Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 12/09/2021

Actemra® (tocilizumab)

HCPCS: J3262

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved age
   b. Diagnosis of rheumatoid arthritis (RA):
      i. Trial and failure of at least 3 months of one disease-modifying anti-rheumatic agent (DMARD) unless contraindicated or not tolerated. Examples include methotrexate, hydroxychloroquine, leflunomide, sulfasalazine
   c. Diagnosis of polyarticular juvenile idiopathic arthritis (pJIA)
      i. Trial and failure of at least 3 months of one disease-modifying anti-rheumatic agent (DMARD) unless contraindicated or not tolerated. Examples include methotrexate and leflunomide
   d. Diagnosis of Still's disease, including systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD)
      i. Trial and treatment failure with one of the following: methotrexate, leflunomide, glucocorticoids, or NSAIDs
   e. Diagnosis of cytokine release syndrome (CRS) (intravenous formulation only)
      i. Prescribed by or in consultation with an oncologist
      ii. Severe or life threatening CRS associated with chimeric antigen receptor (CAR) T cell therapy
   g. Diagnosis of giant cell arteritis (GCA) (subcutaneous formulation only)
   h. Diagnosis of systemic sclerosis-associated interstitial lung disease (SSc-ILD) (subcutaneous formulation only)
      i. Inadequate response to (as evidenced by disease progression - e.g. worsening of pulmonary function) or not a candidate for either mycophenolate mofetil OR cyclophosphamide
   i. Not to be used in combination with other biologics or other targeted DMARDs
   j. Trial and failure of the preferred products as specified in the BCBSM/BCN utilization management medical drug list and/or the BCBSM/BCN prior authorization and step therapy documents

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Initial Authorization Period:

i. RA, pJIA, sJIA, GCA, AOSD: One year at a time
ii. CRS: 1 month

c. Renewal Criteria:
i. RA, pJIA, sJIA, GCA, AOSD: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit
ii. CRS: Not applicable as no further authorization will be provided

***Note: Coverage may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Actemra (tocilizumab) is an interleukin-6 inhibitor (IL-6i) indicated for rheumatoid arthritis, polyarticular and systemic juvenile idiopathic arthritis, giant cell arteritis, and cytokine release syndrome. Actemra is available for both subcutaneous and intravenous administration; however, per the labeling, Actemra may only be administered intravenously for the treatment of cytokine release syndrome and subcutaneously for giant cell arteritis.

- Actemra has not been studied in combination with other biologic disease modifying agents due to an increased risk of infection and increased immunosuppression. As such, use of Actemra in combination with other biologic agents is not recommended.

- Rheumatoid Arthritis

  - The 2021 American College of Rheumatology (ACR) Guidelines for the Treatment of Rheumatoid Arthritis (RA) established recommendations for the care of adult RA patients. The guidelines state that treatment decisions should follow a shared decision-making process and should be reevaluated within a minimum of 3 months based on the efficacy and tolerability of the DMARD(s) chosen.

  - For the initial treatment of symptomatic RA, the guidelines strongly recommend the use of conventional synthetic disease-modifying antirheumatic drug (csDMARD) monotherapy in those who are DMARD-naive. csDMARD monotherapy is a less costly first line treatment option with an extensive safety record accompanied by well-documented clinical efficacy and a large body of clinical experience and familiarity among prescribers. csDMARDs in the guidelines refer to methotrexate (MTX), hydroxychloroquine, leflunomide (LEF), and sulfasalazine. Azathioprine, cyclosporine, minocycline, and gold were not included due to their infrequent use in RA and lack of new data since the prior guidelines were published. Oral MTX is recommended as the preferred initial DMARD for patients with moderate-to-high disease activity, and hydroxychloroquine is recommended as the preferred initial DMARD for patients with low disease activity.

  - If disease activity remains moderate or high despite optimal dosing of methotrexate monotherapy, the use of dual therapy with methotrexate plus biologic DMARD (bDMARD; etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, abatacept, tocilizumab, sarilumab, rituximab) or targeted synthetic DMARD (tsDMARD; tofacitinib, baricitinib, upadacitinib) therapy is conditionally recommended over the use of triple therapy (i.e., addition of sulfasalazine and hydroxychloroquine). The guidelines do not inform preference of bDMARD over tsDMARD therapy (or vice-versa) for use in combination with methotrexate. No one agent has been shown to be superior to another. The guidelines do acknowledge the emergence of safety signals for the JAK inhibitor class (tsDMARD), and state that further modification of this recommendation may be necessary as additional data are published.

