WellMed Doctors helping patients for more than 25 years	**Effective Date: 12/21/22**	**Revision Date(s):** 1/11/2018, 2/25/2019, 4/9/2020, 04/08/2021, 10/20/22
Department: PHARMACY	**MMC Review/ Approval Date(s):** 3/12/2019, 5/12/2020, 5/11/2021, 12/21/22	**Total Number of Pages:** 17

Policy Number: 028.004

Title: Coverage Determination Policy for Tocilizumab (Actemra)

Regions: ☒ **Texas** ☐ **Florida** ☐ **Indiana** ☐ **New Jersey** ☒ **New Mexico**

Impacted Areas:

- ☒ Network Management/Provider Services
- ☐ Member services
- ☐ Quality Management
- ☐ Credentialing
- ☐ IT
- ☐ Administration
- ☐ Compliance/delegation
- ☒ Utilization Management
- ☐ Case management
- ☐ Disease management
- ☒ Claims
- ☐ Human resources
- ☐ Finance
- ☒ Pharmacy
- ☐ ALL

Available LCD/NCD/LCA: None

Disclaimer:

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Title: Coverage Determination Policy for Tocilizumab (Actemra)

Coverage Policy Number: 028.004

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Initial/New Requests:

The following criteria are applicable to **ALL** indications:

- Tocilizumab should **NOT** be initiated in patients with an absolute neutrophil count below 2000/mm(3), platelet count below 100,000/mm(3), or ALT or AST above 1.5 times ULN.
- Patients should be tested for latent TB before use and during therapy, and treated prior to initiating therapy with tocilizumab.

Monitoring:

- Polyarticular Juvenile Idiopathic Arthritis:
  - Neutrophil and platelet counts; at the time of second infusion and every 4 to 8 weeks thereafter
  - ALT and AST levels; at the time of second infusion and every 4 to 8 weeks thereafter.
- Systemic juvenile idiopathic arthritis:
  - Absolute neutrophil and platelet counts at the time of second infusion and every 2 to 4 weeks thereafter
  - ALT and AST levels at the time of second infusion and every 2 to 4 weeks thereafter
- Rheumatoid arthritis:
  - Absolute neutrophil and platelet counts; every 4 to 8 weeks after therapy initiation and every 3 months thereafter
  - ALT, AST, alkaline phosphatase, and total bilirubin: Prior to therapy initiation, every 4 to 8 weeks after starting therapy for the first 6 months, and every 3 months thereafter

Tocilizumab is **proven and medically necessary** for the treatment of:

1. **Rheumatoid arthritis** when ALL of the following criteria are met:

   a. Diagnosis of moderately to severely active rheumatoid arthritis (RA)

   b. One of the following:

   - History of failure to a 3 month trial, contraindication, or intolerance to at least **one** non-biologic DMARD [e.g., methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, minocycline, etc.] OR
   - Patient has been previously treated with a biologic or targeted synthetic DMARD FDA-approved for the treatment of rheumatoid arthritis [e.g., Humira (adalimumab), Simponi (golimumab), Olumiant (baricitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib)]; OR
   - Patient is currently on Actemra

   c. Tocilizumab is initiated and titrated according to US FDA labeled dosing for rheumatoid arthritis:

   - 4 mg/kg every 4 weeks; may titrate up to 8 mg/kg
   - MAXIMUM dose of 800 mg per dose every 4 weeks

d. Patient is **not** receiving tocilizumab in combination with either of the following:

(1) Biologic DMARD [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]

(2) Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]

2. **Systemic juvenile idiopathic arthritis** when **ALL** of the following criteria are met:

a. Diagnosis of active systemic juvenile idiopathic arthritis (SJIA)

b. Tocilizumab is initiated and titrated according to US FDA labeled dosing for systemic juvenile idiopathic arthritis up to a maximum of (or equivalent dose and interval schedule):

(1) 12mg/kg every 2 weeks for patients weighing < 30kg

(2) 8mg/kg every 2 weeks for patients weighing ≥ 30kg

c. Patient is **not** receiving tocilizumab in combination with either of the following:

(1) Biologic DMARD [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]

(2) Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]

3. **Polyarticular juvenile idiopathic arthritis** whenALL of the following criteria are met:

a. Diagnosis of polyarticular juvenile idiopathic arthritis (PJIA)

b. Tocilizumab is initiated and titrated according to US FDA labeled dosing for polyarticular juvenile idiopathic arthritis up to a maximum of (or equivalent dose and interval schedule):

