UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Inflammatory Conditions – Actemra Intravenous Utilization Management Medical Policy
- Actemra® (tocilizumab intravenous infusion – Genentech/Roche)

REVIEW DATE: 05/10/2023

OVERVIEW

Actemra intravenous infusion, an interleukin-6 (IL-6) receptor inhibitor, is indicated for the following conditions:[1]

- **Coronavirus Disease 2019 (COVID-19)**, in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).
- **Cytokine release syndrome**, in patients ≥ 2 years of age with severe or life-threatening disease associated with chimeric antigen receptor (CAR) T-cell therapy.
- **Giant cell arteritis** 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.

Dosing Information

In rheumatoid arthritis, 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 rheumatoid arthritis, reduced dosing of Actemra intravenous generally follows the recommendations for rheumatoid arthritis. Dose interruptions of Actemra intravenous are recommended for certain laboratory abnormalities and are similar to those recommended in rheumatoid arthritis. Dosing modifications are determined by the prescriber. Specifically for cytokine release syndrome associated with CAR T-cell therapy, the median number of Actemra intravenous doses administered in the pivotal trial was one dose (range, 1 to 4 doses).

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.

- **Cytokine Release Syndrome:** The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for Management of Immunotherapy-Related Toxicities (version 1.2023 – March 10, 2023) give specific recommendations for use of Actemra in the management of inflammatory arthritis, cytokine release syndrome, and CAR T-cell-related toxicities.[6]
  - For cytokine release syndrome and CAR T-cell-related toxicities, Actemra is recommended for all grades of disease.
  - For immune checkpoint inhibitor-related inflammatory arthritis, infliximab and Actemra are among the alternatives that may be considered for severe arthritis not responding to steroids.
- **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.[25] 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.[31,32] 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.

- **Polyarticular Juvenile Idiopathic Arthritis:** Guidelines for the treatment of juvenile idiopathic arthritis from the American College of Rheumatology (ACR) [2021] address oligoarthritis and temporomandibular joint (TMJ) arthritis.[31] For oligoarthritis, a biologic is recommended following a trial of a conventional synthetic DMARD. In patients with TMJ arthritis, scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular glucocorticoids are recommended first-line. A biologic is a therapeutic option if there is an inadequate response or intolerance. Additionally, rapid escalation to a biologic ± conventional synthetic DMARD (methotrexate preferred) is often appropriate given the impact and destructive nature of TMJ arthritis. In these guidelines, there is not a preferred biologic that should be initiated for JIA. ACR/Arthritis Foundation has guidelines for the treatment of juvenile idiopathic arthritis (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.
- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic DMARD for a patient taking the maximum tolerated dose of methotrexate who is not at target.[9]
- **Systemic Juvenile Idiopathic Arthritis:** Guidelines for the treatment of JIA from the ACR (2021) address systemic juvenile idiopathic arthritis (SJIA).[31] A brief trial of NSAIDs and/or an interleukin (IL)-1 or IL-6 inhibitor are recommended as initial monotherapy for patients with SJIA without macrophage activation syndrome. In a patient who presents with macrophage activation syndrome, an IL-1 or IL-6 blocker and/or systemic glucocorticoids are recommended.
- **Castleman's Disease:** The NCCN clinical practice guidelines for B-cell Lymphomas (version 2.2023 – February 8, 2023) mention Actemra as a second-line therapy for relapsed or refractory unicentric Castleman's disease in patients who are negative for the human immunodeficiency virus and human herpesvirus-8.[10] For multicentric Castleman's disease, the guidelines list Actemra as a subsequent therapy for relapsed, refractory, or progressive disease.
- **COVID-19 (Coronavirus Disease 2019):** By inhibiting IL-6, Actemra is speculated to be associated with better clinical outcomes in COVID-19, such as decreased systemic inflammation, improved survival rate, better hemodynamics, and improvement of respiratory distress.[24]
- **Stills Disease:** 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, methotrexate, Kineret, and/or a tumor necrosis factor inhibitor.[11-20]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Actemra intravenous. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. 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 a patient treated with Actemra intravenous as well as the monitoring required

for adverse events and long-term efficacy, initial approval requires Actemra intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

