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

DATE REVISED: 03/27/2019

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

1. Chimeric antigen receptor (CAR) T cell-induced, for the treatment of severe or life-threatening cytokine release syndrome in adults and pediatric patients 2 years of age and older; 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 therapy), there are high levels of IL-6; therefore, IL-6 signaling is inhibited with Actemra IV.¹,³,⁵

Guidelines
Actemra features in the guidelines for inflammatory and other conditions.

- NCCN has guidelines in partnership with the American Society of Clinical Oncology (ASCO) [version 1.2019 – November 14, 2018] for Management of Immunootherapy-Related Toxicities.⁶
  - In regard to CAR-T-cell-related toxicities, prompt and urgent attention is required to prevent progression. All patients with Grade 2, 3, and 4 are recommended for treatment with Actemra. In patients with Grade 1 CRS, Actemra is also listed as a therapeutic option for prolonged CRS in patients with significant symptoms and/or comorbidities.
  - For immune checkpoint inhibitor-related toxicities, infliximab or Actemra may be considered for refractory or severe arthritis not responding to steroids and anti-inflammatory agents.
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- 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.7
- 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.8
- Guidelines from the American College of Rheumatology (ACR) [2015] 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).9
- Guidelines for B-Cell lymphomas from the National Comprehensive Cancer Network (NCCN) [version 1.2019 – November 30, 2018] mention Actemra as a second-line therapy for relapsed or refractory unicentric Castleman’s disease in patients who are HIV- and HHV-8-negative. For MCD, the guidelines list Actemra as a subsequent therapy for relapsed, refractory, or progressive MCD.10

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.

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.

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.
**Recommended Authorization Criteria**

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

**FDA-Approved Indications**

1. **Cytokine Release Syndrome (CRS).** [eviCore] 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 (e.g., Kymriah™ [tisagenlecleucel IV suspension], Yescarta™ [axicabtagene ciloleucel IV suspension]).

   **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.

   The median number of Actemra IV doses administered in the pivotal trial was one dose (range, 1 to 4 doses).

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]); OR
      
      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.
      
      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) [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. 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 (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.
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.

Note: Many dose modifications are recommended for the management of dose-related laboratory changes such as increased liver enzymes, neutropenia, and thrombocytopenia. Reduced dosing of Actemra IV has not been studied in PJIA. 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 prescribing physician.

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); AND
      NOTE: 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 (e.g., Cimzia [certolizumab pegol SC injection], an etanercept product [Enbrel, Erelzi], an adalimumab product [Humira], an infliximab product [e.g., Remicade, INFLECTRA, Renflexis], Simponi Aria or SC [golimumab IV infusion; golimumab SC injection], Kevzara [sarilumab SC injection], Kineret [anakinra SC injection], Orencia IV or SC [abatacept IV infusion; abatacept SC injection], and a rituximab product [Rituxan, Truxima]. These patients who have already tried a biologic for RA are not required to “step back” and try a conventional synthetic DMARD.
      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 (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 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.

Note: Many dose modifications are recommended for the management of dose-related laboratory changes such as increased liver enzymes, neutropenia, and thrombocytopenia. Dosing modifications are determined by the prescribing physician. Dosing modifications recommended in the prescribing information are included in Appendix A.

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;
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e.g., methotrexate (MTX), leflunomide, sulfasalazine], or a 1-month trial of a nonsteroidal anti-inflammatory drug [NSAID]); AND

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 infliximab product [e.g., Remicade, Inflectra, Renflexis], 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 (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.

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.

Note: Many dose modifications are recommended for the management of dose-related laboratory changes such as increased liver enzymes, neutropenia, and thrombocytopenia. Reduced dosing of Actemra IV has not been studied in SJIA. Dosing modifications, including 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 prescribing physician. Recommendations from the prescribing information for use of Actemra IV in adults with RA are listed in Appendix A.

Other Uses with Supportive Evidence

5. 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 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 (e.g., normalization of C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], fibrinogen, albumin, and hemoglobin; resolution of constitutional symptoms; increased body mass index [BMI]; reduction in lymphadenopathy) as determined by the prescribing physician.

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.

