Effective Date **6/1/2024**
Coverage Policy Number **IP0227**

Tocilizumab Subcutaneous

Table of Contents

Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for tocilizumab (**Actemra**®) subcutaneous injection.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Tocilizumab (Actemra) subcutaneous is considered medically necessary when ONE of the following is met:

1. **Giant Cell Arteritis.** Individual meets **ALL** of the following criteria:
   A. 18 years of age or older
   B. Documented failure, contraindication or intolerance to **ONE** systemic corticosteroid
   C. Medication is being prescribed by, or in consultation with, a rheumatologist

2. **Interstitial Lung Disease Associated with Systemic Sclerosis (SSc-ILD).** Individual meets **ALL** of the following criteria:

A. 18 years of age or older
B. Elevated acute phase reactants, defined as at least **ONE** of the following:
   i. C-reactive protein (CRP) is at least 6 mg/mL
   ii. Erythrocyte sedimentation rate (ESR) is at least 28 mm/h
   iii. Platelet count is at least 330 x 10^9/L
C. Forced vital capacity (FVC) is greater than 55% of the predicted value
D. Diagnosis is confirmed by high-resolution computed tomography
E. Medication is prescribed by, or in consultation with, a pulmonologist or a rheumatologist

3. **Polyarticular Juvenile Idiopathic Arthritis.** Individual meets **BOTH** of the following criteria:
   A. Medication is being prescribed by, or in consultation with, a rheumatologist
   B. Preferred Product Step Therapy is met, refer to the below table(s) [Employer Group Plans, Individual Family Plans]

4. **Polymyalgia Rheumatica**. Individual meets **ALL** of the following criteria:
   A. 18 years of age or older
   B. Documentation of failure, contraindication or intolerance to **ONE** systemic corticosteroid
   C. Medication is prescribed by, or in consultation with, a rheumatologist

5. **Rheumatoid Arthritis.** Individual meets **ALL** of the following criteria:
   A. 18 years of age or older
   B. Documentation of **ONE** of the following:
      i. Failure to **ONE** conventional synthetic disease-modifying anti-rheumatic drug (csDMARD)
      ii. Contraindication or intolerance to csDMARD therapy
      iii. Already tried a biologic or targeted synthetic DMARD for Rheumatoid Arthritis
   C. Medication is being prescribed by, or in consultation with, a rheumatologist
   D. Preferred Product Step Therapy is met, refer to the below table(s) [Employer Group Plans, Individual Family Plans]

6. **Systemic Juvenile Idiopathic Arthritis.** The medication is prescribed by, or in consultation with, a rheumatologist.

Coverage varies across plans and requires the use of Preferred Products. Refer to the customer's benefit plan document for coverage details.

Employer Group Plans	
Condition	**Preferred Product with Step Therapy Criteria**
Polyarticular Juvenile Idiopathic Arthritis	Documentation of failure, contraindication, or intolerance to **ONE** of the following adalimumab products: A. **Adalimumab-adaz** or **Hyrimoz** (by Sandoz/Novartis) [requires prior authorization] B. **Adalimumab-adbm** or **Cyltezo** [requires prior authorization] C. **Adalimumab-ryvk** or **Simlandi** [requires prior authorization] D. **Humira** (by AbbVie) [requires prior authorization]
Rheumatoid Arthritis	Documentation of failure, contraindication, or intolerance to **ONE** of the following adalimumab products: A. **Adalimumab-adaz** or **Hyrimoz** (by Sandoz/Novartis) [requires prior authorization] B. **Adalimumab-adbm** or **Cyltezo** [requires prior authorization] C. **Adalimumab-ryvk** or **Simlandi** [requires prior authorization] D. **Humira** (by AbbVie) [requires prior authorization]

Individual and Family Plan	
Condition	**Preferred Product with Step Therapy Criteria**
Polyarticular Juvenile Idiopathic Arthritis	Documentation of failure, contraindication, or intolerance to **ONE** of the following adalimumab products**:** A. **Adalimumab-adaz** or **Hyrimoz** (by Sandoz/Novartis) [requires prior authorization] B. **Adalimumab - adbm** or **Cyltezo** [requires prior authorization] C. **Adalimumab-ryvk** or **Simlandi** [requires prior authorization] D. **Humira** (by AbbVie) [requires prior authorization]
Rheumatoid Arthritis	Documentation of failure, contraindication, or intolerance to **ONE** of the following adalimumab products**:** A. **Adalimumab-adaz** or **Hyrimoz** (by Sandoz/Novartis) [requires prior authorization] B. **Adalimumab - adbm** or **Cyltezo** [requires prior authorization] C. **Adalimumab-ryvk** or **Simlandi** [requires prior authorization] D. **Humira** (by AbbVie) [requires prior authorization]

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of tocilizumab (Actemra) subcutaneous is considered medically necessary for **ALL** covered diagnoses when initial criteria are met AND beneficial response is demonstrated.

Authorization Duration

Initial approval duration is up to 12 months.
Reauthorization approval duration is up to 12 months.