- A treat-to-target approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs. Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modification of treatment to minimize disease activity with the goal of reaching a pre-defined target (low disease activity or remission).

- Actemra (tocilizumab) is indicated for treating adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. Actemra may be used as monotherapy or concomitantly with other non-biologic DMARDs as an IV infusion or as a subcutaneous injection for the treatment of RA.

- Polyarticular Juvenile Idiopathic Arthritis

  - Juvenile idiopathic arthritis (JIA) defines a collection of inflammatory arthritides of unknown etiology. JIA onset is prior to 16 years of age with a minimum duration of 6 weeks and other potential causes of synovitis are excluded. JIA can be subdivided into polyarticular JIA (pJIA) and systemic JIA.

  - pJIA is defined by the presence of more than 4 affected joints in the first 6 months of illness and comprises 20-30% of children with JIA. Therapy is directed toward treating the underlying inflammation and preventing JIA-associated complications and adverse effects of its treatment.

  - The 2019 American College of Rheumatology/Arthritis Foundation (ACR/AF) guideline for the treatment of JIA strongly recommends initial therapy for pJIA with a disease-modifying anti-rheumatic agent (DMARD) such as MTX or LEF. MTX is conditionally recommended over LEF as it has a greater volume of data supporting its effectiveness compared to LEF and can be administered subcutaneously (recommended) or orally. The guidelines consider an adequate trial of a DMARD to be 3 months.

  - If moderate or high disease activity persists despite adequate DMARD use, the ACR/AF guidelines recommend biologic agents either in combination with a DMARD or as monotherapy in certain situations. Biologic agents FDA approved for pJIA in patients 2 years of age and older include Humira® (adalimumab), Enbrel® (etanercept), Actemra® (tocilizumab), Orencia® (abatacept), Simponi Aria® (golimumab), Xeljanz (tofacitinib), and Xeljanz (tofacitinib) oral solution.

    - Of note, biologic therapy may be an appropriate initial therapy in pJIA patients with risk factors and involvement of high-risk joints, high disease activity, and/or for those judged to be at high risk of disabling joint damage.

  - There is the most experience with tumor necrosis factor inhibitors (TNFi; Humira, Enbrel, Simponi Aria) as initial biologic therapy; however, the preferred class of initial biologic is not specified in the guideline recommendations due to a lack of comparative data and the consideration that non-TNFi biologics may be preferred in certain patient-specific scenarios. If a TNFi is started as the initial biologic, switching to a non-TNFi (Actemra or Orencia) is recommended over switching to a second TNFi. An exception to this is for those who had a good initial response to the first TNFi.

- Systemic Juvenile Idiopathic Arthritis and Adult Onset Still's Disease

  - Systemic juvenile idiopathic arthritis (sJIA) is a subset of JIA. It accounts for 4-15% of JIA and is defined as arthritis in > 1 joint for at least 6 weeks duration in a child age < 16 years with or preceded by a fever of at least 2 weeks duration that is documented to be daily for at least 3 days and accompanied by one or more of the following: evanescent erythematous rash, generalized lymphadenopathy, hepatomegaly or splenomegaly, and serositis. This condition can occur in adulthood with similar features and is referred to as adult-onset Still's disease (AOSD).

- The inflammatory process underlying sJIA appears to be distinct from other categories of JIA, with interleukin (IL)-1 and IL-6 playing a central role. The goal of therapy focuses on prompt control of active inflammation and symptoms and prevention of disease- and or treatment-related morbidities like growth disturbances, joint damage and functional limitations. Treatment varies depending on the degree of synovitis and the presence of active systemic features (fever, rash, lymphadenopathy, hepatomegaly or splenomegaly, serositis).

- Per the 2013 update of the 2011 American College of Rheumatology (ACR) recommendations for the treatment of JIA, sJIA treatment is typically initiated with a short-term course of systemic glucocorticoid monotherapy or NSAID monotherapy. DMARDs, preferably MTX or LEF per the recommendation, may be beneficial to those without active systemic features but with active joint involvement. Kineret (anakinra) may be of benefit as initial therapy for those with moderate to severe active systemic features irrespective of the number of joints involved.

