Tocilizumab (Actemra, Tofidence, Tyenne) IV

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Instructions for Use

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Related Policies

- N/A

Coverage Rationale

This policy is applicable for tocilizumab for injection for intravenous infusion only.

Acute Graft-Versus-Host Disease

For initial coverage of tocilizumab for Acute Graft-Versus-Host Disease (GVHD), the following will be required:

- Diagnosis of Acute Graft-Versus-Host Disease **and**
- Diagnosis of steroid-refractory acute GVHD

COVID-19

For initial coverage of tocilizumab for Coronavirus disease 2019 (COVID-19), the following will be required:

- Diagnosis of COVID-19 **and**
- Patient is hospitalized **and**
- Currently receiving systemic corticosteroids **and**
- Patient requires one of the following:
  - Supplemental oxygen
  - Non-invasive mechanical ventilation
  - Invasive mechanical ventilation
  - Extracorporeal membrane oxygenation (ECMO)

Cytokine Release Syndrome (CRS) Risk due to CAR T-Cell Therapy

For initial coverage of tocilizumab for Cytokine Release Syndrome (CRS) Risk due to CAR T-Cell Therapy, the following will be required:

- Patient will receive or is receiving chimeric antigen receptor (CAR) T-cell immunotherapy (e.g., Kymriah [tisagenlecleucel], Yescarta [axicabtagene ciloleucel]) **and**
- Prescribed by or in consultation with an oncologist or hematologist

Immune Checkpoint Inhibitor-Related Toxicities

For initial coverage of tocilizumab for Immune Checkpoint Inhibitor-Related Toxicities, the following will be required:

- Patient has received immune checkpoint inhibitor therapy **and**
- Diagnosis of severe immunotherapy-related inflammatory arthritis

Giant Cell Arteritis

For initial coverage of tocilizumab for Giant Cell Arteritis (GCA), the following will be required:

- Diagnosis of giant cell arteritis **and**
- Prescribed by or in consultation with a rheumatologist **and**
- Trial and failure, contraindication, or intolerance to a glucocorticoid

For reauthorization coverage of tocilizumab for Giant Cell Arteritis (GCA), the following will be required:

- Documentation of positive clinical response to therapy

Polyarticular Juvenile Idiopathic Arthritis

For initial coverage of tocilizumab for Polyarticular Juvenile Idiopathic Arthritis (PJIA), the following will be required:

- All of the following:
    - Diagnosis of active polyarticular juvenile idiopathic arthritis **and**
    - Minimum duration of a 6-week trial and failure, contraindication, or intolerance to one of the following conventional therapies at maximally tolerated doses:
        - leflunomide
        - methotrexate
    - Prescribed by or in consultation with a rheumatologist

  OR
- For continuation of Actemra therapy, defined as no more than a 45-day gap in therapy

For reauthorization coverage of tocilizumab for Polyarticular Juvenile Idiopathic Arthritis (PJIA), the following will be required:

- Documentation of positive clinical response to therapy as evidenced by at least one of the following:
    - Reduction in the total active (swollen and tender) joint count from baseline
    - Improvement in symptoms (e.g., pain, stiffness, inflammation) from baseline

Rheumatoid Arthritis

For Initial coverage of tocilizumab for Rheumatoid Arthritis (RA), the following will be required:

- All of the following:
    - Diagnosis of moderately to severely active rheumatoid arthritis **and**
    - Prescribed by or in consultation with a rheumatologist **and**

- Minimum duration of a 3-month trial and failure, contraindication, or intolerance to one of the following conventional therapies at maximally tolerated doses:
  - methotrexate
  - leflunomide
  - sulfasalazine

OR

- For continuation of prior Actemra therapy, defined as no more than a 45-day gap in therapy

For reauthorization coverage of tocilizumab for Rheumatoid Arthritis (RA), the following will be required:

- Documentation of positive clinical response to therapy as evidenced by at least one of the following:
  - Reduction in the total active (swollen and tender) joint count from baseline
  - Improvement in symptoms (e.g., pain, stiffness, inflammation) from baseline