Conditions Not Covered

Any other is use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Concurrent use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Data are lacking evaluating concomitant use of Actemra SC another biologics or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples).[1,11] Combination therapy with another biologic or targeted synthetic DMARD has the potential for higher rate of adverse effects and lack of controlled trial data in support of additive efficacy.[12]

   This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate [MTX], leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Actemra SC.

2. **COVID-19 (Coronavirus Disease 2019).** This includes cytokine release syndrome associated with COVID-19.

3. **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] at least 150 and increased C-reactive protein [CRP]) were randomized, in a double-blind fashion to IV Actemra 8 mg/kg every 2 weeks; or alternating infusions of Actemra 8 mg/kg every 4 weeks and placebo (i.e., alternating with placebo every 2 weeks), or to placebo

every 2 weeks.[13] 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 Actemra every 4 weeks and 1 on Actemra every 2 weeks dropped out. The mean reduction in the CDAI score in the Actemra 8 mg/kg every 2 week group was 88 points – from mean 306 to 218. Further studies are needed.

Background

OVERVIEW

Actemra subcutaneous injection, an interleukin-6 (IL-6) receptor inhibitor, is approved for the following uses:[1]

- **Giant cell arteritis** in adults.
- **Interstitial lung disease associated with systemic sclerosis,** for slowing the rate of decline in pulmonary function in adults.
- **Polyarticular juvenile idiopathic arthritis**, for the treatment of active disease in patients ≥ 2 years of age.
- **Rheumatoid arthritis**, for treatment of adults with moderate to severe active disease who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs).
- **Systemic juvenile idiopathic arthritis**, for the treatment of active disease in patients ≥ 2 years of age.

Guidelines/Clinical Efficacy

IL-6 blockers are mentioned in multiple guidelines for treatment of inflammatory conditions. Clinical data also support use of Actemra in other conditions.

- **Giant Cell Arteritis and Polymyalgia Rheumatica:** Recommendations from the European League Against Rheumatism (EULAR) [2018] state the diagnosis of giant cell arteritis may be made without biopsy if there is a high suspicion of giant cell arteritis and a positive imaging test.[4] In the pivotal trial evaluating Actemra subcutaneous for giant cell arteritis (n = 251), patients were treated with corticosteroids in an open-label fashion (20 mg to 60 mg/day) during the screening period prior to treatment with Actemra subcutaneous.[2-3] Sustained remission at Week 52 was achieved in 56% of patients who received Actemra subcutaneous every week + 26-week prednisone taper and 53% of patients who received Actemra every other week + 26-week prednisone taper vs. in 14% of patients in the 26-week prednisone taper and 18% of patients in the 52-week prednisone taper.

- **Interstitial Lung Disease Associated with Systemic Sclerosis:** EULAR guidelines for systemic sclerosis (2016) do not address Actemra.[14] In the pivotal trial evaluating Actemra subcutaneous for systemic sclerosis-associated interstitial lung disease, patients were required to have a percentage of predicted forced vital capacity (FVC% predicted) > 55%.[15] Among patients with interstitial lung disease confirmed on high-resolution computed tomography scan (n = 136), the change from baseline in FVC% predicted at Week 48 was significantly improved in the group taking Actemra (0.07 vs. -6.40 with placebo).

- **Polyarticular Juvenile Idiopathic Arthritis**: The American College of Rheumatology (ACR)/Arthritis Foundation guidelines for the treatment of Juvenile Idiopathic Arthritis (2019) are specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[8] For patients without risk factors, initial therapy with a DMARD is conditionally recommended over a biologic (including Actemra). Biologics (e.g., Actemra) are conditionally recommended as initial treatment when combined with a DMARD over biologic monotherapy.

- **Rheumatoid Arthritis**: Guidelines from the ACR for the treatment of rheumatoid arthritis (2015) have tumor necrosis factor (TNF) inhibitors and non-TNF biologics (such as Actemra) equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine).[10]

- **Systemic Juvenile Idiopathic Arthritis**: The 2013 update of the 2011 ACR recommendations for the treatment of systemic juvenile idiopathic arthritis mention Actemra as a second- or third-line agent in

patients with varying degrees of synovitis, with or without active systemic features.[9] Nonsteroidal anti-inflammatory drugs, systemic glucocorticoids, Kineret, TNF inhibitors, and methotrexate are among other treatment options.