*Indications and/or approval conditions noted with **[eviCore]** are managed by eviCore healthcare for those clients who use eviCore for oncology and/or oncology-related reviews. For these conditions, a prior authorization review should be directed to eviCore at www.eviCore.com.*

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **COVID-19 (Coronavirus Disease 2019) – Hospitalized Patient.** For a patient who is hospitalized, forward all requests to the Medical Director. For a non-hospitalized patient, do not approve (refer to Conditions Not Recommended for Approval – COVID-19 – Non-Hospitalized Patient). Actemra intravenous is indicated for COVID-19 only in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[1] For COVID-19, the dose is 8 mg/kg (to a maximum of 800 mg) given as a single intravenous infusion. A second dose may be administered at least 8 hours after the initial infusion if clinical signs or symptoms worsen or do not improve after the first dose.
   Note: This includes requests for cytokine release syndrome in a patient hospitalized with COVID-19.

2. **Cytokine Release Syndrome Associated with Chimeric Antigen Receptor (CAR) T-Cell Therapy.** ***[eviCore]*** Approve for 1 week (which is adequate duration to receive four doses) if prescribed for a patient who has been or will be treated with a CAR T-cell therapy.
   Note: Examples of CAR T-cell therapy include Abecma (idecabtagene vicleucel injection), Breyanzi (lisocabtagene maraleucel intravenous infusion), Kymriah (tisagenlecleucel intravenous infusion), Tecartus (brexucabtagene intravenous infusion), and Yescarta (axicabtagene ciloleucel intravenous infusion). If the patient has **Cytokine Release Syndrome 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.

3. **Giant Cell Arteritis.** 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 BOTH of the following (i and ii):
      i. Patient has tried one systemic corticosteroid; AND
      Note: An example of a systemic corticosteroid is prednisone.
      ii. The medication is prescribed by or in consultation with a rheumatologist.
   B) Patient is Currently Receiving Actemra (Subcutaneous or Intravenous). Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Actemra); OR
Note: Examples of objective measures are serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), resolution of fever, and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating Actemra), patient experienced an improvement in at least one symptom, such as decreased headache, scalp, or jaw pain; decreased fatigue; and/or improved vision.

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

A) Approve up to 6 mg/kg to a maximum of 600 mg per dose; AND

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

4. Polyarticular Juvenile Idiopathic Arthritis. 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 BOTH of the following (i and ii):

i. Patient meets one of the following conditions (a, b, c, or d):

a) Patient has tried one other systemic therapy for this condition; OR
Note: Examples of other systemic therapies include methotrexate, sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug (NSAID). A biologic (refer to **Appendix** for examples of biologics used for polyarticular juvenile idiopathic arthritis) also counts as a trial of one systemic therapy.

b) Patient will be starting on Actemra intravenous concurrently with methotrexate, sulfasalazine, or leflunomide; OR

c) Patient has an absolute contraindication to methotrexate, sulfasalazine, or leflunomide; OR
Note: Examples of absolute contraindication to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, and blood dyscrasias.

d) Patient has aggressive disease, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Actemra Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Actemra); OR
Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating Actemra), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less joint pain or

tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living.

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.

5. Rheumatoid Arthritis. 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 both of the following (i and ii):
- **i.** 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 had a 3-month trial of at least one biologic (refer to **Appendix** for examples of biologics used for rheumatoid arthritis). A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD.
- **iii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Actemra Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on therapy for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least ONE of the following (a or b):
  - **a)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
    Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).
  - **b)** Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

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.