6. Inflammatory Arthritis Associated with Checkpoint Inhibitor Therapy. Note: Examples of checkpoint inhibitors are Keytruda (pembrolizumab IV infusion), Opdivo (nivolumab IV
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infusion), Yervoy (ipilimumab IV infusion), Tecentriq (atezolizumab IV infusion), Bavencio (avelumab IV infusion), Imfinzi (durvalumab IV infusion), and Libtayo® (cemiplimab-rwlc IV infusion). Approve for 3 months if the patient meets ONE of the following (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 is symptomatic despite a trial of at least ONE steroid (e.g., methylprednisolone, prednisone); AND
   ii. The patient has tried at least ONE nonsteroidal anti-inflammatory agent (e.g., ibuprofen, 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 (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.

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.

NOTE: In RA, many dose modifications are recommended for the management of dose-related laboratory changes such as increased liver enzymes, neutropenia, and thrombocytopenia. Dosing modifications are determined by the prescribing physician. Dosing modifications recommended in the prescribing information are included in Appendix A.

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 (e.g., 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) as determined by the prescribing physician.

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 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.  

Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., 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. 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**


**Other References Utilized**
## HISTORY

<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes’</th>
<th>Approval Date</th>
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</thead>
<tbody>
<tr>
<td>Annual revision</td>
<td>No criteria changes.</td>
<td>02/22/2017</td>
</tr>
<tr>
<td>Selected revision</td>
<td>Update criteria for PJIA to generally require a previous therapy (e.g., MTX, sulfasalazine, or leflunomide, an NSAID, or a biologic disease-modifying antirheumatic drug), or Actemra IV is started in combination with a csDMARD, or the patient has aggressive disease, as determined by the prescriber. Previously, prior therapy was required to be a TNFi.</td>
<td>05/03/2017</td>
</tr>
<tr>
<td>Selected revision</td>
<td>Approve for 1 week which is adequate to receive 4 doses if the diagnosis is Cytokine Release Syndrome and Actemra is prescribed for a patient who has or will be receiving CAR-T therapy.</td>
<td>11/15/2017</td>
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<tr>
<td>Annual revision</td>
<td>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 NSAID 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 PJIA. Kevzara was added as examples of a biologic that a patient may have previously tried for RA. For SJIA, 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 DMARDs, corticosteroids, and NSAIDs 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.</td>
<td>03/21/2018</td>
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<tr>
<td>Annual revision</td>
<td>Rheumatoid Arthritis: Add Truxima as an example of a rituximab product. <strong>Inflammatory Arthritis Associated with Checkpoint Inhibitor Therapy:</strong> Add Yervoy, Tecentriq, Bavencio, Imfinzi, and Libtayo as examples of checkpoint inhibitors. <strong>Patients Established on Actemra IV or SC:</strong> 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. <strong>Dosing Section:</strong>  - Cytokine Release Syndrome, PJIA, RA, SJIA, 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.</td>
<td>03/27/2019</td>
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### APPENDIX

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<tr>
<th>Brand (generic name)</th>
<th>Mechanism of Action</th>
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<tr>
<td>Cimzia® (certolizumab pegol for SC injection)</td>
<td>Inhibition of TNF</td>
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<td>Enbrel® (etanercept for SC injection)</td>
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<td>Erelzi™ (etanercept-szzs for SC injection)</td>
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<td>Humira® (adalimumab for SC injection)</td>
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<td>Amjevita™ (adalimumab-atto for SC injection)</td>
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<td>Cyltezo® (adalimumab-abdm for SC injection)</td>
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<td>Simponi® Aria™ (golimumab for IV infusion)</td>
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<td>Remicade® (infliximab for IV infusion)</td>
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<td>Inflectra™ (infliximab-dyyb for IV infusion)</td>
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<td>Renflexis® (infliximab-abda for IV infusion)</td>
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<td>Actemra® (tocilizumab for IV infusion)</td>
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<td>Actemra® (tocilizumab for SC injection)</td>
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<tr>
<td>Kevzara® (sarilumab for SC injection)</td>
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<td>Orencia® (abatacept for IV infusion)</td>
<td>T-cell costimulation modulator</td>
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<td>Orencia® (abatacept for SC injection)</td>
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<td>Tremfya® (guselkumab for SC injection)</td>
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<td>Otezla® (apremilast tablets)</td>
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<td>Olumiant® (baricitinib tablets)</td>
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<tr>
<td>Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)</td>
<td>Inhibition of the JAK pathways</td>
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SC – Subcutaneous; TNF – Tumor necrosis factor; IL – Interleukin; IV – Intravenous; PDE4 – Phosphodiesterase 4; JAK – Janus kinase.