PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Actemra® (tocilizumab for subcutaneous administration – Genentech/Roche)

DATE REVIEWED: 03/25/2020

OVERVIEW

Actemra for subcutaneous (SC) injection is a recombinant humanized interleukin-6 (IL-6) receptor inhibitor indicated for the following conditions:[1]

1. ~~1.~~ Rheumatoid arthritis (RA), 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); AND
2. Giant cell arteritis (GCA) in adults; AND
3. Polyarticular juvenile idiopathic arthritis (PJIA), for the treatment of active in patients 2 years of age and older; AND
4. Systemic juvenile idiopathic arthritis (SJIA), for the treatment of active disease in patients two years of age and older.

In RA and PJIA, Actemra SC can be given alone or in combination with methotrexate (MTX) [or with other nonbiologic DMARDs in RA]. Actemra is also available as an intravenous (IV) formulation which, in addition to RA and PJIA and SJIA, is indicated in chimeric antigen receptor (CAR) T-cell-induced severe or life-threatening cytokine release syndrome; however, the IV formulation is not indicated in GCA.

Disease Overview

IL-6 is a pro-inflammatory cytokine that is involved in various physiologic processes.[1] It has been shown to be involved in diverse physiological processes and is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as RA. Actemra binds to soluble and membrane-bound IL-6 receptors and has been shown to inhibit IL-6-mediated signaling through these receptors.

Clinical Efficacy

GCA and Polymyalgia Rheumatica (PMR)

In the pivotal trial evaluating Actemra SC for GCA (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 SC.[2-3] Sustained remission at Week 52 was achieved in 56% of patients who received Actemra SC 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. The pivotal trial evaluating Actemra SC for GCA allowed patients with the presence of PMR and evidence of large-vessel vasculitis by angiography or imaging (e.g., magnetic resonance imaging [MRI], computed tomography angiography [CTA], positron emission tomography – computed tomography [PET/CT]) to be included in the study. This aligns with recent recommendations from the European League Against Rheumatism (EULAR) [2018] which state the diagnosis of GCA may be made without biopsy if there is a high suspicion of GCA and a positive imaging test.[4] Additional small studies and/or case reports support use of Actemra in patients with PMR without documented symptoms of GCA.[5-7]

Guidelines

Il-6 blockers are mentioned in multiple guidelines for treatment of inflammatory conditions.

- PJIA: The American College of Rheumatology (ACR)/Arthritis Foundation guidelines for the treatment of JIA (2019) 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.
- SJIA: The 2013 update of the 2011 ACR recommendations for the treatment of SJIA mention Actemra as a second- or third-line agent in patients with active systemic features and varying degrees of synovitis and in patients without active systemic features and varying degrees of synovitis.[9] Nonsteroidal anti-inflammatory drugs NSAIDs, systemic glucocorticoids, Kineret, TNF inhibitors, and MTX are among other treatment options.
- RA: Guidelines from the ACR (2015) for the treatment of rheumatoid arthritis 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., MTX, leflunomide, hydroxychloroquine, sulfasalazine).[10]

Safety

Actemra SC has Boxed Warnings regarding increased risk of developing serious infections which may lead to hospitalization or death. Patients who develop a serious infection should interrupt treatment with Actemra SC until infection is controlled. Patients should be monitored during and after treatment with Actemra SC, including tuberculosis.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Actemra SC. Because of the specialized skills required for evaluation and diagnosis of patients treated with Actemra SC as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Actemra SC to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the approval duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

All reviews for use of Actemra SC for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Actemra SC is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Giant Cell Arteritis (GCA).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets the following criteria (i and ii):
     - **i.** The patient has tried one systemic corticosteroid; AND
       Note: An example of a systemic corticosteroid is prednisone.
     - **ii.** Actemra SC is prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving Actemra (IV or SC). Approve for 1 year if the patient has had a response, as determined by the prescriber.
     Note: Examples of response include reduced corticosteroid dose, normalization of acute phase reactants (e.g., erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]), reduction or resolution of signs or symptoms of GCA. The patient may not have a full response, but there should have been a recent or past response to Actemra (SC or IV).

