VENTURA COUNTY HEALTH CARE PLAN

Utilization Review Policy

POLICY: Inflammatory Conditions – Actemra® (tocilizumab intravenous infusion – Genentech/Roche)

DATE REVIEWED: 03/25/2020

OVERVIEW

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

1. Cytokine release syndrome, in patients ≥ 2 years of age with severe or life-threatening disease associated with chimeric antigen receptor (CAR) T-cell therapy; AND
2. Polyarticular juvenile idiopathic arthritis (PJIA), for the treatment of active in patients 2 years of age and older; AND
3. 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
4. Systemic juvenile idiopathic arthritis (SJIA), for the treatment of active disease in patients two years of age and older.

Actemra IV has been shown to inhibit and slow structural joint damage, improve physical function, and achieve a major clinical response in patients taking methotrexate (MTX). In RA, Actemra IV can be given alone or in combination with other nonbiologic DMARDs. For PJIA and SJIA, Actemra IV can be given alone or in combination with MTX. Actemra is also available as a subcutaneous (SC) formulation which, in addition to RA, is indicated for giant cell arteritis (GCA).

Disease Overview

Targeting IL-6 is a therapeutic option for treatment of chronic inflammatory diseases such as RA.[2] IL-6 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 is an IL-6 receptor monoclonal antibody that binds to soluble and membrane-bound IL-6 receptors and has been shown to inhibit IL-6-mediated signaling through these receptors.[1] In CRS (reported in 79% to 94% of patients receiving CAR T-cell therapy), there are high levels of IL-6; therefore, IL-6 signaling is inhibited with Actemra IV.[1,3-5]

Dosing Information

In RA, many dose modifications are recommended for the management of dose-related laboratory changes such as increased liver enzymes, neutropenia, and thrombocytopenia.[1] In conditions other than RA, reduced dosing of Actemra IV generally follows the receommendations for RA. Dose interruptions of Actemra IV are recommended for certain laboratory abnormalities and are similar to those recommended in RA. Dosing modifications are determined by the prescriber. Specifically for cytokine release syndrome associated with CAR T-cell therapy, the median number of Actemra IV doses administered in the pivotal trial was one dose (range, 1 to 4 doses).

Guidelines

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

- Cytokine Release Syndrome: The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for Management of Immunotherapy-Related Toxicities (version 1.2020 – December 16, 2019) give specific recommendations for use of Actemra in the

management of inflammatory arthritis, cytokine release syndrome, and CAR T-cell-related toxicities.[6]
    - For immune checkpoint inhibitor-related inflammatory arthritis, infliximab or Actemra may be considered for refractory or severe arthritis not responding to steroids and anti-inflammatory agents.
- 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.[7] 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.
- 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).[9]
- 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.[8] Nonsteroidal anti-inflammatory drugs NSAIDs, systemic glucocorticoids, Kineret, TNF inhibitors, and MTX are among other treatment options.
- Castleman's Disease: The NCCN clinical practice guidelines for B-cell Lymphomas (version 1.2020 – January 22, 2020) mention Actemra as a second-line therapy for relapsed or refractory unicentric Castleman's disease in patients who are HIV- and HHV-8-negative.[10] For multicentric Castleman's disease (MCD), the guidelines list Actemra as a subsequent therapy for relapsed, refractory, or progressive MCD.

Other Uses With Supportive Evidence

Still's disease presents in adults with features similar to those of SJIA.[11] Actemra IV has been effective in reducing fever, symptoms, and markers of inflammation in patients who were refractory to treatment with prednisone, MTX, Kineret, and/or a TNF antagonist.[11-20] Prospective, randomized, controlled trials are needed.

COVID-19 (Coronavirus Disease 2019)

COVID-19 is a novel coronavirus that has not previously been identified and with no approved treatments.[24] COVID-19 can cause mild to severe illness, including symptoms of fever, cough, shortness of breath, myalgia, and/or fatigue. In COVID-19, the body may respond to the virus by overproducing immune cells and their signaling molecules in a phenomenon called cytokine release storm.[25] By inhibiting IL-6, Actemra is speculated to associated with better clinical outcomes, such as decreased systemic inflammation, improved survival rate, better hemodynamic and improved of respiratory distress. Clinical trials are underway evaluating Actemra in patients with severe or critical cytokine release syndrome.

