.

J. Thyroid Eye Disease

Authorization of 12 months may be granted for treatment of active Graves' orbitopathy that has not responded to corticosteroids.

IV. CONTINUATION OF THERAPY

A. Cytokine release syndrome, immunotherapy-related inflammatory arthritis, and acute graft versus host disease
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

B. Rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, systemic sclerosis-associated interstitial lung disease, and thyroid eye disease
All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Actemra.
2. The member is receiving benefit from therapy.

C. All other diagnoses
All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization of 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with Actemra.
2. Actemra is being used to treat an indication enumerated in Section III.
3. The member is receiving benefit from therapy. Benefit is defined as:
    i. No evidence of unacceptable toxicity while on the current regimen AND
    ii. No evidence of disease progression while on the current regimen.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Actemra.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Hematopoietic cell transplantation
4. NCCN Guideline: Management of immunotherapy-related toxicities
5. NCCN Guideline: B-cell lymphomas
6. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Actemra are covered in addition to the following:
1. Rheumatoid arthritis with no previous treatment failure

2. Unicentric Castleman disease
3. Multicentric Castleman disease
4. Immunotherapy-related inflammatory arthritis
5. Acute graft versus host disease
6. Cytokine release syndrome (other than severe or life-threatening CAR T-cell induced CRS)
7. Thyroid eye disease

VI. EXPLANATION OF RATIONALE

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

Support for using Actemra 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 Actemra 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 Actemra 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 Actemra 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 Actemra 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 Actemra 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 Actemra 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 infliximab for the management of the following immunotherapy-related conditions:

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

Support for using Actemra 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 Actemra can be considered as supportive care for patients with severe cytokine release syndrome related to blinatumomab therapy.

Support for using Actemra to treat thyroid eye disease can be found in the 2021 European Group on Grave's orbitopathy (EUGOGO) clinical practice guidelines. Actemra 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 IV in combination with oral mycophenolate sodium (or mofetil) is first-line treatment.

VII. REFERENCES

1. Actemra [package insert]. South San Francisco, CA: Genetech, Inc.; December 2022.
2. Micromedex Solutions [database online]. Ann Arbor, MI: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed January 12, 2023.
3. National Comprehensive Cancer Network. The NCCN Drugs & Biologics Compendium. https://www.nccn.org. Accessed January 12, 2023.
4. Burmester GR, Rigby WF, van Vollenhoven RF, et al: Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. Ann Rheum Dis 2016; 75(6):1081-1091.
5. Burmester GR, Rigby WF, van Vollenhoven RF, et al: Tocilizumab combination therapy or monotherapy or methotrexate monotherapy in methotrexate-naive patients with early rheumatoid arthritis: 2-year clinical and radiographic results from the randomised, placebo-controlled FUNCTION trial. Ann Rheum Dis 2017; 76(7):1279-1284.
6. Bartalena L, Kahaly GJ, Baldeschi L, et al: The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol 2021; 185(4):G43-G67.