Clinical Policy: Tocilizumab (Actemra)

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Line of Business: Illinois Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Tocilizumab (Actemra®) is an interleukin 6 (IL-6) receptor antagonist.

FDA Approved Indication(s)
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 anti-rheumatic drugs (DMARDs)
- Adult patients with giant cell arteritis (GCA)
- Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD)
- 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)
- 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 (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Actemra is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Cytokine Release Syndrome (must meet all)**:**
1. Request is for IV formulation;
2. Age ≥ 2 years;
3. Member meets one of the following (a or b):
   a. Member has a scheduled CAR T cell therapy (e.g., Kymriah™, Yescarta™);
   b. Member has developed refractory (i.e., inadequate response to steroids, vasopressors) CRS related to blinatumomab therapy;
4. Request meets one of the following (a or b):*
   a. Dose does not exceed 800 mg per infusion for 4 total doses;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: Up to 4 doses total

B. 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. Age ≥ 18 years;

5. Failure of a ≥ 3 consecutive month trial of a systemic corticosteroid at up to maximally tolerated doses in conjunction with MTX or azathioprine, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed 162 mg every week.

Approval duration: 6 months

C. Polyarticular Juvenile Idiopathic Arthritis (must meet all)**:**
1. Diagnosis of PJIA as evidenced by ≥ 5 joints with active arthritis;
2. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 2 years;
4. Documented baseline 10-joint clinical juvenile arthritis disease activity score (cJADAS-10) (*see Appendix H*);
5. Member meets one of the following (a, b, c, or d):
   a. Failure of a ≥ 3 consecutive month trial of MTX at up to maximally indicated doses;
   b. Member has intolerance or contraindication to MTX (*see Appendix D*), and failure of a ≥ 3 consecutive month trial of leflunomide or sulfasalazine at up to maximally indicated doses, unless clinically significant adverse effects are experienced or both are contraindicated;
   c. For sacroiliitis/axial spine involvement (i.e., spine, hip), failure of a ≥ 4 week trial of an NSAID at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   d. Documented presence of high disease activity as evidenced by a cJADAS-10 > 8.5 (*see Appendix H*);
6. Failure of Enbrel® AND Humira®, each used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for etanercept and adalimumab*
7. Dose does not exceed one of the following (*see Appendix E for dose rounding guidelines*) (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

D. Rheumatoid Arthritis (must meet all)**:**
1. Diagnosis of RA per American College of Rheumatology (ACR) criteria (*see Appendix E*);
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 a ≥ 3 consecutive month trial of methotrexate (MTX) at up to maximally indicated doses;
   b. Member has intolerance or contraindication to MTX (*see Appendix D*), and failure of a ≥ 3 consecutive month trial of at least ONE conventional DMARD (e.g., sulfasalazine, leflunomide, hydroxychloroquine) at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated;
5. Failure of at least TWO of the following, each used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced: Enbrel, Humira, Cimzia®, Xeljanz®/Xeljanz® XR;
   **Prior authorization may be required for Enbrel, Humira, Cimzia, and Xeljanz/Xeljanz XR*
6. Documentation of one of the following baseline assessment scores (a or b):
   a. Clinical disease activity index (CDAI) score (*see Appendix F*);
   b. Routine assessment of patient index data 3 (RAPID) score (*see Appendix G*);
7. Dose does not exceed one of the following (a or b):
   a. IV: 800 mg every 4 weeks;
   b. SC: 162 mg every week.

Approval duration: 6 months

E. 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. Member meets one of the following (a or b):
   a. Failure of a ≥ 3 consecutive month trial of MTX or leflunomide at up to maximally indicated doses, unless clinically significant adverse effects are experienced or both are contraindicated;
   b. Failure of a ≥ 2-week trial of a systemic corticosteroid at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed one of the following (a or b):
   a. IV following (*see Appendix E for dose rounding guidelines*):
      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

F. Systemic Sclerosis-Associated Interstitial Lung Disease (must meet all):
1. Diagnosis of SSc-ILD;
2. Request is for SC formulation;
3. Prescribed by or in consultation with a pulmonologist;
4. Member meets both of the following (a and b):
   a. Pulmonary fibrosis on high-resolution computed tomography (HRCT);
   b. Additional signs of SSc are identified (*see Appendix I*);
5. Failure of ≥ 3 consecutive month trial of cyclophosphamide or mycophenolate mofetil, at up to maximally indicated doses, unless both are contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed 162 mg every week.

