RxAdvance

Clinical Policy Title:	tocilizumab
Policy Number:	RxA.730
Drug(s) Applied:	Actemra®
Original Policy Date:	04/18/2022
Last Review Date:	04/18/2022
Line of Business Policy Applies to:	All lines of business

Background

Actemra® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist indicated for 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).

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
tocilizumab (Actemra®)	RA	Intravenous: 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response. Subcutaneous: Weight < 100 kg: 162 mg every other week, followed by an increase to every week based on clinical response. Weight ≥ 100 kg: 162 mg every week.	Intravenous: 800 mg every 4 weeks Subcutaneous: 162 mg every week
	GCA	Intravenous: 6 mg/kg every 4 weeks in combination with a tapering course of glucocorticoids. It can be used alone following discontinuation of glucocorticoids. Subcutaneous: 162 mg subcutaneously once every week in combination with a tapering course of glucocorticoids.	Intravenous: 6 mg/kg Subcutaneous: 162 mg every week

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
		(Every other week may be given based on clinical considerations.)	
	PJIA	Weight < 30 kg: 10 mg/kg intravenously every 4 weeks or 162 mg subcutaneously every 3 weeks. Weight ≥ 30 kg: 8 mg/kg intravenously every 4 weeks or 162 mg subcutaneously every 2 weeks.	Intravenous: Weight < 30 kg: 10 mg/kg every 4 weeks; ≥ 30 kg: 8 mg/kg every 4 weeks Subcutaneous: Weight < 30 kg: 162 mg every 3 weeks; ≥ 30 kg: 162 mg every 2 weeks;
	SJIA	Weight < 30 kg: 12 mg/kg intravenously every 2 weeks or 162 mg subcutaneously every 2 weeks. Weight ≥ 30 kg: 8 mg/kg intravenously every 2 weeks or 162 mg subcutaneously every week.	Intravenous: Weight < 30 kg: 12 mg/kg every 2 weeks; ≥ 30 kg: 8 mg/kg every 2 weeks Subcutaneous: Weight < 30 kg: 162 mg every 2 weeks; ≥ 30 kg: 162 mg every week;
	CRS	Weight < 30 kg: 12 mg/kg intravenously per infusion Weight ≥ 30 kg: 8 mg/kg intravenously 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.	Intravenous: 800 mg/infusion, up to 4 doses
	SSc-ILD	162 mg given once every week as a subcutaneous injection	162 mg given once every week

Dosage Forms

- Intravenous Infusion: Single-use vial: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20

mg/mL)
- Subcutaneous Injection: Single-dose prefilled syringe: 162 mg/0.9 mL
- Subcutaneous Injection :Single-dose prefilled autoinjector: 162 mg/0.9 mL

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Rheumatoid Arthritis (must meet all):
1. Diagnosis of Rheumatoid Arthritis (RA);
2. Prescribed by or in consultation with a rheumatologist;
3. Age is ≥ 18 years;
4. Trial and failure of a ≥ 3 months of at least one conventional systemic therapy (methotrexate [MTX], sulfasalazine, leflunomide, hydroxychloroquine) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   *Exception: If one biologic DMARD that is FDA-approved for rheumatoid arthritis has been previously tried, then trial of a conventional systemic agent is not required;
5. Trial and failure of at least two (2) of the following agents: Cimzia®, Humira®, Simponi®/ Simponi Aria®, Rinvoq® or Xeljanz/XR® unless contraindicated or clinically significant adverse effects are experienced;
   *Exception: If a total of two TNF inhibitors (Humira®, Cimzia®, Simponi®/ Simponi Aria®, Enbrel®) has previously been tried and failed, trial of a third TNF inhibitor is not required;
6. Dose does not exceed 800 mg every 4 weeks for intravenously use and 162 mg every week for Subcutaneous use.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

B. Giant Cell Arteritis (must meet all):
1. Diagnosis of Giant cell Arthritis (GCA);
2. Request is for subcutaneous formulation of Actemra®;
3. Prescribed by or in consultation with a rheumatologist;
4. Age is ≥ 18 years;
5. Trial and failure of a ≥ 3 months of a systemic corticosteroid at up to maximally tolerated doses in conjunction with methotrexate (MTX) or azathioprine, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed 162 mg subcutaneously every week.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

C. Juvenile Idiopathic Arthritis (must meet all):
1. Diagnosis of Polyarticular Juvenile Idiopathic Arthritis (PJIA) and Systemic Juvenile Idiopathic Arthritis (SJIA);
2. Prescribed by or in consultation with a rheumatologist;