Systemic Juvenile Idiopathic Arthritis

For initial coverage of tocilizumab for Systemic Juvenile Idiopathic Arthritis (SJIA), the following will be required:

- Diagnosis of active systemic juvenile idiopathic arthritis **and**
- Prescribed by or in consultation with a rheumatologist **and**
- Trial and failure, contraindication, or intolerance to one of the following conventional therapies at maximally tolerated doses:
  - Minimum duration of a 3-month trial and failure of methotrexate
  - Minimum duration of a 1-month trial of nonsteroidal anti-inflammatory drug (NSAID) (e.g., ibuprofen, naproxen)
  - Minimum duration of a 2-week trial of systemic glucocorticoid (e.g., prednisone)

For reauthorization coverage of tocilizumab for Systemic Juvenile Idiopathic Arthritis (SJIA), the following will be required:

- Documentation of positive clinical response to therapy as evidenced by at least one of the following:
  - Reduction in the total active (swollen and tender) joint count from baseline
  - Improvement in clinical features or symptoms (e.g., pain, fever, inflammation, rash, lymphadenopathy, serositis) from baseline

Systemic Sclerosis-Associated Interstitial Lung Disease

For initial coverage of tocilizumab for Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD), the following will be required:

- Diagnosis of Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD) as documented by the following:
  - Exclusion of other known causes of interstitial lung disease (ILD) **and**
  - One of the following:
    - In patients not subjected to surgical lung biopsy, the presence of idiopathic interstitial pneumonia (e.g., fibrotic nonspecific interstitial pneumonia [NSIP], usual interstitial pneumonia [UIP] and centrilobular fibrosis) pattern on high-resolution computed tomography (HRCT) revealing SSc-ILD or probable SSc-ILD **or**
    - In patients subjected to a lung biopsy, both HRCT and surgical lung biopsy pattern revealing SSc-ILD or probable SSc-ILD **and**

- Prescribed by or in consultation with a rheumatologist or pulmonologist

For reauthorization coverage of tocilizumab for Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD), the following will be required:

- Documentation of positive clinical response to therapy

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J3262	Injection, tocilizumab, 1 mg
M0249	Intravenous infusion, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ecmo) only, includes infusion and post administration monitoring, first dose
M0250	Intravenous infusion, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ecmo) only, includes infusion and post administration monitoring, second dose
Q0249	Injection, tocilizumab, for hospitalized adults and pediatric patients (2 years of age and older) with covid-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ecmo) only, 1 mg
Q5133	Injection, tocilizumab-bavi (tofidence), biosimilar, 1 mg
Q5135	Injection, tocilizumab-aazg (Tyenne), biosimilar, 1 mg

ICD-10 Code	Description
D89.810	Acute graft-versus-host disease
D89.831	Cytokine release syndrome, grade 1
D89.832	Cytokine release syndrome, grade 2
D89.833	Cytokine release syndrome, grade 3
D89.834	Cytokine release syndrome, grade 4
D89.835	Cytokine release syndrome, grade 5
D89.839	Cytokine release syndrome, grade unspecified
J12.82	Pneumonia due to coronavirus disease 2019
M05.00–M05.09	Felty's syndrome (rheumatoid arthritis with splenoadenomegaly and leukopenia
M05.10–M05.19	Rheumatoid lung disease with rheumatoid arthritis of unspecified site
M05.20–M05.29	Rheumatoid vasculitis with rheumatoid arthritis