- For those with continued disease activity despite initial treatment, potential treatment options for sJIA may include (in no particular order): Kineret (anakinra), Actemra (tocilizumab), Ilaris (canakinumab), Orencia (abatacept), tumor necrosis factor inhibitors (TNFi; adalimumab, etanercept and infliximab), glucocorticoids, and DMARDs. The recommended choice and order of therapy is dependent on the continued presence (or lack) of active systemic features, the physician global assessment score, active joint count, and previously trialed treatments. The detailed recommendations for subsequent therapies can be found in the 2013 update of the ACR Recommendations for the treatment of JIA (see figures 1 and 2 within the recommendation).

- Actemra and Ilaris are FDA approved for the treatment of sJIA in patients 2 years of age and older, while Ilaris is the only drug approved for the treatment of AOSD. There are no guidelines for treating AOSD; however, literature recommends a similar treatment approach to sJIA. The use of Actemra in AOSD is supported by a small randomized trial and several case reports and case series that have shown efficacy in patients with AOSD with both the intravenous and subcutaneous formulations. Actemra's efficacy in patients with sJIA also serves as additional evidence to support its use in AOSD.

- Cytokine Release Syndrome

    - Cytokine release syndrome (CRS) is an acute systemic inflammatory syndrome that is characterized by fever with or without multiple organ dysfunction occurring in response to chimeric antigen receptor (CAR)-T cell therapy, therapeutic antibodies and haploidentical allogeneic hematopoietic cell transplantation (HCT). The incidence of CRS varies based on the causative treatment and underlying malignancy. It most often occurs following targeted cellular immunotherapy for B cell acute lymphoblastic leukemia/lymphoma (ALL/LBL), non-Hodgkin's lymphoma (NHL), Chronic lymphocytic leukemia (CLL), and multiple myeloma (MM), and is less common following immunotherapy with bispecific antibodies and in the treatment of solid tumors.

    - The systemic inflammatory reaction that occurs with CRS involves increased levels of inflammatory cytokines and activation of T lymphocytes, macrophages, and endothelial cells; IL-6 appears to have a central role in CRS pathophysiology. The resulting manifestation of the CRS inflammatory response includes fever, which may be accompanied by fatigue, headache, rash, diarrhea, arthralgia, and myalgia. Mild CRS may progress to a more severe form, which may include hypotension, hypoxia, and uncontrolled systemic inflammatory response with circulatory collapse, vascular leakage, peripheral and/or pulmonary edema, renal failure, cardiac dysfunction, and multiorgan system failure. Neurologic manifestations may also develop in severe CRS, including aphasia, altered level of consciousness, impaired cognitive skills, motor weakness, seizures, and cerebral edema.

- Diagnosis is made by clinical presentation and the temporal relationship to the triggering immune therapy. CRS typically begins within 1-14 days after CAR-T cell therapy with resolution within a few days to 2-3 weeks post CAR-T infusion. CRS diagnosis requires a fever (≥38°C) at onset, with or without hypotension, hypoxia, and/or other end-organ dysfunction in the hours to days after treatment with immune therapy like CAR-T. Due to variability of laboratory findings in CRS, laboratory studies are not required for diagnosis though they may be beneficial for differential diagnosis.

- The severity of CRS is graded differently based on the causative immune therapy; literature includes diverse grading scales as there are various grading scales proposed for CRS. CAR-T therapy grading proposed by the American Society for Transplantation and Cellular Therapy (ASTCT) is based on the degree and type of interventions required for patient management.

    - Grade 1: Temperature ≥38°C and no hypotension and no hypoxia (defined by a requirement for supplemental oxygen to correct an oxygen deficit vs. a specific level of oxygen saturation). Patients may have malaise, myalgias, or arthralgias, but the severity of these constitutional symptoms does not affect the grade of CRS

    - Grade 2: Temperature ≥38°C plus hypotension that does not require vasopressors and/or hypoxia that requires low-flow nasal cannula (≤6 L/minute or blow-by oxygenation). See the notes below regarding aspects of the management of hypotension and hypoxia that may affect grading.

    - Grade 3: Temperature ≥38°C plus hypotension that requires one vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow nasal cannula (≥6 L/minute), facemask, non-rebreather mask, or Venturi mask that is not attributable to any other cause.