3. Age is ≥ 2 years;
4. Trial and failure of a ≥ 3 months of at least one (1) conventional systemic therapy (methotrexate [MTX] or leflunomide [Arava®]) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   *Exception: If one biologic DMARD that is FDA-approved for rheumatoid arthritis has been previously tried, then trial of a conventional systemic agent is not required;
5. For PJIA:Trial and failure of Humira® unless contraindicated or clinically significant adverse effects experienced;
   *Exception: If a total of two TNF inhibitors (Humira, Simponi Aria, Enbrel®) has previously been tried and failed, trial of a third TNF inhibitor is not required.
6. Dose does not exceed
   a. Intravenous: Weight < 30 kg: 12 mg/kg every 2 weeks; ≥ 30 kg: 8 mg/kg every 2 weeks
   b. Subcutaneous: Weight < 30 kg: 162 mg every 2 weeks; ≥ 30 kg: 162 mg every weeks;

Approval Duration
Commercial: 12 months
Medicaid: 12 months

D. Cytokine Release Syndrome (must meet all):
1. Member has a scheduled chimeric antigen receptor (CAR) T-cell therapy (e.g., Kymriah™, Yescarta™);
2. Age is ≥ 2 years;
3. Request is for an intravenous formulation of Actemra®;
4. Dose does not exceed 800 mg per infusion for up to 4 total doses.

Approval Duration
Commercial: Up to 4 total doses
Medicaid: Up to 4 total doses

E. Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD) (must meet all):
1. Diagnosis of Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD);
2. Prescribed by or in consultation with a Pulmonologist;
3. Age is ≥ 18 years;
4. Member meets all of the following (a, b and c):
   a. Onset of disease (first non-Raynaud symptom) of ≤ 5 years;
   b. Modified Rodnan Skin Score (mRSS) of ≥ 10 and ≤ 35 at screening;
   c. Elevated inflammatory markers (or platelets), and active disease based on at least one of the following (i or ii or ii or iv or v):
      i. Disease duration ≤ 18 months;
      ii. Increase in mRSS ≥ 3 units over 6 months;
      iii. Involvement of one new body area and an increase in mRSS of ≥ 2 over 6 months;
      iv. Involvement of two new body areas within the previous 6 months;
      v. Presence of at least one tendon friction rub;
5. Dose does not exceed 162 mg given once every week.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all):

1. Member meets one of the following (a or b):
   a. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy.;
   b. Documentation supports that member is currently receiving intravenous Actemra for CAR T cell-induced CRS and member has not yet received 4 total doses;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed maximum dose indicated in dosing information.

Approval Duration
For CRS:
Commercial: Up to 4 doses total
Medicaid: Up to 4 doses total
For all other indications:
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
RA: Rheumatoid arthritis
DMARDs: Disease-Modifying Anti-Rheumatic Drugs
GCA: Giant cell arteritis
SSC (ILD): Systemic Sclerosis-Associated Interstitial Lung Disease
PJIA: Polyarticular juvenile idiopathic arthritis
SJIA: systemic juvenile idiopathic arthritis
CAR: Chimeric antigen receptor
CRS: cytokine release syndrome
Mrss: Modified Rodnan Skin Score

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
azathioprine (Azasan®, Imuran®)	**RA:** 1 mg/kg/day orally once daily or divided twice daily	2.5 mg/kg/day
d-penicillamine (Cuprimine®)	**RA (off-label)** Initial dose: 125 or 250 mg orally once daily Maintenance dose: 500 – 750 mg/day orally once daily	1,500 mg/day
cyclosporine (Sandimmune®, Neoral®)	**RA:** 2.5 – 4 mg/kg/day orally divided twice daily	RA: 4 mg/kg/day
hydroxychloroquine (Plaquenil®)	**RA (off-label)** Initial dose: 400 – 600 mg/day orally once daily Maintenance dose: 200 – 400 mg/day orally once daily	600 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
leflunomide (Arava®)	**PJIA (off-label)** Weight < 20 kg: 10 mg every other day Weight 20 - 40 kg: 10 mg/day Weight > 40 kg: 20 mg/day **RA:** 100 mg orally once daily for 3 days, then 20 mg orally once daily	PJIA, RA: 20 mg/day
methotrexate	**PJIA(off- label):** 10 – 20 mg/m^2/week orally, subcutaneous, or intramuscular **RA:** 7.5 mg/week orally, subcutaneous, or intramuscular or 2.5 mg orally every 12 hr for 3 doses/week	30 mg/week
Ridaura®	**RA:** 6 mg orally once daily or 3 mg orally twice daily	9 mg/day (3 mg three times daily)
sulfasalazine (Azulfidine®)	**PJIA(off-label):** 30-50 mg/kg/day orally divided twice daily **RA:** 2 g/day orally in divided doses	PJIA: 2 g/day RA: 3 g/day
Biologic DMARDs		
Humira®	**RA**: 40 mg subcutaneously every other week Some patients with RA not receiving concomitant methotrexate may benefit from increasing the frequency to 40 mg every Week or 80 mg every other week **PJIA:** Weight 10 kg (22 lbs) to < 15 kg (33 lbs): 10 mg subcutaneously every other week Weight 15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg subcutaneously every other week Weight ≥ 30 kg (66 lbs): 40 mg subcutaneously every other week	**RA**: 40 mg/week **PJIA:** 40 mg every other week
infliximab (Remicade®) Renflexis®, Inflectra®, Avsola®	**RA:** In conjunction with MTX <u>Initial dose:</u> 3 mg/kg intravenously at weeks 0, 2 and 6 <u>Maintenance dose:</u> 3 mg/kg intravenously every 8 weeks Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks	**RA:** 10 mg/kg every 4 weeks
Simponi Aria®	**RA:** <u>Initial dose:</u> 2 mg/kg intravenously at weeks 0 and 4 <u>Maintenance dose:</u>	**RA**: 2 mg/kg every 8 weeks