ICD-10 Code	Description
M05.30–M05.39	Rheumatoid heart disease with rheumatoid arthritis
M05.40–M05.49	Rheumatoid myopathy with rheumatoid arthritis
M05.50–M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis
M05.60–M05.69	Rheumatoid arthritis with involvement of other organs and systems
M05.70–M05.79	Rheumatoid arthritis with rheumatoid factor without organ or systems
M05.7A	Rheumatoid arthritis with rheumatoid factor of other specified site
M05.80–M05.8A	Other rheumatoid arthritis with rheumatoid factor
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.00–M06.09	Rheumatoid arthritis without rheumatoid factor
M06.0A	Rheumatoid arthritis without rheumatoid factor, other specified site
M06.1	Adult-onset Still's disease
M06.20–M06.29	Rheumatoid bursitis
M06.30–M06.39	Rheumatoid nodule
M06.80–M06.8A	Other specified rheumatoid arthritis
M06.9	Rheumatoid arthritis, unspecified
M08.20–M08.29	Juvenile rheumatoid arthritis with systemic onset
M08.2A	Juvenile rheumatoid arthritis with systemic onset, other specified site
M08.3	Juvenile rheumatoid polyarthritis (seronegative)
M08.80	Other juvenile arthritis, unspecified site
M08.90	Juvenile arthritis, unspecified, unspecified site
M31.5	Giant cell arteritis with polymyalgia rheumatica
M31.6	Other giant cell arteritis
M34.81	Systemic sclerosis with lung involvement (systemic sclerosis-associated interstitial lung)
T45.1X5A	Adverse effect of antineoplastic and immunosuppressive drugs, initial encounter
T45.1X5D	Adverse effect of antineoplastic and immunosuppressive drugs, subsequent encounter
T45.1X5S	Adverse effect of antineoplastic and immunosuppressive drugs, sequela
T80.82XA	Complication of immune effector cellular therapy, initial encounter
T80.82XD	Complication of immune effector cellular therapy, subsequent encounter
T80.82XS	Complication of immune effector cellular therapy, sequela
T80.89XA	Other complications following infusion, transfusion and therapeutic injection, initial encounter
T80.89XD	Other complications following infusion, transfusion and therapeutic injection, subsequent encounter
T80.89XS	Other complications following infusion, transfusion and therapeutic injection, sequela
T80.90XA	Unspecified complication following infusion and therapeutic injection, initial encounter
T80.90XD	Unspecified complication following infusion and therapeutic injection, subsequent encounter
T80.90XS	Unspecified complication following infusion and therapeutic injection, sequela
T81.89XA	Other complications of procedures, not elsewhere classified, initial encounter
T81.89XD	Other complications of procedures, not elsewhere classified, subsequent encounter
T81.89XS	Other complications of procedures, not elsewhere classified, sequela
T81.9XXA	Unspecified complication of procedure, initial encounter

ICD-10 Code	Description
T81.9XXD	Unspecified complication of procedure, subsequent encounter
T81.9XXS	Unspecified complication of procedure, sequela
T86.5	Complications of stem cell transplant
U07.1	COVID-19
Z92.850	Personal history of Chimeric Antigen Receptor T-cell therapy

Background

Tocilizumab is a human monoclonal antibody targeting the IL-6 receptor. T cells, B cells, and cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) play a key role in the inflammatory and immune process (Choy et al 2001). This has led to the development of biologic agents to target these areas. Actemra (tocilizumab) has activity directed against the IL-6 receptor. Biosimilar products have also been approved: Tyenne (tocilizumab-aazg) and Tofidence (tocilizumab-bavi).

Immunomodulators treat a wide variety of conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), hidradenitis suppurativa (HS), alopecia areata, atopic dermatitis (AD), and uveitis (UV), as well as several less common conditions.

Clinical Evidence

The efficacy and safety of Actemra (tocilizumab) were assessed in several randomized, double-blind, multicenter studies in patients age ≥ 18 years with active RA. Patients were diagnosed according to ACR criteria, with at least 8 tender and 6 swollen joints at baseline. Tocilizumab was given every 4 weeks as monotherapy (AMBITION), in combination with MTX (LITHE and OPTION) or other DMARDs (TOWARD) or in combination with MTX in patients with an inadequate response to TNF antagonists (RADIATE). In all studies, mild to moderate AEs were reported, occurring in similar frequencies in all study groups. The most common AEs in all studies were infections and gastrointestinal symptoms (Emery et al 2008, Genovese et al 2008, Jones et al 2010, Kremer et al 2011, Smolen et al 2008).

