Clinical Policy: Tocilizumab (Actemra)

Reference Number: PA.CP.PHAR.263
Effective Date: 01/18
Last Review Date: 04/19 Revision Log

Description
Tocilizumab (Actemra®) is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody.

FDA approved indication
Actemra is indicated for the treatment of:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs)
- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (PJIA)
- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis (SJIA)
- Adult patients with giant cell arteritis (GCA)
- 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)

Policy/Criteria
Provider must submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of Pennsylvania Health and Wellness® that Actemra is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Polyarticular Juvenile Idiopathic Arthritis (must meet all)**:**

1. Diagnosis of PJIA;
2. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 2 years;
4. Member meets one of the following (a or b):
   a. Failure of methotrexate (MTX) for ≥ 3 consecutive months at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   b. If intolerance or contraindication to MTX (*see Appendix D*), failure of sulfasalazine or leflunomide for ≥ 3 consecutive months at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Failure of etanercept *(Enbrel is preferred)* AND adalimumab *(Humira is preferred),* each used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced, or member is currently receiving Actemra;
   **Prior authorization is required for etanercept and adalimumab*

6. Dose does not exceed one of the following (a or b):
   a. Weight < 30 kg: 10 mg/kg IV every 4 weeks or 162 mg SC every 3 weeks;
   b. Weight ≥ 30 kg: 8 mg/kg IV every 4 weeks or 162 mg SC every 2 weeks

Approval duration: 6 months

B. Systemic Juvenile Idiopathic Arthritis(must meet all)**:**
1. Diagnosis of SJIA;
2. Prescribed by or in consultation with a dermatologist, rheumatologist, or gastroenterologist;
3. Age ≥ 2 years;
4. Failure of one of the following therapies (a or b), unless all are contraindicated or clinically significant adverse effects are experienced:
   a. A corticosteroid for 2 weeks;
   b. MTX or leflunomide for ≥ 3 consecutive months;
5. Prescribed route of administration is IV infusion;
6. Dose does not exceed one of the following (a or b):
   a. IV:
      i. Weight < 30 kg: 12 mg/kg every 2 weeks;
      ii. Weight ≥ 30 kg: 8 mg/kg every 2 weeks;
   b. SC:
      i. Weight < 30 kg: 162 mg every 2 weeks;
      ii. Weight ≥ 30 kg: 162 mg every week.

Approval duration: 6 months

C. Rheumatoid Arthritis (must meet all)**:**
1. Diagnosis of RA per American College of Rheumatology (ACR) criteria (refer to Appendix B);
2. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. Failure of MTX for ≥ 3 consecutive months at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   b. If intolerance or contraindication to MTX (*see Appendix D*), failure of sulfasalazine, leflunomide, or hydroxychloroquine for ≥ 3 consecutive months at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Failure of etanercept *(Enbrel is preferred)* AND adalimumab *(Humira is preferred)*, each used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced, or member is currently receiving Actemra;
   **Prior authorization is required for etanercept and adalimumab*
6. Dose does not exceed the following:
   a. IV: 800mg every 4 weeks;
   b. Subcutaneous (SC): 162mg every week.

Approval duration: 6 months

D. Giant Cell Arteritis (must meet all)**:**

1. Diagnosis of GCA;
2. Request is for SC formulation;
3. Prescribed by or in consultation with a rheumatologist;
4. Failure of at least a 12-week trial of a corticosteroid at up to maximally tolerated doses in conjunction with MTX or azathioprine, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 162 mg SC every week.

Approval duration: 6 months

E. Cytokine Release Syndrome (must meet all):
1. Request is for IV formulation;
2. Member has a scheduled CAR T cell therapy (e.g., Kymriah™ , Yescarta™);
3. Dose does not exceed 800 mg per infusion for up to 4 total doses.

Approval duration: Up to 4 doses total

F. Other diagnoses/indications
1. Refer to PA.CP.PMN.53.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via PA Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed the following (a, b, c, d, or e):
   a. RA (i or ii):
      i. IV: 800 mg every 4 weeks;
      ii. SC: 162 mg every week;
   b. GCA: 162 mg SC every week;
   c. PJIA (i or ii):
      i. Weight < 30 kg: 10 mg/kg IV every 4 weeks or 162 mg SC every 3 weeks;
      ii. Weight ≥ 30 kg: 8 mg/kg IV every 4 weeks or 162 mg SC every 2 weeks;
   d. SJIA (i or ii):
      i. Weight < 30 kg: 12 mg/kg IV every 2 weeks;
      ii. Weight ≥ 30 kg: 8 mg/kg IV every 2 weeks;
   e. CRS: 800 mg per infusion for up to 4 doses total.

Approval duration: CRS: Up to 4 doses total, all other indications: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via PA Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.

Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to PA.CP.PMN.53.

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CAR: chimeric antigen receptor
CRS: cytokine release syndrome
DMARDs: disease-modifying anti-rheumatic drugs
FDA: Food and Drug Administration
GCA: giant cell arteritis
GI: gastrointestinal
IL-6: interleukin 6
MTX: methotrexate
PJIA: polyarticular juvenile idiopathic arthritis
RA: rheumatoid arthritis
SJIA: systemic juvenile idiopathic arthritis