(1) 10mg/kg every 4 weeks for patients weighing < 30kg

(2) 8mg/kg every 4 weeks for patients weighing ≥ 30kg

c. Patient is **not** receiving tocilizumab in combination with either of the following:

(1) Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]

(2) Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]

4. Cytokine release syndrome when ALL of the following criteria are met:

a**.** Diagnosis of severe or life-threatening Cytokine release syndrome (CRS); and patient has received treatment with one of the following:

- Chimeric antigen receptor (CAR) T cell therapy [e.g., Kymriah (tisagenlecleucel), Yescarta (axicabtagene ciloleucel)]
- Blincyto (blinatumomab)

b. Tocilizumab is initiated and titrated according to US FDA labeled dosing for cytokine release syndrome up to a maximum of 800 mg/IV infusion.

(1) For patients < 30 kg, 12 mg/kg IV infusion over 60 minutes, alone or in combination with corticosteroids; if no improvement in signs and symptoms, may give up to 3 additional doses at least 8 hours apart

(2) For patients 30 kg or greater, 8 mg/kg IV infusion over 60 minutes, alone or in combination with corticosteroids; if no improvement in signs and symptoms, may give up to 3 additional doses at least 8 hours apart

c. Actemra® is prescribed for a maximum of 4 doses.

5. Giant Cell Arteritis (GCA)/Temporal Arteritis when ALL of the following criteria are met:

a. Diagnosis of giant cell arteritis

b. Patient is not receiving Actemra in combination with either of the following:

(1) Biologic DMARD [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]

(2) Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]

c. Actemra is dosed according to U.S. Food and Drug Administration (FDA) labeled dosing for giant cell arteritis

6. Acute Graft-Versus-Host Disease (GVHD) when ALL of the following criteria are met:

a. Diagnosis of steroid-refractory acute GVHD

b. One of the following:

- Patient is receiving Actemra in combination with systemic corticosteroids; OR
- Patient is intolerant to systemic corticosteroid therapy

c. Initial authorization is for no more than 4 doses

7. Immune Checkpoint Inhibitor-Related Toxicities when ALL of the following criteria are met:

a. Patient has recently received checkpoint inhibitor therapy [e.g., Keytruda (Pembrolizumab), Opdivo (Nivolumab)]
b. Diagnosis of severe immunotherapy-related inflammatory arthritis
c. No symptom improvement after 7 days of starting high-dose corticosteroids
d. History of failure, contraindication, or intolerance to infliximab (e.g., Inflectra, Remicade)
e. One of the following:
    i. Patient is receiving Actemra in combination with systemic corticosteroids
    ii. Patient is intolerant to systemic corticosteroid therapy
f. Authorization is for no more than 4 doses

Renewal/Continuation of Therapy Requests:

Renewal requests for Tocilizumab (Actemra) for Rheumatoid arthritis, Systemic juvenile idiopathic arthritis, Polyarticular juvenile idiopathic arthritis, Giant Cell Arteritis or Cytokine release syndrome will be approved only if in addition to the indication specific data ALL of the following criteria are met:

- Documentation of positive clinical response to Actemra therapy
- Actemra is dosed according to FDA labeled dosing
- Patient is not receiving Actemra in combination with either of the following:
  - Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
  - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]

For acute graft-versus-host disease (GVHD), all of the following must be met:

a. Documentation of positive clinical response
b. Patient continues to experience acute GVHD
c. One of the following:
   i. Patient is receiving Actemra in combination with systemic corticosteroids OR
   ii. Patient is intolerant to systemic corticosteroid therapy
d. Authorization is for no more than 4 doses

FDA Approved Dose and Indication

Rheumatoid arthritis	Starting dose is 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response	
	Doses exceeding 800 mg per infusion are not recommended in RA patients	
RA patient with Liver Enzyme Abnormalities	Greater than 1 to 3x ULN	Dose modify concomitant DMARDs (RA) or immunomodulatory agents (GCA) if appropriate For persistent increases in this range: • For patients receiving intravenous Actemra®, reduce dose to 4 mg per kg or hold Actemra® until ALT or AST have normalized • For patients receiving subcutaneous Actemra®, reduce injection frequency to every other week or hold dosing until ALT or AST have normalized. Resume Actemra® at every other week and increase frequency to every week as clinically appropriate.
	Greater than 3 to 5x ULN (confirmed by repeat testing)	Hold Actemra® dosing until less than 3x ULN and follow recommendations above for greater than 1 to 3x ULN For persistent increases greater than 3x ULN, discontinue Actemra®
	Greater than 5x ULN	Discontinue Actemra®
RA patient with Low ANC	ANC greater than 1000	Maintain dose
	ANC 500 to 1000	Hold Actemra® dosing When ANC > 1000 cells per mm3: • For patients receiving intravenous Actemra®, resume Actemra® at 4 mg per kg and increase to 8 mg per kg as clinically appropriate • For patients receiving subcutaneous Actemra®, resume Actemra® at every other week and increase frequency to every week as clinically appropriate
	ANC less than 500	Discontinue Actemra®
RA patient with low platelet count	50,000 to 100,000 Cells/mm^3	Hold Actemra® dosing When platelet count is greater than 100,000 cells per mm3: • For patients receiving intravenous Actemra®, resume Actemra® at 4 mg per kg and increase to 8 mg per kg as clinically appropriate • For patients receiving subcutaneous Actemra®, resume Actemra® at every other week and increase frequency to every week as clinically appropriate

	Less than 50,000 Cells/mm^3	Discontinue Actemra®
Polyarticular juvenile idiopathic arthritis	Patients < 30 kg	10 mg/kg every 4 weeks
	Patients ≥30 kg	8 mg/kg every 4 weeks
Systemic juvenile idiopathic arthritis	Patients < 30 kg	12 mg/kg every 2 weeks
	Patients ≥30 kg	8mg/kg every 2 weeks
Cytokine Release Syndrome	Patients < 30 kg	12 mg/kg for a maximum of 4 doses
	Patients ≥30 kg	8mg/kg up to a maximum of 800mg per infusion and for a maximum of 4 doses
Giant Cell Arteritis	6 mg/kg IV every 4 weeks in combination with a tapering course of glucocorticoids, and continued as monotherapy thereafter; MAX 600 mg	

General Background:

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

Tocilizumab is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). For this indication, tocilizumab may be used alone or in combination with methotrexate or other DMARDs. Dosing adjustments should be made when a patient has liver enzyme abnormalities, low platelet counts or low Absolute Neutrophil Counts; please refer to the authorization and dosing section below for details.

Tocilizumab is also indicated for the treatment of active polyarticular juvenile idiopathic arthritis and active systemic juvenile idiopathic arthritis in patients 2 years of age and older. For these indications, tocilizumab may be used alone or in combination with methotrexate. Dose reduction of Actemra® has not been studied in the PJIA and SJIA populations. Dose interruptions of ACTEMRA are recommended for liver enzyme abnormalities, low neutrophil counts, and low platelet counts in patients with PJIA and SJIA at levels similar to what is outlined above for patients with RA and GCA. If appropriate, dose modify or stop concomitant methotrexate and/or other medications and hold Actemra® dosing until the clinical situation has been evaluated. In PJIA and SJIA the decision to discontinue Actemra® for a laboratory abnormality should be based upon the medical assessment of the individual patient.

Subcutaneous Tocilizumab is indicated for giant cell arteritis, rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis. When transitioning from Actemra® intravenous therapy to subcutaneous administration, administer the first subcutaneous dose when the next scheduled intravenous dose is due.

Medicare does not have a National Coverage Determination (NCD) for Actemra® (tocilizumab). Local Coverage Determinations (LCDs) do not exist at the time of this policy revision.

Black Box Warning:

Patients treated with tocilizumab are at increased risk for infections, some progressing to serious infections leading to hospitalization or death. These infections have included bacterial infection, tuberculosis, invasive fungal, or other opportunistic infections.

- Evaluate for latent tuberculosis and treat if necessary prior to initiation of therapy.
- Monitor patients receiving tocilizumab for signs and symptoms of infection, including tuberculosis, even if initial latent tuberculosis test is negative.

Clinical Evidence/Professional Guidelines:

Rheumatoid Arthritis

Huizinga et al, published the analysis for the 2-year and 3-year results of the double-blind, placebo-controlled, parallel-group ACT-RAY trial that assessed the efficacy and safety of tocilizumab (TCZ) plus methotrexate/placebo (MTX/PBO) and the course of disease activity in patients who discontinued TCZ due to sustained remission. During the first 24 weeks, all patients (N = 556) were randomized either to continue oral MTX with the addition of open-label TCZ 8 mg/kg intravenously every 4 weeks (add-on strategy) or switch to TCZ alone with PBO (switch strategy). Between weeks 24 and 52, treatment with TCZ plus blinded MTX/PBO continued unchanged; however, if Disease Activity Score in 28 joints based on erythrocyte sedimentation rate (DAS28-ESR) was >3.2 at week 24, an open-label conventional synthetic disease-modifying antirheumatic drug (csDMARD) (sulfasalazine, leflunomide, hydroxychloroquine or azathioprine; choice and dose at investigator's discretion) was added. If DAS28-ESR was >3.2 at week 36 with an added csDMARD, the patient was moved to the maintenance arm (TCZ+blinded MTX/PBO + open-label csDMARD) for the remainder of the study, with the option to receive an additional open-label csDMARD per the investigator's discretion. Between weeks 52 and 104, open-label treatment was adapted based on response every 12 weeks, and patients continued the study in one of four treat-to-target strategies. The primary endpoint has previously been published. Secondary endpoints included rate and time to TCZ-free and drug-free remission, time to flare after TCZ-free remission, and time to restart of treatment after TCZ-free remission. Radiographic endpoints included progression of joint destruction based on the Genant-modified Sharp Score (GSS) at weeks 24, 52, and 104 among others. Of the randomized patients, 76% (472) completed year 2, where 50.4% discontinued TCZ by week 104, with no significant difference between treatment groups [129 (53.1%) add-on vs. 109 (47.6%) switch patients; p = 0.170)]. Twenty-eight (11.8%) of 238 patients achieved total drug-free remission due to sustained achievement of DAS28-ESR <2.6. A significantly higher proportion of patients in the add-on arm achieved drug-free remission compared with patients in the switch arm [21/243 (8.6%) vs 7/229 (3.1%); p=0.010]. A total of 200 patients subsequently flared following TCZ-free remission, with 82.5% (95% CI 75.4% to 88.5%) and 88.5% (95% CI 81.5% to 93.7%) of patients in the add-on and switch arms, respectively, experiencing flare within 52 weeks after achieving TCZ-free remission. At week 104, the majority of patients demonstrated minimal progression of radiographic structural damage. The adjusted mean change in total GSS was 0.35 for add-on and 0.95 for switch (p=0.034). The overall safety profile was similar for both treatment groups. The frequencies of adverse events (AE), serious AE (SAE), and discontinuations due to AEs were similar between the two treatment groups. The investigators concluded that treat-to-target strategies could be successful with TCZ to achieve a sustained free remission after discontinuation. TCZ free remission was maintained on average of three months prior to flaring, which then was controlled with resumption of TCZ.

The 2015 American College of Rheumatology (ACR) RA treatment guideline addresses the use of DMARDS, biologics, tofacitinib, and glucocorticoids in early (<6 months) and established (≥ 6 months) RA and the use of various treatment approaches in frequently encountered clinical scenarios, including treat-to-target, switching between therapies, tapering of therapy, the use of biologics and DMARDs in high-risk RA patients, vaccination in patients with RA receiving DMARDs or biologics, TB screening with biologics or tofacitinib, and laboratory monitoring with DMARDs. The guideline recommendations apply to common

clinical situations, since the panel considered issues common to most patients, not exceptions. Recommendations are classified as either strong or conditional. A strong recommendation means that the panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation. A conditional recommendation means that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of patients, but some may not want to follow the recommendation. As a result, conditional recommendations are preference sensitive and warrant a shared decision-making approach.

Juvenile Idiopathic Arthritis

The 2019 American College of Rheumatology (ACR) and Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis includes the use of tocilizumab.

- General medication recommendations for children and adolescents with JIA and polyarthritis:
    - Biologic DMARDS: In children and adolescents with JIA and polyarthritis initiating treatment with a biologic (etanercept, adalimumab, golimumab, abatacept, or tocilizumab) combination therapy with a DMARD is conditionally recommended over biologic monotherapy
- General guidelines for the initial and subsequent treatment of children and adolescents with JIA and polyarthritis
- Subsequent therapy: Moderate/high disease activity (cJADAS-10 > 2.5)
    - If patient is receiving DMARD monotherapy: Adding a biologic to original DMARD is conditionally recommended over changing to a second DMARD. Adding a biologic is conditionally recommended over changing to triple DMARD therapy.
    - If patient is receiving first TNFi (± DMARD): Switching to a non-TNFi biologic (tocilizumab or abatacept) is conditionally recommended over switching to a second TNFi. A second TNFi may be appropriate for patients with good initial response to their first TNFi (i.e., secondary failure). If patient is receiving second biologic: Using TNFi, abatacept, or tocilizumab (depending on prior biologics received) is conditionally recommended over rituximab.