Approval duration: 6 months

G. Castleman's Disease (off-label) (must meet all)**:**
1. Diagnosis of Castleman's disease;
2. Disease is relapsed/refractory or progressive;
3. Member is human immunodeficiency virus (HIV)-negative and human herpesvirus 8 (HHV-8)-negative;
4. Prescribed as second-line therapy as a single agent;
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 8 mg/kg per infusion every 2 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

H. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
   b. Documentation supports that member is currently receiving Actemra IV for CAR T cell-induced CRS and member has not yet received 4 doses total;

2. Member meets one of the following (a, b, or c):
   a. For RA: Member is responding positively to therapy as evidenced one of the following (i or ii):
      i. A decrease in CDAI (*see Appendix F*) or RAPID3 (*see Appendix G*) score from baseline;
      ii. Medical justification stating ability to conduct CDAI re-assessment, and submission of RAPID3 score associated with disease severity that is similar to initial CDAI assessment or improved;
   b. For pJIA: Member is responding positively to therapy as evidenced by a decrease in cJADAS-10 from baseline (*see Appendix H*);
   c. For all other indications: Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed one of the following (a, b, c, d, e, or f):
   a. RA (i or ii):
      i. IV: 800 mg every 4 weeks;
      ii. SC: 162 mg every week;
   b. GCA, SSc-ILD: 162 mg SC every week;
   c. PJIA (*see Appendix E for dose rounding guidelines*) (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 (*see Appendix E for dose rounding guidelines*) (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, or dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*);
   f. Castleman's disease (i or ii):*
      i. Dose does not exceed 8 mg/kg per infusion every 2 weeks;
      ii. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

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

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents;

B. Combination use of biological disease-modifying antirheumatic drugs (bDMARDs), including any tumor necrosis factor (TNF) antagonists [Cimzia®, Enbrel®, Simponi®, Avsola™, Inflectra™, Remicade®, Renflexis™], interleukin agents [Arcalyst® (IL-1 blocker), Ilaris® (IL-1 blocker), Kineret® (IL-1RA), Actemra® (IL-6RA), Kevzara® (IL-6RA), Stelara® (IL-12/23 inhibitor), Cosentyx® (IL-17A inhibitor), Taltz® (IL-17A inhibitor), Siliq™ (IL-17RA), Ilumya™ (IL-23 inhibitor), Skyrizi™ (IL-23 inhibitor), Tremfya® (IL-23 inhibitor)], janus kinase inhibitors (JAKi) [Xeljanz®/Xeljanz® XR, Rinvoq™], anti-CD20 monoclonal antibodies [Rituxan®, Riabni™, Ruxience™, Truxima®, and Rituxan Hycela®], selective co-stimulation modulators [Orencia®], or integrin receptor antagonists [Entyvio®] because of the possibility of increased immunosuppression, neutropenia and increased risk of infection.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CAR: chimeric antigen receptor
CDAI: clinical disease activity index
cJADAS: clinical juvenile arthritis disease activity score
CRS: cytokine release syndrome
DMARDs: disease-modifying anti-rheumatic drugs
FDA: Food and Drug Administration
GCA: giant cell arteritis
HHV-8: human herpesvirus 8
HIV: human immunodeficiency virus
IL-6: interleukin 6
MTX: methotrexate
PJIA: polyarticular juvenile idiopathic arthritis
RA: rheumatoid arthritis
RAPID3: routine assessment of patient index data 3
SJIA: systemic juvenile idiopathic arthritis
SSc-ILD: systemic sclerosis – associated interstitial lung disease

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 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
cyclophosphamide (Cytoxan®, Neosar®)	**SSc-ILD*** PO: 1 – 2 mg/kg/day IV: 600 mg/m^2/month	PO: 2 mg/kg/day IV: 600 mg/m^2/month
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 **SJIA*** 100 mg PO every other day for 2 days, then 10 mg every other day	PJIA, RA: 20 mg/day SJIA: 10 mg every other day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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
mycophenolate mofetil (CellCept®)	**SSc-ILD*** PO: 1 – 3 g/day	3 g/day
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)	**PJIA** Weight < 63 kg: 0.8 mg/kg SC once weekly Weight ≥ 63 kg: 50 mg SC once weekly **RA** 25 mg SC twice weekly or 50 mg SC once weekly	50 mg/week
Humira® (adalimumab)	**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 SC every other week (may increase to once weekly)	RA: 40 mg/week PJIA: 40 mg every other week
Cimzia® (certolizumab)	**RA** Initial dose: 400 mg SC at 0, 2, and 4 weeks Maintenance dose: 200 mg SC every other week (or 400 mg SC every 4 weeks)	400 mg every 4 weeks
Xeljanz® (tofacitinib, immediate-release)	**RA** 5 mg PO BID	10 mg/day
Xeljanz XR® (tofacitinib, extended-release)	**RA** 11 mg PO QD	11 mg/day

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

Appendix E: The 2010 ACR Classification Criteria for RA
Add score of categories A through D; a score of ≥ 6 out of 10 is needed for classification of a patient as having definite RA.