    - Grade 4: Temperature ≥38°C plus hypotension that requires multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (e.g., continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation and mechanical ventilation). Intubation for reasons other than hypoxia alone does not meet criteria for Grade 4 CRS.

- The National Comprehensive Cancer Network (NCCN) guidelines for management of CAR T-cell related toxicities recommends treatment with Actemra (tocilizumab) for patients with Grade 2, 3 or 4 CRS either as monotherapy or in conjunction with IV corticosteroids. NCCN recommends considering Actemra treatment for prolonged (> 3 days) Grade 1 CRS in patients with significant symptoms and/or comorbidities.

- Actemra is FDA approved for treating severe or life-threatening CRS due to CAR-T cell therapy in patients 2 years of age and older. If there is no improvement after the first dose, the dose may be repeated in 8 hours for a maximum of 3 doses in 24 hours and 4 doses total. The need for subsequent dosing must be assessed after each dose.

- CAR-T therapy is currently only administered as one dose per lifetime; it has not been studied in patients who received prior treatment with any CAR-T therapy or other genetically-modified T-cell therapy. As such, the use of Actemra for CRS related to CAR-T is limited to a one-time treatment.

- The FDA REMS program regulates CAR-T cell products in the United States. REMS guidelines should be consulted for specific details of CRS management as guidelines for treating CRS associated with CAR-T cell therapy varies according to the specific product.

- Giant Cell Arteritis

    - Giant cell arteritis (GCA, also known as Horton disease, cranial arteritis, and temporal arteritis) is the most common systemic vasculitis in North America, affecting adults over 50 years of age with a peak incidence between ages 70 and 79. Symptoms and signs of GCA typically results from vascular inflammation of the small extracranial branches of the carotid arteries; however, the disease is systemic and may involve the aorta and large arteries, leading to aneurysms of the thoracic and abdominal aorta ischemic symptoms in the extremities, respectively.

    - Manifestations of GCA vary between patients and may be transient or fluctuating. Systemic symptoms are frequent and may include fever, fatigue and weight loss. Diagnosis of GCA should be considered in patients over 50 years old complaining of or found to have one or more of the following symptoms, the significance of which is heightened if a patient has a current or prior diagnosis of polymyalgia rheumatica.

        - New headache
        - Abrupt onset of visual disturbances, in particular transient monocular visual loss
        - Jaw claudication
        - Unexplained fever or anemia
        - Elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP)

    - The most significant complication of GCA is vision loss, which most frequently arises from cranial arteritis, a major phenotype of GCA. Approximately 25-50% of untreated patients who present with vision loss in one eye will develop bilateral blindness, and once visual impairment due to GCA is established, it is rarely reversible. Another concern is subclinical involvement of the aorta and large arteries (large vessel GCA), which occurs frequently and may result in aortic aneurysm and dissection.

    - Temporal artery biopsy is the gold standard for GCA diagnosis; scheduling of the biopsy, however, should not interfere with treatment initiation when there is a high likelihood of GCA as a delay can put patients at risk of significant complications, particularly vision loss. In patients with a negative biopsy but high GCA suspicion, large vessel involvement may be considered. The diagnostic procedure of choice for suspected large vessel GCA is advanced imaging of the torso (i.e. CT, MRI, PET scan).

    - High dose glucocorticoid treatment (typically prednisone for 2-4 weeks) followed by a slow glucocorticoid taper is typically the mainstay of therapy for GCA and should be instituted promptly if a diagnosis of GCA is strongly suspected, especially in the event of recent or threatened vision loss. Prompt glucocorticoid treatment reduces the risk of sight loss to less than 1% in patients with intact vision at time of treatment initiation. Glucocorticoid effectiveness in GCA is well established by decades of clinical experience, producing prompt improvement of signs and symptoms generally within 24 to 48 hours of treatment initiation. Relapses may occur and are most common at prednisone doses less than 20 mg/day; these are treated with increases in the glucocorticoid dose appropriate to the relapse. Given the variable duration of GCA, the length of treatment duration may extend from one to multiple years though glucocorticoid treatment can eventually be discontinued in the majority of patients.

    - Potential toxicities of glucocorticoids are of concern in patients of advanced age, with comorbid conditions (e.g. preexisting diabetes mellitus, osteoporosis, significant obesity), and utilizing glucocorticoid therapy for extended periods of time. The prevalence of significant glucocorticoid-related adverse events correlates with increased patient age and cumulative glucocorticoid dose. Based on the patient population affected by GCA and the prolonged exposure to glucocorticoids, early implementation of glucocorticoid sparing agents like Actemra (tocilizumab) may be preferred to minimize toxicity risk.