In a retrospective analysis from China, 21 patients with severe or critical COVID-19 were treated with Actemra IV (18 patients received one dose [400 mg IV] and 3 patients received a second dose within 12 hours).[26] All patients had a 1-week history of routine treatment prior to Actemra. All patients received standard therapy, including lopinavir, methylprednisolone, other symptom relievers, and oxygen therapy. The mean age of enrolled patients was 57 years (range 25 to 88 years), and the majority (n = 18/21) were male. Overall, 17 patients were categorized with severe disease (defined as respiratory rate ≥ 30 breaths/min, peripheral oxygen saturation [SpO2] ≤ 93% [room air], and/or partial pressure of arterial oxygen/percentage of inspired oxygen [PaO2/FiO2] ≤

300 mmHg). There were also four patients categorized as critical (defined as respiratory failure requiring mechanical ventilation; shock; or intensive care unit admission combined with other organ failure). All patients had abnormal computed tomography (CT) of the chest, primarily with plaque-like, ground-glass opacities and focal consolidation, mainly distributed in the peripheral (especially the subpleural) region. Mean IL-6 expression levels (132.38 ± 278.54 pg/ml) prior to administration of Actemra suggested upregulation of IL-6. Body temperature of all patients normalized on the first day after receiving Actemra and remained stable thereafter. After treatment, CT scans showed that the chest lesions were absorbed in 19 patients (90.5%). At the time this analysis was published, 19 patients (90.5%) were discharged (average of 13.5 days after the treatment with Actemra) and the remaining patients continued to recover. There have been no reports of subsequent pulmonary infection, deterioration of illness, or death.

Safety

Actemra has boxed warnings concerning risks of serious infection.[1] Prior to initiating therapy, patients should be evaluated for active tuberculosis (TB) infection, and periodically during therapy patients should be assessed for latent TB infection. If a serious infection develops, treatment with Actemra should be interrupted until infection is controlled. The prescribing information for Kymriah and Yescarta have Boxed Warnings regarding CRS that may be severe or life-threatening.[3-4] Both have a Risk Evaluation and Mitigation Strategy (REMS) which requires at least two doses of Actemra on hand prior to infusion and during the recovery process.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Actemra IV. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Actemra IV as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Actemra IV to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **Cytokine Release Syndrome (CRS) Associated with Chimeric Antigen Receptor (CAR) T-Cell Therapy.** Approve Actemra IV for 1 week (which is adequate duration to receive 4 doses) if prescribed for a patient who has been or will be treated with a chimeric antigen receptor (CAR) T-cell therapy.
   Note: Examples of CAR T-cell therapy include Kymriah™ (tisagenlecleucel IV suspension) and Yescarta™ (axicabtagene ciloleucel IV suspension). If the patient has **CRS due to COVID-19** (coronavirus disease 2019) refer to criteria for Other Uses With Supportive Evidence (below).

Dosing. Approve the following regimens:
A) Each individual dose must meet the following (i or ii):
  i. *Patient is < 30 kg:* Approve up to 12 mg/kg to a maximum of 800 mg per dose.
  ii. *Patient is ≥ 30 kg*: Approve up to 8 mg/kg to a maximum of 800 mg per dose.
B) Approve up to four doses if there will be an interval of at least 8 hours between doses.

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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 PJIA) also counts as a trial of one agent for PJIA; OR
    b) The patient will be starting on Actemra IV 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. The agent is prescribed by or in consultation with a rheumatologist.
B) Patients 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 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.

Dosing. Approve dosing that meets the following (A and B):
A) Each individual dose must meet the following (i or ii):
  i. *Patient is < 30 kg*: Approve up to 10 mg/kg up to a maximum of 800 mg per dose.
  ii. *Patient is ≥ 30 kg*: Approve up to 8 mg/kg up to a maximum of 800 mg per dose.
B) There must be an interval of at least 4 weeks between doses.

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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.
  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 had a 3-month trial of 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; AND

iii. The agent is prescribed by or in consultation with a rheumatologist.

B) Patients 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 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 IV or SC.

