Actemra® (tocilizumab injection) is indicated for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis. Tocilizumab exerts therapeutic effects by binding to soluble and membrane-bound IL-6 receptors which prevents IL-6-mediated signaling, resulting in decreased inflammatory processes. Adverse effects include upper respiratory tract infections, nasopharyngitis, headache, hypertension, and increased ALT.

**Recommended authorization criteria**

**FDA-Approved Indications**

1. **Adults with rheumatoid arthritis (RA).** Approve in patients who meet *both* of the following criteria (a and b):
   a. Patient has have tried one of the following tumor necrosis factor (TNF) antagonists: adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi™), or infliximab (Remicade®) for at least 2 months or was intolerant to one of these TNF antagonists, *AND*
   b. Tocilizumab is prescribed by a rheumatologist or in consultation with a rheumatologist.

   Tocilizumab is Food and Drug Administration (FDA)-approved for the treatment of adults with moderate to severe active RA who have had an inadequate response to ≥ 1 TNF antagonists. Tocilizumab can be used alone or in combination with methotrexate (MTX) or other non-biologic disease modifying antirheumatic drugs (DMARDs). In the pivotal trial establishing efficacy of tocilizumab in patients with an inadequate response to a TNF antagonist, tocilizumab was given in combination with MTX.

2. **Active systemic juvenile idiopathic arthritis (SJIA).** Approve in children/adolescents who meet *both* of the following criteria (a and b):
   a. tocilizumab is prescribed by or in consultation with a rheumatologist, *AND*
   b. the patient has tried a systemic corticosteroid, or MTX, leflunomide, or sulfasalazine, or a biologic agent such as etanercept, adalimumab, infliximab, or anakinra.
Initiating therapy with a biologic agent such as tocilizumab alone should be rare. Most patients will have received initial therapy with another agent (e.g., an NSAID, systemic glucocorticoids, anakinra, TNF inhibitor, or MTX). Some patients with systemic arthritis with active systemic features and features of poor prognosis (e.g., arthritis of the hip, radiographic damage) may be started early on a biologic agent. If tocilizumab is prescribed by or in consultation with a rheumatologist, these patients will be evaluated by a pharmacist and/or physician on a case-by-case basis to determine a coverage recommendation for the client. This criterion is recommended based on the professional opinion of specialized physicians.

Tocilizumab is FDA-approved for the treatment of children ≥ 2 years of age with active SJIA and can be used alone or in combination with MTX. In the pivotal trial establishing efficacy of tocilizumab in patients with active SJIA, patients had an inadequate response to NSAIDs or corticosteroids and some were treated with MTX.

3. **Polyarticular Juvenile Idiopathic Arthritis (PJIA).** Approve if the patient meets the following criteria (a and b):

   a) Patient has tried at least ONE TNF inhibitor (e.g., Enbrel, Humira); AND
   b) Actemra is prescribed by or in consultation with a rheumatologist.

Actemra is indicated for the treatment of active PJIA in patients ≥ 2 years of age. In the pivotal trial establishing efficacy of Actemra in PJIA, patients with PJIA were required to have failed MTX. The 2011 ACR recommendations for the treatment of JIA (published prior to the approval of Actemra for PJIA) propose initial DMARD treatment with MTX in most patients; however, the guidelines note that TNF antagonists may be used for JIA with active arthritis but have relatively poor effectiveness for systemic JIA with active systemic features *without* active arthritis. In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.

### Other Uses with Supportive Evidence

4. **Castleman’s disease.** Approve if the patient is under the care of an oncologist or hematologist. Tocilizumab is a preferred treatment for multicentric Castleman’s disease (MCD) in patients without human immunodeficiency virus (HIV) infection. In a prospective, open-label study conducted in Japan, 28 HIV-negative adults with MCD (plasma-cell type) received tocilizumab 8 mg/kg every 2 weeks for 16 weeks and then entered an open-label extension of the study where the dose and interval (maximum dose 8 mg/kg and minimum interval one week) could be adjusted according to symptoms and laboratory parameters. Only 2 patients were seropositive for Kaposi’s sarcoma-associated herpes virus/human herpes virus 8 (KSHV/HHV8). The primary efficacy end point was improvement in disease activity assessed by biochemical markers such as CRP, hemoglobin, and serum albumin, and general fatigue. Other parameters were measured such as changes in the size of swollen lymph nodes. With tocilizumab therapy, lymphadenopathy improved and laboratory markers of inflammation improved. Fatigue measured by visual analog scale improved significantly by Week 16 (P = 0.008).

Efficacy and safety of tocilizumab in HIV-positive patients with MCD have not been established. In patients who are HIV-positive, optimal therapy for multicentric Castleman’s disease includes highly active antiretroviral therapy (HAART), chemotherapy (e.g., etoposide), rituximab, and antiviral therapy to inhibit HHV8 replication.

5. **Adult with Still’s Disease.** Approve if the patient has tried a corticosteroid AND has had an inadequate response to one non-biologic DMARD such as methotrexate given for at least 2 months or was intolerant to a non-biologic DMARD. Tocilizumab has been effective in reducing fever, symptoms, and markers of inflammation in patients who were refractory to treatment with prednisone and MTX. Prospective, randomized, controlled trials are needed.

6. **Patient has been started on tocilizumab.** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications and Other Uses with Supportive Evidence). (In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.)
Exclusions (Limitations)

Coverage of tocilizumab is not recommended in the following circumstances:

1. **Children and adolescents ≤ 18 years of age.** Exceptions can be made for children/adolescents with systemic onset JIA or Castleman’s disease. Safety and efficacy of tocilizumab in pediatric patients have not been established. In the five pivotal RA trials, patients were greater than 18 years of age.

2. **Tocilizumab should not be given in combination with TNF antagonists** (adalimumab [Humira®], certolizumab pegol [Cimzia®], etanercept [Enbrel®], golimumab [Simponi™], infliximab [Remicade®]), abatacept (Orencia®), anakinra (Kineret®), or rituximab (Rituxan®). Combination therapy with two biologic agents is not recommended due to a higher rate of adverse effects with combinations and lack of additive efficacy.

3. **Juvenile idiopathic arthritis (JIA), other types beside systemic onset.** A Phase III trial is underway in children with polyarticular course JIA. Abatacept, adalimumab, and etanercept are FDA-approved for polyarticular course JIA. Published information is not available on the use of tocilizumab in any of the subtypes of JIA, beside systemic onset. Studies are needed to establish safety and efficacy.

4. **Crohn’s disease.** In a 12-week pilot study conducted in Japan, 36 adults with active Crohn’s disease (Crohn’s Disease Activity Index [CDAI] ≥ 150 and increased CRP) were randomized, double-blind to IV tocilizumab 8 mg/kg every 2 weeks; or alternating infusions of tocilizumab 8 mg/kg every 4 weeks and placebo (i.e., alternating with placebo every 2 weeks), or to placebo every 2 weeks. At baseline the CDAI means ranged from 287 to 306. Patients had been treated with corticosteroids, mesalamine-type drugs, metronidazole, or elemental diet. Six patients in the placebo group, 4 on tocilizumab every 4 weeks and 1 on tocilizumab every 2 weeks dropped out. The mean reduction in the CDAI score in the tocilizumab 8 mg/kg every 2 week group was 88 points – from mean 306 to 218. Further studies are needed.

5. **Other indications.** Exceptions not recommended. Because of its unique mechanism of action tocilizumab is being studied for many other conditions.

6. **Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria.** Criteria will be updated as new published data are available.
References