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	2 mg/kg intravenously every 8 weeks **PJIA:** Initial dose: 80 mg/m^2 at weeks 0 and 4 Maintenance dose: 80 mg/m^2 intravenously every 8 weeks	**PJIA:** 80 mg/m^2 every 8 weeks
Xeljanz® / Xeljanz® oral Solution, Xeljanz® XR	Xeljanz®: **RA**: 5 mg orally twice daily RA: monotherapy or use in combination with nonbiologic disease-modifying antirheumatic drugs Xeljanz® / Xeljanz® oral Solution: **PJIA**: 5 mg twice daily or weight-based equivalent twice daily: • 10 kg ≤ body weight <20 kg: 3.2 mg (3.2 mL oral solution) twice daily • 20 kg ≤ body weight <40 kg: 4 mg (4 mL oral solution) twice daily Body weight ≥40 kg: 5 mg (one 5 mg tablet or 5 mL oral solution) twice daily Xeljanz® XR: **PsA, RA**: 11 mg orally once daily	Xeljanz®: **RA:** 10 mg/day Xeljanz® / Xeljanz® oral Solution: 5 mg or 5 ml twice daily Xeljanz® XR: 11 mg/day
Kevzara®	**RA:** 200 mg subcutaneously once every two weeks	200 mg/2 Weeks
Kineret®	**RA:** 100 mg subcutaneously once daily	100 mg/day
Olumiant®	**RA:** 2 mg orally once daily	2 mg/day
Cimzia®	**RA:** Initial dose: 400 mg subcutaneously at 0, 2, and 4 weeks. Maintenance dose: 200 mg subcutaneously every other week (or 400 mg subcutaneous every 4 weeks)	**RA:** 400 mg every 4 weeks
Simponi®	**RA:** 50 mg subcutaneously once monthly	50 mg/month
Orencia®	**RA:** Intravenous: weight-based dose at weeks 0, 2, and 4, followed by every 4 weeks Weight < 60 kg: 500 mg per dose Weight 60 to 100 kg: 750 mg per dose Weight > 100 kg: 1,000 mg per dose Subcutaneous: 125 mg once weekly **PJIA:** Intravenous: in pediatric patients ≥ 6 years old weight-based dose at weeks 0, 2, and 4, followed by every 4 weeks Weight < 75 kg: 10 mg/kg per dose Weight 75 to 100 kg: 750 mg per dose Weight >100 kg: 1,000 mg per dose Subcutaneous: In pediatric patients ≥ 2 years old weight-based dose	**RA**: Intravenous: 1000 mg every 4 weeks Subcutaneous: 125 mg every week **PJIA:** Intravenous: 1,000 mg every 4 weeks Subcutaneous: 125 mg/week

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	once weekly Weight 10 to < 25 kg: 50 mg per dose Weight 25 to < 50 kg: 87.5 mg per dose Weight ≥ 50 kg: 125 mg per dose	
Rinvoq®	**RA:** 15 mg orally once daily Can be used as monotherapy or in combination with methotrexate or other non biologic DMARDs. *For use in adults who have had an inadequate response or intolerance to one or more TNF blockers	15 mg/day
Enbrel®	**RA:** 25 mg subcutaneously twice weekly or 50 mg subcutaneously once Weekly **PJIA:** Weight < 63 kg: 0.8 mg/kg subcutaneously once weekly Weight ≥ 63 kg: 50 mg subcutaneously once weekly	50 mg/week

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

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Known hypersensitivity to tocilizumab.