Dosing. Approve dosing that meets the following (A and B):

A) Approve up to 8 mg/kg to a maximum of 800 mg per dose; AND

B) There must be an interval of at least 4 weeks between doses.

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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. The agent is prescribed by or in consultation with a rheumatologist.

B) Patients 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 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.

Dosing. Approve the following dosing regimens:

A) Each individual dose must meet the following (i or ii):

i. *Patient is < 30 kg*: Approve up to 12 mg/kg per dose.

ii. *Patient is ≥ 30 kg*: Approve up to 8 mg/kg per dose.

B) There must be an interval of at least 1 week between doses.

Other Uses with Supportive Evidence

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5. Castleman's Disease. Approve for the duration noted if the patient meets ONE of the following conditions (A or B):

A) Initial Approval. Approve for 4 months if the agent is prescribed by or in consultation with an oncologist or hematologist; OR

B) Patient is Currently Receiving Actemra (IV or SC). Approve for 1 year if the patient has responded, as determined by the prescriber.
Note: Examples of response include normalization of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, albumin, and hemoglobin; resolution of constitutional symptoms; increased body mass index (BMI), and reduction in lymphadenopathy.

Dosing. Approve the following dosing regimen:

A) Approve up to 8 mg/kg per dose.

B) There must be an interval of at least 1 week between doses.

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5. COVID-19 (Coronavirus Disease 2019). Approve for 1 week if, according to the prescriber, the patient has cytokine release syndrome associated with COVID-19.
Note: Denials for patients diagnosed with COVID-19 are forwarded to the Medical Director.

Dosing. Approve the requested dose.

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6. Inflammatory Arthritis Associated with Checkpoint Inhibitor Therapy. Approve for 3 months if the patient meets ONE of the following (A or B):
Note: Examples of checkpoint inhibitors are Keytruda (pembrolizumab IV infusion), Opdivo (nivolumab IV infusion), Yervoy (ipilimumab IV infusion), Tecentriq (atezolizumab IV infusion), Bavencio (avelumab IV infusion), Imfinzi (durvalumab IV infusion), and Libtayo® (cemiplimab-rwlc IV infusion).

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

i. The patient is symptomatic despite a trial of at least ONE systemic corticosteroid.
Note: Examples of a corticosteroid include methylprednisolone and prednisone; AND

ii. The patient has tried at least ONE systemic nonsteroidal anti-inflammatory agent (NSAID).
Note: Examples of systemic NSAIDs include ibuprofen and naproxen; AND

iii. The agent is prescribed by or in consultation with a rheumatologist or an oncologist.

B) Patients 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 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 IV or SC.

Dosing. Approve dosing that meets the following (A and B):

A) Approve up to 8 mg/kg to a maximum of 800 mg per dose.

B) There must be an interval of at least 4 weeks between doses.

7. **Still's Disease.** Approve for the duration noted if the patient meets the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):
     - **i.** The patient has tried one corticosteroid; AND
     - **ii.** The patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) such as methotrexate (MTX) given for at least 2 months or was intolerant to a conventional synthetic DMARD; AND
     - **iii.** The agent is prescribed by or in consultation with a rheumatologist; OR
   - **B)** Patients Currently Receiving Actemra (IV or SC). Approve for 1 year if the patient has responded, as determined by the prescriber.
     Note: Examples of response include normalization of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or ferritin serum levels; decrease in number of tender or swollen joints; resolution of fever.

Dosing. Approve dosing that meets the following (A and B):
- **A)** Approve up to 8 mg/kg per dose.
- **B)** There must be an interval of at least 2 weeks between doses.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Actemra IV 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 IV another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see **Appendix** for examples). 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.[21-22]
   Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate [MTX], leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Actemra IV.