6. Systemic Juvenile Idiopathic Arthritis. 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 other systemic therapy for this condition; AND
  Note: Examples of other systemic therapies include a corticosteroid (oral, intravenous), a conventional synthetic disease-modifying antirheumatic drug (DMARD) [e.g., methotrexate,

leflunomide, sulfasalazine], or a 1-month trial of a nonsteroidal anti-inflammatory drug (NSAID). A previous trial of a biologic such as Kineret (anakinra subcutaneous injection), a tumor necrosis factor inhibitor (e.g., an etanercept product, an adalimumab product, or an infliximab product, or Ilaris [canakinumab subcutaneous injection]) also counts towards a trial of one other systemic agent for systemic juvenile idiopathic arthritis.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Actemra Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

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

7. Castleman's Disease. ***[eviCore]*** Approve for the duration noted if the patient meets ONE of the following conditions (A or B):

A) Initial Approval. Approve for 6 months if the medication is prescribed by or in consultation with an oncologist or hematologist.

B) Patient is Currently Receiving Actemra Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate, fibrinogen, albumin, and/or hemoglobin), increased body mass index, and/or reduction in lymphadenopathy.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as improvement or resolution of constitutional symptoms (e.g., fatigue, physical function).

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.

8. Inflammatory Arthritis Associated with Checkpoint Inhibitor Therapy. Approve for the duration noted if the patient meets ONE of the following (A or B):
Note: Examples of checkpoint inhibitors are Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Yervoy (ipilimumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Bavencio (avelumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), and Libtayo (cemiplimab-rwlc intravenous infusion).
A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
i. Patient is symptomatic despite a trial of at least ONE systemic corticosteroid; AND
Note: Examples of a corticosteroid include methylprednisolone and prednisone.
ii. Patient has tried at least ONE systemic nonsteroidal anti-inflammatory agent (NSAID); AND
Note: Examples of systemic NSAIDs include ibuprofen and naproxen.
iii. The medication is prescribed by or in consultation with a rheumatologist or an oncologist.
B) Patient is Currently Receiving Actemra Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):
i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
ii. Patient meets at least ONE of the following (a or b):
a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate) and/or reduced dosage of corticosteroids.
b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

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.

9. Polymyalgia Rheumatica. 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 BOTH of the following (i and ii):
i. Patient has tried one systemic corticosteroid; AND
Note: An example of a systemic corticosteroid is prednisone.
ii. The medication is prescribed by or in consultation with a rheumatologist.
B) Patient is Currently Receiving Actemra (Subcutaneous or Intravenous). Approve for 1 year if the patient meets BOTH of the following (i and ii):
i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Actemra); OR
Note: Examples of objective measures are serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), resolution of fever, and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating Actemra), patient experienced an improvement in at least one symptom, such as decreased shoulder, neck, upper arm, hip, or thigh pain or stiffness; improved range of motion; and/or decreased fatigue.

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

A) Approve up to 6 mg/kg to a maximum of 600 mg per dose; AND

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

10. Still's Disease. Approve for the duration noted if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient has tried one corticosteroid; AND

ii. Patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) such as methotrexate given for at least 2 months or was intolerant to a conventional synthetic DMARD; AND

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

B) Patient is Currently Receiving Actemra Intravenous or Subcutaneous. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on this medication for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

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

Coverage of Actemra Intravenous is not recommended in the following situations:

1. COVID-19 (Coronavirus Disease 2019) – Non-Hospitalized Patient. Actemra intravenous is only indicated in hospitalized adults with COVID who are receiving systemic corticosteroids and requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[1] For COVID-19, the dose is 8 mg/kg (to a maximum of 800 mg) given as a single intravenous infusion. A second dose may be administered at least 8 hours after the initial infusion if clinical signs or symptoms worsen or do not improve after the first dose.

2. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Data are lacking evaluating concomitant use of Actemra intravenous in combination with 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, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Actemra intravenous.