    - Actemra is FDA approved for the treatment of GCA in adults based on safety and efficacy data from pivotal

trials that evaluated Actemra for both new-onset and relapsing GCA. For the treatment of GCA, Actemra should be administered subcutaneously and is recommended in combination with a tapering course of glucocorticoids; monotherapy with Actemra may be continued following glucocorticoid discontinuation.

- Systemic sclerosis-associated interstitial lung disease (SSc-ILD)

    - SSc-ILD is a rare autoimmune disease affecting about 75,000 people in the U.S. It is characterized by thickening, hardening, and scarring of the skin and caused by the accumulation of excess collagen in the skin and internal organs, such as the heart, lungs, kidneys, and intestinal tract, leading to organ damage. An estimated 80% of patients have ILD due to the buildup of scar tissue and inflammation in the lungs. ILD is a progressive disease that can significantly impact lung function.

    - Mycophenolate and cyclophosphamide are considered standard of care as initial therapy as supported by numerous clinical trials and the European League Against Rheumatism (EULAR) guidelines for SSc (updated in 2017). Mycophenolate is often preferred in practice as it has comparable benefit to cyclophosphamide but has a better toxicity profile. Ofev® and more recently Actemra subcutaneous injection received FDA approval for this indication and are options for patients who are not candidates for mycophenolate or cyclophosphamide.

    - The approval of Actemra was based on the results of a Phase III, placebo-controlled trial. The trial did not meet its primary goal of a change on a standard skin fibrosis measurement called the modified Rodnan Skin Score (mRSS). However, based on a post hoc subgroup analysis, a benefit was apparent in patients with confirmed SSc-ILD. Analyses found that these Actemra-treated patients, relative to those on placebo, had a smaller decline in mean forced vital capacity (FVC).

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<tr><td>2.8</td><td>Effective Date: 12/09/2021</td><td>Removed FDA approved indications criteria</td></tr>
<tr><td>2.7</td><td>Effective Date: 04/08/2021</td><td>Updated to include criteria for new indication of SSc-ILD</td></tr>
<tr><td>2.6</td><td>Effective Date: 02/04/2021</td><td>Addition of criteria for coverage of Still's disease, including AOSD</td></tr>
<tr><td>2.5</td><td>Effective Date: 12/03/2020</td><td>Criteria updated to align management between pharmacy and medical benefit for all listed indications
Updated all background information</td></tr>
<tr><td>2.4</td><td>Effective Date: 10/08/2020</td><td>Annual Review of Medical Policy</td></tr>
<tr><td>2.3</td><td>Effective Date: 11/07/2019</td><td>Annual Review of Medical Policy</td></tr>
<tr><td>2.2</td><td>Effective Date: 11/01/2018</td><td>Updated policy with new preferred product verbiage to apply to all indications</td></tr>
<tr><td>2.1</td><td>Effective Date: 08/09/2018</td><td>Updated policy with new preferred product verbiage</td></tr>
<tr><td>2.0</td><td>Effective Date: 02/08/2018</td><td>Criteria Update: GCA and CRS</td></tr>
<tr><td>1.9</td><td>Effective Date: 07/05/2017</td><td>UM medical management system update for MAPPO and BCNA
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<tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr>
<tr><td>BCBS</td><td>Yes</td></tr>
<tr><td>BCN</td><td>Yes</td></tr>
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<tr><td>1.8</td><td>Effective Date: 03/23/2017</td><td>New coverage criteria for biologics that treat rheumatoid conditions</td></tr>
<tr><td>1.7</td><td>Effective Date: 02/09/2017</td><td>Updated: PJIA & SJIA formatting within the coverage criteria section.</td></tr>
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<tr><td>1.2</td><td>Effective Date: 01/22/2013</td><td>UM medical management system update for BCBS
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- Custom/Clinical Formulary: May Add
- Part D: B vs D; if D then specialty tier based on pricing
- Part D formulary chapter: 6D Miscellaneous Rheumatologic Agents
Immunology and Hematology:
- Miscellaneous Immunologic and Hematologic Agents</td></tr>
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*