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 CRP) were randomized, in a double-blind fashion to Actemra 8 mg/kg IV every 2 weeks; or alternating infusions of Actemra 8 mg/kg IV every 4 weeks and placebo (i.e., alternating with placebo every 2 weeks), or to placebo every 2 weeks.[23] 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, four patients on Actemra IV every 4 weeks and one patient on Actemra IV every 2 weeks dropped out. The mean reduction in the CDAI score in the Actemra 8 mg/kg IV 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

1. Actemra® injection for intravenous infusion [prescribing information]. South San Francisco, CA: Genentech; June 2019.
2. Schoels MM, van der Heijde D, Breedveld FC, et al. Blocking the effects of interleukin-6 in rheumatoid arthritis and other inflammatory rheumatic diseases: systematic literature review and meta-analysis informing a consensus statement. *Ann Rheum Dis*. 2013;72(4):583-589.
3. Yescarta™ suspension for intravenous infusion [prescribing information]. Santa Monica, CA: Kite Pharma; May 2019.
4. Kymriah™ suspension for intravenous infusion [prescribing information]. East Hanover, NJ: Novartis Oncology; June 2019.
5. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-195.
6. The NCCN Management of Immunotherapy-Related Toxicities Clinical Practice Guidelines in Oncology (Version 1.2020 – December 16, 2019). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 2, 2020.
7. 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.
8. 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.
9. Singh J, Saag K, Bridges Jr. SL, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2016;68(1):1-25.
10. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 2, 2020.
11. Riera E, Olivé A, Narváez J, et al. Adult onset Still's disease: review of 41 cases. *Clin Exp Rheumatol*. 2011;29(2):331-336.
12. Puéchal X, de Bandt M, Berthelot JM, et al. Tocilizumab in refractory adult Still's disease. *Arthritis Care Res (Hoboken)*. -2011;63(1):155-159.
13. Perdan-Pirkmajer K, Praprotnik S, Tomšič M. A case of refractory adult-onset Still's disease successfully controlled with tocilizumab and a review of the literature. *Clin Rheumatol*. 2010;29(12):1465-1467.
14. Sabnis GR, Gokhale YA, Kulkarni UP. Tocilizumab in Refractory Adult-Onset Still's Disease with Aseptic Meningitis-Efficacy of Interleukin-6 Blockade and Review of the Literature. *Semin Arthritis Rheum*. 2011;40(4):365-368.
15. De Bandt M, Saint-Marcoux B. Tocilizumab for multirefractory adult-onset Still's disease. *Ann Rheum Dis*. 2009;68(1):153-154.
16. Yoshimura M, Makiyama J, Koga T, et al. Successful treatment with tocilizumab in a patient with refractory adult-onset Still's disease (AOSD). *Clin Exp Rheumatol*. 2010;28(1):141-142.
17. Nakahara H, Mima T, Yoshio-Hoshino N, et al. A case report of a patient with refractory adult-onset Still's disease who was successfully treated with tocilizumab over 6 years. *Mod Rheumatol*. 2009;19(1):69-72.