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] ≥ 150 and increased C-reactive protein) were randomized, in a double-blind fashion to Actemra 8 mg/kg intravenous 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.[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 intravenous every 4 weeks and one patient on Actemra intravenous 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

1. Actemra® intravenous infusion [prescribing information]. South San Francisco, CA: Genentech; December 2022.
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™ intravenous infusion [prescribing information]. Santa Monica, CA: Kite Pharma; May 2019.
4. Kymriah™ 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 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 5, 2023.
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. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. *Arthritis Rheumatol*. 2022 Mar 1 [Online ahead of print].
9. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2021;73(7):1108-1123.
10. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 2.2023 – February 8, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 5, 2023.
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; 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). Available at: https://www.cdc.gov/coronavirus/2019-ncov/index.html/. Accessed on May 5, 2023.
25. 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.
26. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A*. 2020;117(20):10970-10975.
27. Strohbehn GW, Heiss BL, Rouhani SJ, et al. COVIDOSE: A Phase II Clinical Trial of Low-Dose Tocilizumab in the Treatment of Noncritical COVID-19 Pneumonia. *Clin Pharmacol Ther*. 2021;109(3):688-696.
28. Dastan F, Saffaei A, Haseli S, et al. Promising effects of tocilizumab in COVID-19: A non-controlled, prospective clinical trial. *Int Immunopharmacol*. 2020;88:106869.
29. Galvan-Roman JM, Rodriguez-Garcia SC, Roy-Vallejo E, et al. IL-6 serum levels predict severity and response to tocilizumab in COVID-19: An observational study. *J Allergy Clin Immunol*. 2021;147(1):72-80.
30. Zhao H, Zhu Q, Zhang C, et al. Tocilizumab combined with favipiravir in the treatment of COVID-19: A multicenter trial in a small sample size. *Biomed Pharmacother*. 2021;133:110825.
31. 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.
32. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med*. 2017 ;377(4):317-328.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Giant Cell Arteritis:** This indication was added to the policy. **Polyarticular Juvenile Idiopathic Arthritis:** Initial approval duration was changed to 6 months (previously was 4 months). Note was clarified to state that a previous trial of a biologic applies to one biologic other than the requested drug. For a patient currently receiving, it was clarified that this applies to a patient who is taking for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Rheumatoid Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to one biologic other than the requested drug. For a patient currently receiving, it was clarified that this applies to a patient who is taking for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Systemic Juvenile Idiopathic Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to one biologic other than the requested drug. For a patient currently receiving, it was clarified that this applies to a patient who is taking for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Castleman's Disease:** Initial approval duration was changed to 6 months (previously was 4 months). For a patient currently receiving, it was clarified that this applies to a patient who is taking for ≥ 6 months. A requirement was added for a patient who is currently receiving	05/04/2022

	to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Inflammatory Arthritis Associated with Checkpoint Inhibitor Therapy:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving, it was clarified that this applies to a patient who is taking for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Polymyalgia Rheumatica:** This indication was added to the policy. **Still's Disease:** Initial approval duration was changed to 6 months (previously was 3 months). Note was clarified to state that a previous trial of a biologic applies to one biologic other than the requested drug. For a patient currently receiving, it was clarified that this applies to a patient who is receiving for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber.	
Selected Revision	**COVID-19 (Coronavirus Disease 2019) – Hospitalized Patient:** To align with recent FDA approval in hospitalized patients with COVID-19, this condition was placed in the FDA-Approved Uses section of the policy. A qualifier that these criteria only apply to hospitalized patients was added. The requirement that, according to the prescriber, the patient has cytokine release syndrome was removed. All potential approvals are now reviewed by a Medical Director. **Conditions Not Recommended for Approval:** COVID-19 in a non-hospitalized patient was added to the Conditions not Recommended for Approval. The direction that all denials are forwarded to a Medical Director was removed from the policy. Now, only potential approvals (for hospitalized patients) require Medical Director review.	01/18/2023
Annual Revision	No criteria changes.	05/10/2023

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, 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: JIA, PsA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
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, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection)	Inhibition of IL-23	PsA, PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, RA, PsA, UC
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of 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; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARDs – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis.