Clinical Policy: Tocilizumab (Actemra)

Reference Number: CP.PHAR.263
Effective Date: 07.01.16
Last Review Date: 05.18
Line of Business: HIM, Medicaid

Coding Implications
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)
- 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.

It is the policy of health plans affiliated with Centene Corporation® that Actemra is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Rheumatoid Arthritis (must meet all)**:**

1. Diagnosis of RA;
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, unless contraindicated or clinically significant adverse effects are experienced;
   b. If intolerance or contraindication to MTX (*see Appendix C*), 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 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;

**Prior authorization is required for etanercept and adalimumab*

6. 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

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;
2. Request is for IV formulation;
3. Prescribed by or in consultation with a rheumatologist;
4. Age ≥ 2 years;
5. Member meets one of the following (a or b):
   a. Failure of a ≥ 3 consecutive month trial of MTX at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   b. If intolerance or contraindication to MTX (*see Appendix C*), failure of a ≥ 3 consecutive month trial of sulfasalazine or leflunomide at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
6. 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;
   **Prior authorization is required for etanercept and adalimumab*
7. Dose does not exceed one of the following (a or b):
   a. Weight < 30 kg: 10 mg/kg every 4 weeks or 162 mg SC every 3 weeks;
   b. Weight ≥ 30 kg: 8 mg/kg every 4 weeks or 162 mg SC every 2 weeks.

Approval duration: 6 months

D. Systemic Juvenile Idiopathic Arthritis (must meet all)**:**

1. Diagnosis of SJIA;
2. Request is for IV formulation;
3. Prescribed by or in consultation with a dermatologist, rheumatologist, or gastrointestinal (GI) specialist;
4. Age ≥ 2 years;
5. 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 contraindicated or clinically significant adverse effects are experienced;
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;

6. Dose does not exceed one of the following (a or b)
   a. Weight < 30 kg: 12 mg/kg every 2 weeks;
   b. Weight ≥ 30 kg: 8 mg/kg every 2 weeks.

Approval duration: 6 months

E. Cytokine Release Syndrome (must meet all):
1. Request is for IV formulation;
2. Age ≥ 2 years;
3. Member has a scheduled CAR T cell therapy (e.g., Kymriah™, Yescarta™);
4. 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 the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PHAR.21 for health insurance marketplace and CP.PMN.53 for Medicaid.

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 Centene benefit 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 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, 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;
   c. 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;
   d. 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 Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PHAR.21 for health insurance marketplace and CP.PMN.53 for Medicaid.

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 policies – HIM.PHAR.21 for health insurance marketplace and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. 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*** <u>Initial dose:</u> 125 or 250 mg PO QD <u>Maintenance dose:</u>	1,500 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	500 – 750 mg/day PO QD	
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 **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
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	50 mg/week

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	PJIA Weight < 63 kg: 0.8 mg/kg SC once weekly Weight ≥ 63 kg: 50 mg SC once weekly	
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: 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

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

Indication	Dosing Regimen	Maximum Dose
	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	Weight < 30 kg: 12 mg/kg IV every 2 weeks Weight ≥ 30 kg: 8 mg/kg IV every 2 weeks	IV: 12 mg/kg every 2 weeks
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

VI. 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

VII. References

1. Actemra Prescribing Information. South San Francisco, CA: Genentech; May 2018. Available at https://www.actemra.com/. Accessed July 5, 2018.
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.; 2018. Available at: http://www.clinicalpharmacology-ip.com/.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-

date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J3262	Injection, tocilizumab, 1 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy split from CP.PHAR.86.Arthritis Treatments PJIA, SJIA and RA: Removed criteria related to HBV, malignant disease, concomitant use with other biologics, and concurrent administration of live vaccines; added dosing requirements. PJIA: removed question related to number of affected joints; modified criteria to require trial of MTX, unless contraindicated; added sulfasalazine as an alternative to MTX is contraindicated; added requirement for trial and failure of PDL Enbrel and Humira, unless contraindicated; SJIA: removed question related to active systemic features; modified duration of treatment of NSAIDs and corticosteroids to for ≥ 1 month and ≥ 2 weeks, respectively; added MTX or leflunomide as an option for failure; added requirement specifying route of administration per PI. RA: changed age requirement to 18 years per PI/FDA labeling; modified criteria to require trial of methotrexate, unless contraindicated; added sulfasalazine and hydroxychloroquine as alternatives to methotrexate if methotrexate is contraindicated; added requirement for trial and failure of PDL Enbrel and Humira, unless contraindicated; Re-auth: combined into All Indications; added dosing and reasons to discontinue. Modified approval duration to 6 months for initial and 12 months for renewal;	06.16	07.16
Policy converted to new template. Added criteria for new FDA indication Giant Cell Arteritis. Revised criteria for confirmation of RA diagnosis per 2010 ACR Criteria. Removed safety requirements per updated CPAC Safety Precaution in PA Policies approach.	07.17	07.17
SJIA: Removed requirement for trial/failure of NSAID as it not a first line therapy recommended by the SJIA guidelines. GCA: Added age requirement as safety and efficacy have not been established in pediatric populations.	08.17.17	11.17
Added criteria for new indication of cytokine release syndrome	09.26.17	11.17
Corrected continued approval duration for “all other indications” from “6 months or member’s renewal date, whichever is longer” to 12 months	11.30.17	
2Q 2018 annual review: policies combined for HIM and Medicaid lines of business; HIM: removed specific diagnosis requirements for RA,	02.27.18	05.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
removed trial and failure of NSAIDs for SJIA as it is not first line; Medicaid and HIM: modified trial and failure for RA to at least one conventional DMARD, modified requirement of corticosteroid trial to be 3 consecutive months for GCS, removed TB testing for all indications, added dermatologist and GI specialist as prescriber specialists for SJIA; added age requirement for CRS; added weight-based max dosing requirements for PJIA and SJIA; references reviewed and updated.		
No significant changes: newly FDA-approved subcutaneous dosing for PJIA added.	07.16.18	

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.