18. Matsumoto K, Nagashima T, Takatori S, et al. Glucocorticoid and cyclosporine refractory adult onset Still's disease successfully treated with tocilizumab. *Clin Rheumatol*. 2009;28(4):485-487.
19. Iwamoto M, Nara H, Hirata D, et al. Humanized monoclonal anti-interleukin-6 receptor antibody for treatment of intractable adult-onset Still's disease. *Arthritis Rheum*. 2002;46(12):3388-3389.
20. Rech J, Ronneberger M, Englbrecht M, et al. Successful treatment of adult-onset Still's disease refractory to TNF and IL-1 blockade by IL-6 receptor blockade. *Ann Rheum Dis*. 2011;70(2):390-392.
21. 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.
22. Xeljanz® tablets [prescribing information]. New York, NY: Pfizer Inc; February 2016.
23. 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.
24. Centers for Disease Control and Prevention (Web site). Coronavirus (COVID-19). Updated March 22, 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/index.html/. Accessed on March 23, 2020.
25. US National Institutes of Health. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2020 Mar 23]. Available from: https://clinicaltrials.gov/ct2/results?cond=Coronavirus&term=tocilizumab&cntry=&state=&city=&dist=. Search terms: coronavirus, tocilizumab.
26. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Available at: file:///C:/Users/MMedina/Downloads/202003.00026v1%20(1).pdf. Accessed on March 23, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	Add approval criteria for Inflammatory Arthritis associated with checkpoint inhibitors (3 months initial) if the patient has tried at least one steroid and at least one nonsteroidal anti-inflammatory drug and if prescribed by or in consultation with a rheumatologist or an oncologist; approval is for 1 year if patient is currently responding to therapy. Throughout the policy, references to Humira, Enbrel, and Rituxan were reworded as adalimumab, etanercept, and rituxumab products, respectively, with the innovator names listed as examples of these products. Renflexis and Erelzi were also added as respective examples of infliximab and etanercept products. Abatacept SC was added as an example of a biologic that a patient may have previously tried for Polyarticular Juvenile Idiopathic Arthritis. Kevzara was added as examples of a biologic that a patient may have previously tried for Rheumatoid Arthritis. For Systemic Juvenile Idiopathic Arthritis, the criterion that directs patients to a systemic agent prior to approval was reworded to clarify its intent such that patients are now directed to a systemic agent, with conventional synthetic disease-modifying antirheumatic drugs, corticosteroids, and nonsteroidal anti-inflammatory drugs listed as examples. A note was added that prior use of a biologic agent would count towards this requirement; previously, criteria were worded more generally as a "systemic" agent and both conventional and biologic agents were listed together as examples.	03/21/2018
Annual revision	**Rheumatoid Arthritis:** Add Truxima as an example of a rituximab product. **Inflammatory Arthritis Associated with Checkpoint Inhibitor Therapy:** Add Yervoy, Tecentriq, Bavencio, Imfinzi, and Libtayo as examples of checkpoint inhibitors. **Patients Established on Actemra IV or SC:** Remove this criterion for patients currently established on Actemra for ≥ 90 days. Patients currently taking Actemra are now addressed in the criteria section for each specific indication. **Dosing Section:** • Cytokine Release Syndrome, Polyarticular Juvenile Idiopathic Arthritis, Rheumatoid Arthritis, Systemic Juvenile Idiopathic Arthritis, Inflammatory Arthritis Associated with Checkpoint Inhibitor Therapy, Still's Disease, Castleman's Disease: In the dosing section, adjust approval to allow for approval of up to the maximal weight-based dose (previously required dose to be the listed weight-based dose). • Castleman's Disease, Still's Disease: In the dosing section, change the treatment interval to be the shortest allowed interval.	03/27/2019
Annual revision	**Cytokine Release Syndrome:** This condition was clarified to specify that it must be Associated with Chimeric Antigen Receptor (CAR) T-Cell Therapy to be reviewed under this condition for coverage. Examples of chimeric antigen receptor T-cell therapy were moved to a Note in the policy (previously listed as examples within the criteria). **Polyarticular Juvenile Idiopathic Arthritis:** For the exception applying to patients with aggressive disease, wording was updated to more generally allow this determination by the	03/25/2020

	prescriber (criteria previously specified this was according to the prescribing physician). Examples of one other agent tried for Polyarticular Juvenile Idiopathic Arthritis were moved to a Note in the policy (previously listed as examples within the criteria). Examples of biologics for Polyarticular Juvenile Idiopathic Arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section). Examples of an absolute contraindication to methotrexate, sulfasalazine, or leflunomide were move to a Note in the policy (previously listed as examples within the criteria). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). For the Dosing Note, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). **Rheumatoid Arthritis:** Examples of conventional synthetic disease-modifying antirheumatic drugs were moved to a Note in the policy (previously listed as examples within the criteria). Examples of biologics for Rheumatoid Arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). For the Dosing Note, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). **Systemic Juvenile Idiopathic Arthritis:** Examples of one other systemic agent tried for Systemic Juvenile Idiopathic Arthritis were moved to a Note in the policy (previously listed as examples within the criteria). For the Dosing Note, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). **Castleman's Disease:** For the exception applying to patients currently receiving Actemra who have responded, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). **Inflammatory Arthritis Associated with Checkpoint Inhibitor Therapy:** Examples of a steroid were moved to a Note in the policy (previously listed as examples within the criteria). Examples of a nonsteroidal anti-inflammatory agent were moved to a Note in the policy (previously listed as examples within the criteria). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). For the Dosing Note, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Criteria requiring a previous therapy were clarified to specify systemic therapies must have been tried (i.e., systemic corticosteroid, systemic NSAID). **Still's Disease:** For the exception applying to patients currently receiving Actemra who have responded, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). **COVID-19:** This off-label indication was added to the policy as an approval if the patient has cytokine release syndrome.	

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 spondylitis; 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.