References

1. Actemra® [prescribing information]. South San Francisco, CA: Genentech; March 2021.
2. Tuckwell K, Collinson N, Dimonaco S, et al. Newly diagnosed vs. relapsing giant cell arteritis: baseline data from the GiACTA trial. *Semin Arthritis Rheum*. 2017;46(5):657-664.
3. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med*. 2017 ;377(4):317-328.
4. Dejaco C, Ramiro S, Duftner C, et al. Recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis*. 2018;77(5):636-643.
5. Lally L, Forbess L, Hatzis C, Spiera R. Brief report: a prospective open-label Phase IIa trial of tocilizumab in the treatment of polymyalgia rheumatica. *Arthritis Rheumatol.* 2016;68(10):2550-2554.
6. Devauchelle-Pensec V, Berthelot JM, Cornec D, et al. Efficacy of first-line tocilizumab therapy in early polymyalgia rheumatica: a prospective longitudinal study. *Ann Rheum Dis*. 2016;75(8):1506-1510.
7. Macchioni P, Boiardi L, Catanoso M, et al. Tocilizumab for polymyalgia rheumatica: report of two cases and review of the literature. *Semin Arthritis Rheum*. 2013;43(1):113-118.
8. Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. *Arthritis Care Res (Hoboken).* 2019;71(6):717-734.
9. Ringold S, Weiss PF, Beukelman T, et al. 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 Rheum*. 2013;65(10):2499-2512.
10. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol*. 2016;68(1):1-26.
11. Furst DE, Keystone EC, So AK, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. *Ann Rheum Dis*. 2013;72 Suppl 2:ii2-34.
12. Xeljanz® tablets [prescribing information]. New York, NY: Pfizer; December 2019.
13. Ito H, Takazoe M, Fukuda Y, et al. A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology.* 2004;126:989-996.
14. Kowal-Bielecka OK, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis*. 2017;76(8):1327-1339.
15. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2020;8(10):963-974.

APPENDIX

Table 1. Approved TNFis for Targeted Indications.

	Rheumatology					Dermatology	Gastroenterology	
	RA	**JIA**	**AS**	**nr-axSpA**	**PsA**	**PsO**	**CD**	**UC**
Tumor Necrosis Factor Inhibitors								
Cimzia	√	--	√	√	√	√	√	--
Enbrel	√	√	√	--	√	√	--	--
Adalimumab products (Humira, biosimilars)	√	√	√	--	√	√	√	√
Infliximab Products	√	--	√	--	√	√	√	√
Simponi Subcutaneous	√	--	√	--	√	--	--	√
Simponi Aria	√	√	√	--	√	--	--	--

TNFis – Tumor necrosis factor inhibitors; RA – Rheumatoid arthritis; JIA – Juvenile idiopathic arthritis; AS – Ankylosing spondylitis; nr-axSpA – Non-radiographic spondyloarthritis; PsA – Psoriatic arthritis; PsO – Plaque psoriasis; CD – Crohn's disease; UC – Ulcerative colitis.

Table 2. Approved IL-17, IL-23, and IL-12/23 Blockers for Targeted Indications.

	Rheumatology			Dermatology	Gastroenterology	
	Ankylosing Spondylitis	**nr-axSpA**	**Psoriatic Arthritis**	**Plaque Psoriasis**	**Crohn's Disease**	**Ulcerative Colitis**
Interleukin-17 Blockers						
Cosentyx	√	√	√	√	--	--
Siliq	--	--	--	√	--	--
Taltz	√	√	√	√	--	--
Interleukin-23 Blockers						
Ilumya	--	--	--	√	√	--
Skyrizi Intravenous	--	--	--	--	√#	--
Skyrizi Subcutaneous	--	--	√	√	√^	--
Tremfya	--	--	√	√	--	--
Interleukin-12/23 Blockers						
Stelara Subcutaneous	--	--	√	√	√^	√^
Stelara Intravenous	--	--	--	--	√#	√#

IL – Interleukin; nr-axSpA – Non-radiographic spondyloarthritis; ^ Maintenance dosing only; # Induction dosing only

Table 3. Approved Oral tsDMARDs for Targeted Indications.

	Rheumatology					Dermatology	Gastro-enterology
	Rheumatoid Arthritis	**Juvenile Idiopathic Arthritis**	**Ankylosing Spondylitis**	**nr-axSpA**	**Psoriatic Arthritis**	**Plaque Psoriasis**	**Ulcerative Colitis**
Janus Kinases Inhibitors							
Olumiant	√	--	--	--	--	--	--
Rinvoq	√	--	√	√	√	--	√
Xeljanz tablets	√	√#	√	--	√	--	√
Xeljanz oral solution	--	√#	--	--	--	--	--
Xeljanz XR	√	--	√	--	√	--	√
Phosphodiesterase Type 4 Inhibitor							
Otezla	--	--	--	--	√	√	--
Sphingosine 1-Phosphate Receptor Modulator							
Zeposia	--	--	--	--	--	--	√
Tyrosine Kinase 2 Inhibitor							
Sotyktu	--	--	--	--	--	√	--

tsDMARDs – Targeted synthetic disease-modifying antirheumatic drugs; # Indicated in polyarticular JIA.

Table 4. Other Approved Biologics for Targeted Indications.

	Rheumatology		
	Rheumatoid Arthritis	**Juvenile Idiopathic Arthritis**	**Psoriatic Arthritis**
Interleukin-6 Blockers			
Actemra Intravenous	√	√^	--
Actemra Subcutaneous	√	√^	--
Kevzara	√	--	--
Interleukin-1 Blocker			
Kineret	√	--	--
T-Cell Costimulation Modulator			
Orencia Intravenous	√	√#	√
Orencia Subcutaneous	√	√#	√

CD20-Directed Cytolytic Antibody			
Rituximab Intravenous Products	√	--	--

^ Indicated in polyarticular and systemic JIA; # Indicated in polyarticular JIA.