VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

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

TAC APPROVAL DATE: 03/27/2019

OVERVIEW

Actemra for subcutaneous (SC) injection is a recombinant humanized interleukin-6 (IL-6) receptor inhibitor indicated for the following conditions:[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 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. Sustained remission at Week 52 was achieved in 56% of patients who received Actemra SC QW + 26-week prednisone taper and 53% of patients who received Actemra QOW + 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.[2-3] 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

Actemra features in the guidelines for inflammatory and other conditions.

- The 2011 ACR recommendations for the treatment of JIA (published prior to the approval of Actemra IV for PJIA) propose initial DMARD treatment with MTX in most patients; however, sulfasalazine is recommended for patients with enthesitis-related arthritis and may also be used in certain patients with sacroiliac arthritis.[8]
- Updated guidelines from the American College of Rheumatology (ACR) for treatment of SJIA (2013) 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; NSAIDs, systemic glucocorticoids, Kineret, TNFis, and MTX are among other treatment options.[9]
- Guidelines from the American College of Rheumatology (ACR) [2015] for RA have 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 (Tb).

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.

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 (e.g., 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 (e.g., 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), as determined by the prescriber. 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 (e.g., methotrexate [MTX], sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug [NSAID]).
NOTE: A biologic (e.g., an etanercept product [Enbrel, Erelzi], an adalimumab product [Humira], Orencia [abatacept IV infusion, abatacept SC injection], an infliximab product [Remicade, Inflectra, Renflexis], or Kineret [anakinra SC injection]) 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) [e.g., pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias], sulfasalazine, or leflunomide; OR

d) The patient has aggressive disease, as determined by the prescribing physician; 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 (e.g., has 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), as determined by the prescriber. 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 (e.g., methotrexate [oral or injectable], leflunomide, hydroxychloroquine, and sulfasalazine).
NOTE: 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 (e.g., Cimzia [certolizumab pegol SC injection], an etanercept product [e.g., Enbrel], adalimumab product [e.g., Humira], infliximab product [e.g., Remicade, Renflexis, Inflectra], Simponi [golimumab SC injection], Simponi Aria [golimumab IV infusion], Kevzara [sarilumab SC injection], Kineret [anakinra SC injection], Orencia [abatacept IV infusion; abatacept SC injection], or a rituximab product [e.g, Rituxan, Truxima]. These patients who have already tried a biologic for RA are not required to "step back" and try a conventional synthetic DMARD); AND

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 (e.g., 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), as determined by the prescriber. 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 (e.g., 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]);
       NOTE: A previous trial of a biologic such as Kineret (anakinra SC injection), a tumor necrosis factor (TNF) inhibitor (e.g., an etanercept product [Enbrel, Erelzi], an adalimumab product [Humira], or an infliximb product [e.g., Remicade, Inflectra, Renflexis], or Ilaris [canakinumab for SC injection]) also counts towards a trial of one other systemic agent for SJIA; 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 (e.g., has 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), as determined by the prescriber. 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 (e.g., 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 (e.g., 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), as determined by the prescriber. 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 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 DMRADs 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., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Actemra SC.

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.

REFERENCES

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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.
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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.
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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.
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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.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Selected revision	Add criteria for GCA and PMR, to approve for 6 months of initial therapy if the patient has tried corticosteroids and if prescribed by or in consultation with a rheumatologist (for PMR, evidence of large-vessel vasculitis also required). Continuation of therapy is authorized if the patient has a response to therapy.	06/07/2017
Annual revision	For **RA**, Kevzara was added as an example of an agent that may have been tried prior to Actemra SC. Humira, Enbrel, Remicade, and Rituxan were reworded as adalimumab, etanercept, infliximab, and rituximab products, respectively, with the innovator names listed as examples of these products. Renflexis and Inflectra were also added as examples of an infliximab product.	10/11/2017
Early annual revision	Add criteria for **PJIA**. Criteria approve for initial therapy (4 months) if prescribed by or in consultation with a rheumatologist, and if another therapy has been tried (e.g., MTX, sulfasalazine, or leflunomide, an NSAID, or a biologic disease-modifying antirheumatic drug [prior use of a biologic agent would count towards this requirement]), or Actemra SC is started in combination with a csDMARD, or the patient has aggressive disease, as determined by the prescriber. Patients currently taking Actemra IV or SC can get authorization for 3 years if there has been a response to therapy. Due to the approval in PJIA, remove this indication from the conditions not recommended for coverage.	05/23/2018
Selected revision	**PMR:** Due to overlap of GCA and PMR and updated guidelines for diagnosis, remove requirement that patients with PMR have imaging results suggestive of large vessel vasculitis.	09/05/2018
Selected revision	**SJIA:** Criteria were added to approve for this FDA-approved indication. Initial approval is for 3 months if a systemic agent has been tried, and if Actemra SC is prescribed by or in consultation with a rheumatologist. For patients currently taking Actemra IV or SC, the approval is for 3 years if the patient has responded to therapy. Due to this approval, SJIA was removed from the conditions not recommended for coverage.	09/19/2018
Early annual revision	**Rheumatoid Arthritis:** Add Truxima as an example of a rituximab product.	03/27/2019

* For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; TAC – Therapeutic Assessment Committee; RA – Rheumatoid arthritis; DMARD – Disease-modifying antirheumatic drug; SC – Subcutaneous; TNFi – Tumor necrosis factor inhibitor; GCA – Giant cell arteritis; PMR – Polymyalgia rheumatic;

APPENDIX

Brand (generic name)	Mechanism of Action
Cimzia® (certolizumab pegol for SC injection)	Inhibition of TNF
Enbrel® (etanercept for SC injection)	Inhibition of TNF
Erelzi™ (etanercept-szzs for SC injection)	Inhibition of TNF
Humira® (adalimumab for SC injection)	Inhibition of TNF
Amjevita® (adalimumab-atto for SC injection)	Inhibition of TNF
Cyltezo® (adalimumab-adbm for SC injection)	Inhibition of TNF
Simponi® (golimumab for SC injection)	Inhibition of TNF
Simponi® Aria™ (golimumab for IV infusion)	Inhibition of TNF
Remicade® (infliximab for IV infusion)	Inhibition of TNF
Inflectra™ (infliximab-dyyb for IV infusion)	Inhibition of TNF
Renflexis® (infliximab-abda for IV infusion)	Inhibition of TNF
Actemra® (tocilizumab for IV infusion)	Inhibition of IL-6
Actemra® (tocilizumab for SC injection)	Inhibition of IL-6
Kevzara® (sarilumab for SC injection)	Inhibition of IL-6
Orencia® (abatacept for IV infusion)	T-cell costimulation modulator
Orencia® (abatacept for SC injection)	T-cell costimulation modulator
Rituxan® (rituximab for IV infusion)	CD20-directed cytolytic antibody
Truxima® (rituximab-abbs injection for intravenous use)	CD20-directed cytolytic antibody
Kineret® (anakinra for subcutaneous SC injection)	Inhibition of IL-1
Stelara® (ustekinumab for SC injection)	Inhibition of IL-12/23
Stelara® (ustekinumab for IV infusion)	Inhibition of IL-12/23
Siliq™ (brodalumab SC injection)	Inhibition of IL-17
Cosentyx™ (secukinumab for SC injection)	Inhibition of IL-17A
Taltz® (ixekizumab for SC injection)	Inhibition of IL-17A
Tremfya™ (guselkumab for SC injection)	Inhibition of IL-23
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23
Otezla® (apremilast tablets)	Inhibition of PDE4
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathway
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways

SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin;PDE4 – Phosphodiesterase 4; JAK – Janus kinase.