The 2013 update to the 2011 ACR recommendations includes the use of tocilizumab in those patients with systemic JIA with continued disease activity and synovitis. For patients with systemic JIA with active systemic features and varying degrees of synovitis: Tocilizumab was recommended as a therapeutic option for patients with continued disease activity following systemic glucocorticoid (GC) monotherapy (level A), MTX or leflunomide (level B), or anakinra (level B) irrespective of the physician global assessment (MD global) and active joint count (AJC). Tocilizumab was also recommended for patients with an MD global ≥5 irrespective of the AJC despite prior NSAID monotherapy (level C). For patients with systemic JIA without active systemic features and varying degrees of active synovitis: Initiation of tocilizumab was recommended for an AJC >0 following treatment with anakinra (level B) or MTX or leflunomide (level B).

Giant Cell Arteritis

The 2021 American College of Rheumatology and Vasculitis Foundation guideline for the management of giant cell arteritis and Takayasu arteritis includes the use of tocilizumab.

Recommendations and ungraded position statements for the management of giant cell arteritis (GCA):

- For patients with newly diagnosed GCA, the use of oral glucocorticoids with tocilizumab over oral glucocorticoids alone is conditionally recommended.
- For patients with GCA with active extracranial large vessel involvement, treatment with oral glucocorticoids combined with a nonglucocorticoid immunosuppresive agent (e.g., tocilizumab, methotrexate) over oral glucocorticoids alone is conditionally recommended.
- For patients with GCA who experience disease relapse with cranial symptoms while receiving glucocorticoids, adding tocilizumab and increasing the dose of glucocorticoids over adding methotrexate and increasing the dose of glucocorticoids is conditionally recommended.

NCCN Recommended Uses

According to the NCCN Drugs & Biologics Compendium, NCCN recommends (2A) tocilizumab (Actemra) for the treatment of:

- Acute lymphoblastic leukemia; Consider as supportive care for patients who develop refractory cytokine release syndrome (CRS) related to blinatumomab therapy.
- Acute graft-versus-host disease (GVHD) as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options
- Immune checkpoint inhibitor-related toxicities - Consider adding tocilizumab (Actemra) for the management of immunotherapy-related:
  - Severe Inflammatory Arthritis:
    - Hold or permanently discontinue immunotherapy.
    - Prednisone/methylprednisolone 1mg/kg/day
      - If no improvement by week 1 or if unable to taper steroids by week 2, rheumatology consultation for consideration of additional disease-modifying anti-rheumatic drugs depending on clinical phenotype of inflammatory arthritis. Options include: infliximab, methotrexate, **tocilizumab**, sulfasalazine, azathioprine, adalimumab, etanercept, hydroxychloroquine

- CAR T-Cell-Related Toxicities
- Prolonged (> 3 days) G1 cytokine release syndrome (CRS) in patients with significant symptoms and/or comorbidities
  - Assess need for subsequent dosing after each dose (no more than 3 doses in 24 hours up to a maximum of 4 doses)
- G2-4 cytokine release syndrome (CRS)

- Assess need for subsequent dosing after each dose (no more than 3 doses in 24 hours up to a maximum of 4 doses)

- G1-4 neurotoxicity as additional single-dose therapy if concurrent CRS
  - Repeat dosing as needed (no more than 3 doses in 24 hours up to a maximum of 4 doses) if not responsive to IV fluids or increasing supplemental oxygen

HCPCS Code:

HCPCS Code:	Description:
J3262	Injection, Toclizumab (Actemra), 1mg

Acronyms:

DMARD = disease-modifying anti-rheumatic drugs; IL-6 = interleukin 6; NCD = National Coverage Determination; LCD = Local Coverage Determinations; RA = rheumatoid arthritis; FDA = Food and Drug Administration; SJIA = systemic juvenile idiopathic arthritis; PJIA = polyarticular juvenile idiopathic arthritis; TCZ = tocilizumab; MTX = methotrexate; PBO = placebo; GSS = Genant-modified Sharp Score; AE = adverse events; SAE = serious adverse events; ACR = American College of Rheumatology; GC = glucocorticoid; AJC = active joint count; CRS = cytokine release syndrome; cJADAS-10 = Clinical Juvenile Disease Activity Score based on 10 joints; TNFi = tumor necrosis factor inhibitor; GCA = Giant Cell Arteritis

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