A	**Joint involvement**	Score
	1 large joint	0
	2-10 large joints	1
	1-3 small joints (with or without involvement of large joints)	2
	4-10 small joints (with or without involvement of large joints)	3
	> 10 joints (at least one small joint)	5
B	**Serology (at least one test result is needed for classification)**	
	Negative rheumatoid factor (RF) *and* negative anti-citrullinated protein antibody (ACPA)	0
	Low positive RF *or* low positive ACPA ** Low: < 3 x upper limit of normal*	2
	High positive RF *or* high positive ACPA ** High: ≥ 3 x upper limit of normal*	3
C	**Acute phase reactants (at least one test result is needed for classification)**	
	Normal C-reactive protein (CRP) and normal erythrocyte sedimentation rate (ESR)	0
	Abnormal CRP or abnormal ESR	1
D	**Duration of symptoms**	
	< 6 weeks	0
	≥ 6 weeks	1

Appendix F: Clinical Disease Activity Index (CDAI) Score
The Clinical Disease Activity Index (CDAI) is a composite index for assessing disease activity in RA. CDAI is based on the simple summation of the count of swollen/tender joint count of 28 joints along with patient and physician global assessment on VAS (0–10 cm) Scale for estimating disease activity. The CDAI score ranges from 0 to 76.

CDAI Score	Disease state interpretation
≤ 2.8	Remission
> 2.8 to ≤ 10	Low disease activity
> 10 to ≤ 22	Moderate disease activity
> 22	High disease activity

Appendix G: Routine Assessment of Patient Index Data 3 (RAPID3) Score
The Routine Assessment of Patient Index Data 3 (RAPID3) is a pooled index of the three patient-reported ACR core data set measures: function, pain, and patient global estimate of status. Each of the individual measures is scored 0 – 10, and the maximum achievable score is 30.

RAPID3 Score	Disease state interpretation
≤ 3	Remission
3.1 to 6	Low disease activity
6.1 to 12	Moderate disease activity
> 12	High disease activity

Appendix H: Clinical Juvenile Arthritis Disease Activity Score based on 10 joints (cJADAS-10)
The cJADAS10 is a continuous disease activity score specific to JIA and consisting of the following three parameters totaling a maximum of 30 points:

- Physician's global assessment of disease activity measured on a 0-10 visual analog scale (VAS), where 0 = no activity and 10 = maximum activity;
- Parent global assessment of well-being measured on a 0-10 VAS, where 0 = very well and 10 = very poor;
- Count of joints with active disease to a maximum count of 10 active joints*

**ACR definition of active joint: presence of swelling (not due to currently inactive synovitis or to bony enlargement) or, if swelling is not present, limitation of motion accompanied by pain, tenderness, or both*

cJADAS-10	Disease state interpretation
≤ 1	Inactive disease
1.1 to 2.5	Low disease activity
2.51 to 8.5	Moderate disease activity
> 8.5	High disease activity

Appendix I: American College of Rheumatology (ACR) 2013 SSc Classification Criteria
While the majority of patients with SSc experience skin thickening and variable involvement of internal organs, there is no one confirmatory test for SSc. Similar to the IPF guidelines above, ACR lists HRCT as a diagnostic method for determining pulmonary fibrosis in SSc- ILD. The other diagnostic parameters below are drawn from ACR's scoring system purposed for clinical trials. While informative, ACR cautions that the scoring system parameters are not all inclusive of the myriad of SSc manifestations that may occur across musculoskeletal, cardiovascular, renal, neuromuscular and genitourinary systems.

Examples of SSc skin/internal organ manifestations and associated laboratory tests:

- Skin thickening of the fingers
- Fingertip lesions
- Telangiectasia
- Abnormal nailfold capillaries
- Raynaud's phenomenon
- SSc-ILD
- Pulmonary arterial hypertension
- SSc-related autoantibodies
- Anticentromere
- Anti-topoisomerase I (anti-Scl-70)
- Anti-RNA polymerase III

V. 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	IV: 800 mg every 4 weeks SC: 162 mg every week

Indication	Dosing Regimen	Maximum Dose
	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	
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
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/60 minute infusion, up to 4 doses

VI. Product Availability

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

VII. References

1. Actemra Prescribing Information. South San Francisco, CA: Genentech; March 2021. Available at: https://www.actemra.com/. Accessed March 18, 2021.
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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	04.21.21	05.21

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.