2. **Polyarticular Juvenile Idiopathic Arthritis (PJIA).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 4 months if the patient meets BOTH of the following criteria (i and ii):
     - **i.** The patient meets one of the following conditions (a, b, c, or d):
       - **a)** The patient has tried one other agent for this condition.
         Note: Examples of one other agent tried include methotrexate (MTX), sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug (NSAID). A biologic (refer to **Appendix** for examples of biologics used for JIA) also counts as a trial of one agent for JIA; OR
       - **b)** The patient will be starting on Actemra SC concurrently with methotrexate (MTX), sulfasalazine, or leflunomide; OR
       - **c)** The patient has an absolute contraindication to methotrexate (MTX), sulfasalazine, or leflunomide.
         Note: Examples of absolute contraindication to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, and blood dyscrasias; OR
       - **d)** The patient has aggressive disease, as determined by the prescriber; AND
     - ~~**ii.**~~ Actemra SC is prescribed by or in consultation with a rheumatologist.
   - ~~**B)**~~ Patients Currently Receiving Actemra (IV or SC). Approve for 3 years if the patient has had a response, as determined by the prescriber.
     Note: Examples of response include improvement in limitation of motion; less joint pain or tenderness; improved function or activities of daily living; decreased duration of morning stiffness or fatigue; reduced dosage of corticosteroids; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values. The patient may not have a full response, but there should have been a recent or past response to Actemra IV or SC.

3. **Rheumatoid Arthritis (RA).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):
     - **i.** The patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
       Note: Examples of one conventional DMARD tried include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-

month trial at least one biologic (refer to **Appendix** for examples of biologics used for RA). These patients who have already tried a biologic for RA are not required to "step back" and try a conventional synthetic DMARD.

ii. Actemra SC is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Actemra (SC or IV). Approve for 3 years if the patient has had a response, as determined by the prescriber.

Note: Examples of response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Actemra (SC or IV).

4. Systemic Juvenile Idiopathic Arthritis (SJIA). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):

i. The patient has tried one other systemic agent for this condition; AND

Note: Examples of one other systemic agent tried include a corticosteroid (oral, IV), a conventional synthetic disease-modifying antirheumatic drug (DMARD) [e.g., methotrexate {MTX}, leflunomide, sulfasalazine], or a 1-month trial of a nonsteroidal anti-inflammatory drug (NSAID). A previous trial of a biologic such as Kineret (anakinra SC injection), a tumor necrosis factor (TNF) inhibitor (e.g., an etanercept product, an adalimumab product, or an infliximb product, or Ilaris [canakinumab for SC injection]) also counts towards a trial of one other systemic agent for SJIA.

ii. Actemra SC is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Actemra (IV or SC). Approve for 3 years if the patient has had a response, as determined by the prescriber.

Note: Examples of response include improvement in limitation of motion; less joint pain or tenderness; decreased duration of morning stiffness or fatigue; improved function or activities of daily living; reduced dosage of corticosteroids; less joint pain or tenderness; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values. The patient may not have a full response, but there should have been a recent or past response to Actemra IV or SC.

Other Uses with Supportive Evidence

5. Polymyalgia Rheumatica (PMR). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i and ii):

i. The patient has tried one systemic corticosteroid.

Note: An example of a systemic corticosteroid is prednisone; AND

ii. Actemra SC is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Actemra (IV or SC). Approve for 1 year if the patient has had a response, as determined by the prescriber.

Note: Examples of response include reduced corticosteroid dose, normalization of acute phase reactants (e.g., erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]), reduction or resolution of signs or symptoms of PMR. The patient may not have a full response, but there should have been a recent or past response to Actemra (SC or IV).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Actemra SC has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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 biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lack of controlled trial data in support of additive efficacy.[12] Note: 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).** Forward all requests to the Medical Director.
   Note: This includes requests for cytokine release syndrome associated with COVID-19.

2. **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] ≥ 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.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondlylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Sytemice juvenile idiopathic arthritis; UC – Ulcerative colitis. ^ Off-label use of SJIA supported in guidelines.