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
azathioprine (Azasan®, Imuran®)	**RA** 1 mg/kg/day PO QD or divided BID **GCA*** 1.5 – 2 mg/kg/day PO	2.5 mg/kg/day
corticosteroids	**GCA*, SJIA*** Various	Various
Cuprimine® (d-penicillamine)	**RA*** Initial dose: 125 or 250 mg PO QD Maintenance dose: 500 – 750 mg/day PO QD	1,500 mg/day
cyclosporine (Sandimmune®, Neoral®)	**RA** 2.5 – 4 mg/kg/day PO divided BID	4 mg/kg/day
hydroxychloroquine (Plaquenil®)	**RA*** Initial dose: 400 – 600 mg/day PO QD Maintenance dose: 200 – 400 mg/day PO QD	600 mg/day
leflunomide (Arava®)	**PJIA*** Weight < 20 kg: 10 mg every other day Weight 20 - 40 kg: 10 mg/day Weight > 40 kg: 20 mg/day **RA** 100 mg PO QD for 3 days, then 20 mg PO QD	PJIA, RA: 20 mg/day SJIA: 10 mg every other day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	SJIA* 100 mg PO every other day for 2 days, then 10 mg every other day	
methotrexate (Rheumatrex®)	**GCA*** 20 – 25 mg/week PO **PJIA*** 10 – 20 mg/m^2/week PO, SC, or IM **RA** 7.5 mg/week PO, SC, or IM or 2.5 mg PO Q12 hr for 3 doses/week **SJIA*** 0.5-1 mg/kg/week PO	30 mg/week
Ridaura® (auranofin)	**RA** 6 mg PO QD or 3 mg PO BID	9 mg/day (3 mg TID)
sulfasalazine (Azulfidine®)	**PJIA*** 30-50 mg/kg/day PO divided BID **RA** 2 g/day PO in divided doses	PJIA: 2 g/day RA: 3 g/day
Enbrel® (etanercept)	**RA** 25 mg SC twice weekly or 50 mg SC once weekly **PJIA** Weight < 63 kg: 0.8 mg/kg SC once weekly Weight ≥ 63 kg: 50 mg SC once weekly	50 mg/week
Humira® (adalimumab)	**RA** 40 mg SC every other week (may increase to once weekly) **PJIA** Weight 10 kg (22 lbs) to <15 kg (33 lbs): 10 mg every other week Weight 15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg every other week Weight ≥ 30 kg (66 lbs): 40 mg every other week	RA: 40 mg/week PJIA: 40 mg every other week

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

**Off-label*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): known hypersensitivity to Actemra
- Boxed warning(s): risk of serious infections

Appendix D: General Information

- Definition of failure of MTX or DMARDs
  - Child-bearing age is not considered a contraindication for use of MTX. Each drug has risks in pregnancy. An educated patient and family planning would allow use of MTX in patients who have no intention of immediate pregnancy.
  - Social use of alcohol is not considered a contraindication for use of MTX. MTX may only be contraindicated if patients choose to drink over 14 units of alcohol per week. However, excessive alcohol drinking can lead to worsening of the condition, so patients who are serious about clinical response to therapy should refrain from excessive alcohol consumption.
- Examples of positive response to therapy may include, but are not limited to:
  - Reduction in joint pain/swelling/tenderness
  - Improvement in ESR/CRP levels
  - Improvements in activities of daily living

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
RA	IV: 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response SC: Weight < 100 kg: 162 mg SC every other week, followed by an increase to every week based on clinical response Weight ≥ 100 kg: 162 mg SC every week	IV: 800 mg every 4 weeks SC: 162 mg every week
GCA	162 mg SC every week (every other week may be given based on clinical considerations)	SC: 162 mg every week
PJIA	Weight < 30 kg: 10 mg/kg IV every 4 weeks or 162 mg SC every 3 weeks Weight ≥ 30 kg: 8 mg/kg IV every 4 weeks or 162 mg SC every 2 weeks	IV: 10 mg/kg every 4 weeks SC: 162 mg every 2 weeks
SJIA	IV: Weight < 30 kg: 12 mg/kg IV every 2 weeks Weight ≥ 30 kg: 8 mg/kg IV every 2 weeks SC: Weight < 30 kg: 162 mg SC every 2 weeks Weight ≥ 30 kg: 162 mg SC every week	IV: 12 mg/kg every 2 weeks SC: 162 mg every week

Indication	Dosing Regimen	Maximum Dose
CRS	Weight < 30 kg: 12 mg/kg IV per infusion Weight ≥ 30 kg: 8 mg/kg IV per infusion If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of Actemra may be administered. The interval between consecutive doses should be at least 8 hours.	IV: 800 mg/infusion, up to 4 doses

V. Product Availability

- Single-use vial: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL
- Single-dose prefilled syringe: 162 mg/0.9 mL
- Single-dose prefilled autoinjector: 162 mg/0.9 mL

VIII. References

1. Actemra Prescribing Information. South San Francisco, CA: Genentech; December 2018. Available at https://www.actemra.com/. Accessed February 26, 2019.
2. Ringold, S., Weiss, P. F., Beukelman, T., DeWitt, E. M., Ilowite, N. T., Kimura, Y., Laxer, R. M., Lovell, D. J., Nigrovic, P. A., Robinson, A. B. and Vehe, R. K. (2013), 2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for the Medical Therapy of Children With Systemic Juvenile Idiopathic Arthritis and Tuberculosis Screening Among Children Receiving Biologic Medications. Arthritis & Rheumatism, 65: 2499–2512.
3. European League Against Rheumatism. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2009;68:318–323.
4. Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Rheumatology 2016. 68(1):1-26.
5. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: http://www.clinicalpharmacology-ip.com/.

Reviews, Revisions, and Approvals	Date	Approval Date
2Q 2018 annual review: removed TB testing for all indications, added dermatologist and GI specialist as prescriber specialists for SJIA; references reviewed and updated.	2.27.18	
2Q 2019 annual review: revised GI specialist to gastroenterologist for specialist requirement for SJIA; added autoinjector formulation; references reviewed and updated.	04.17.19	