  *Contraindications listed reflect direct statements made in the manufacturer's package insert; for additional uses, warnings, and precautions, please refer to clinical guidelines.

- Boxed Warning(s):
  - Risk of serious infections.

APPENDIX D: General Information

- Safety:
  - These agents are immunosuppressives and have the potential to increase the risk of infection and reactivate latent, chronic infections. They should not be administered to patients with a clinically important infection. Caution should be used in patients with chronic infections or history of recurrent infection. If patient develops a serious infection these agents should be discontinued.
  - Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-blocking agent, etanercept, with no added benefit compared to etanercept alone. Because of the nature of the adverse reactions with this combination therapy, similar toxicities may also result from combination of anakinra and other TNF blocking agents.
- Polyarticular Juvenile Idiopathic Arthritis:
  - Failure of MTX in PJIA is defined as disease activity remaining moderate to high despite treatment with MTX.
  - In PJIA, response to treatment is reflected by improvement of disease activity level and poor prognostic features including : reduction in the number of active joints, ESR or CRP, Physician global assessment, patient/parent global assessment, arthritis of the hip or cervical spine, positive RF or ACPA, radiographic damage.

References

1. Actemra Prescribing Information. South San Francisco, CA: Genentech; March 2021. Available at: https://www.actemra.com/ . Accessed February 10, 2022.
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3. Drug. Lexi-Drug. Lexicomp. Wolters Kluwer. Hudson, OH. Available at: http://online.lexi.com. Accessed February 10, 2022.
4. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2022. Available at: http://www.clinicalpharmacology-ip.com/. Accessed February 10, 2022.
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Review/Revision History	Review/Revision Date	P&T Approval Date
RxA.592.Biologic_DMARDs was last reviewed and updated on 01/05/2022 and archived on 04/18/2022. For details, please refer to RxA.592.Biologic_DMARDs.	01/05/2022	04/18/2022
Drug specific policy for Actemra® was created based on RxA.592.Biologic_DMARDs 1. Dosing Information, Maximum Dose, Actemra: Updated maximum dosing information from general dosing to weight based dosing for indication PJIA and SJIA. 2. Initial Approval Criteria, I.A.5: Updated to remove prior trial and failure criteria "Failure of two (2) of the following, each used for ≥ 3 months, unless contraindicated or clinically significant adverse effects are experienced: Humira®, Cimzia®, Inflectra®, Rinvoq™, Renflexis™, Simponi®, Simponi Aria®, or Xeljanz®/ Xeljanz XR®". 3. Initial Approval Criteria, I.A.5: Updated to include new trial and failure criteria Trial and failure of at least two (2) of the following agents: Cimzia®, Humira®, Simponi®/ Simponi Aria®, Rinvoq® or Xeljanz/XR® unless contraindicated or clinically significant adverse effects are experienced; *Exception: If a total of two TNF inhibitors (Humira®, Cimzia®, Simponi®/ Simponi Aria®, Enbrel®) has previously been tried and failed, trial of a third TNF inhibitor is not required; 4. Initial Approval Criteria, I.C: Updated to include new criteria pertaining to indication SJIA. 5. Initial Approval Criteria, I.C.5: Updated to include new trial and failure criteria Trial and failure of Humira® unless contraindicated or clinically significant adverse effects experienced;	02/10/2022	04/18/2022

*Exception: If a total of two TNF inhibitors (Humira, Simponi Aria, Enbrel®) has previously been tried and failed, trial of a third TNF inhibitor is not required. 6. Initial Approval Criteria, I.C.6: Updated dosing criteria from Dose does not exceed maximum dose indicated in dosing information to Dose does not exceed (a or b): a. Intravenous: Weight < 30 kg: 12 mg/kg every 2 weeks; ≥ 30 kg: 8 mg/kg every 2 weeks b. Subcutaneous: Weight < 30 kg: 162 mg every 2 weeks; ≥ 30 kg: 162 mg every weeks; 7. Initial Approval Criteria, I.D: Updated to remove approval criteria for Juvenile Idiopathic Arthritis. 8. Appendix B, Drug Name: Updated to include brand-name therapeutic alternative of other biological DMARDs. 9. Disclaimer about contraindications "Contraindications listed reflect statements made in the manufacturer's package insert..." was added to Appendix C. 10. Appendix D, General Information: Updated to remove information regarding: (a, b and c) a. Rheumatoid Arthritis; b. Definition of failure of MTX or DMARDs; c. Examples of positive response to therapy. 11. References were reviewed and updated.		