AMBITION evaluated the safety and efficacy of tocilizumab monotherapy vs MTX in patients with active RA for whom previous treatment with MTX or biological agents had not failed. A total of 673 patients were randomized to 1 of 3 treatment arms, tocilizumab 8 mg/kg every 4 weeks, MTX 7.5 mg/week and titrated to 20 mg/week within 8 weeks, or placebo for 8 weeks followed by tocilizumab 8 mg/kg. The primary endpoint was the proportion of patients achieving ACR 20 response at week 24. The results showed that tocilizumab monotherapy when compared to MTX monotherapy produced greater improvements in RA signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. Additionally, more patients treated with tocilizumab achieved remission at week 24 when compared to patients treated with MTX (Jones et al 2010).

LITHE evaluated 1,196 patients with moderate to severe RA who had an inadequate response to MTX. Patients treated with tocilizumab had 3 times less progression of joint damage, measured by Total Sharp Score, when compared to patients treated with MTX alone. Significantly more patients treated with tocilizumab 8 mg/kg were also found to achieve remission at 6 months as compared to MTX (33% vs 4%), and these rates continued to increase over time to 1 year (47% vs 8%) (Kremer et al 2011). These benefits were maintained or improved at 2 years with no increased side effects (Fleishmann et al 2013).

OPTION evaluated tocilizumab in 623 patients with moderate to severely active RA. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo IV every 4 weeks, with MTX at stable pre-study doses (10 to 25 mg/week). Rescue therapy with tocilizumab 8 mg/kg was offered at week 16 to patients with < 20% improvement in swollen and tender joint

counts. The primary endpoint was ACR 20 at week 24. The findings showed that ACR 20 was seen in significantly more patients receiving tocilizumab than in those receiving placebo at week 24 ($p < 0.001$). Significantly more patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 as well ($p < 0.001$). Greater improvements in physical function, as measured by the HAQ-DI, were seen with tocilizumab when compared to MTX (-0.52 vs -0.55 vs -0.34; $p < 0.0296$ for 4 mg/kg and $p < 0.0082$ for 8 mg/kg) (Smolen et al 2008).

TOWARD examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1220 patients with active RA. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every 4 weeks for 24 weeks. At week 24, significantly more patients taking tocilizumab with DMARDs achieved an ACR 20 response than patients in the control group. The authors concluded that tocilizumab, combined with any of the DMARDs evaluated (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide), was safe and effective in reducing articular and systemic symptoms in patients with an inadequate response to these agents. A greater percentage of patients treated with tocilizumab also had clinically meaningful improvements in physical function when compared to placebo (60% vs 30%; p value not reported) (Genovese et al 2008).

RADIATE evaluated the safety and efficacy of tocilizumab in patients with RA refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to ≥ 1TNF antagonists were randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every 4 weeks with stable MTX doses (10 to 25 mg/week) for 24 weeks. ACR 20 responses and safety endpoints were assessed. This study found that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile. The ACR 20 response in both tocilizumab groups was also found to be comparable to those seen in patients treated with Humira (adalimumab) and Remicade (infliximab), irrespective of the type or number of failed TNF antagonists (Emery et al 2008). In the ADACTA trial, patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab. The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group (Gabay et al 2013).

Results of a randomized, double-blind trial evaluating Actemra (tocilizumab) in early RA were published (Bijlsma et al 2016). Patients (n = 317) had been diagnosed with RA within 1 year, were DMARD-naïve, and had a DAS28 score of ≥ 2.6. Patients were randomized to 1 of 3 groups: tocilizumab plus MTX, tocilizumab plus placebo, or MTX plus placebo. Tocilizumab was given at a dose of 8 mg/kg every 4 weeks (maximum 800 mg per dose), and MTX was given at a dose of 10 mg orally per week, increased to a maximum of 30 mg per week as tolerated. Patients not achieving remission switched from placebo to active treatments, and patients not achieving remission in the tocilizumab plus MTX group switched to a standard of care group (usually a TNF inhibitor plus MTX). The primary endpoint was the proportion of patients achieving sustained remission (defined as DAS28 < 2.6 with a swollen joint count ≤4, persisting for at least 24 weeks). The percentages of patients achieving a sustained remission on the initial regimen were 86%, 84%, and 44% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively ($p < 0.0001$ for both comparisons vs MTX). The percentages of patients achieving sustained remission during the entire study were 86%, 88%, and 77% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively ($p = 0.06$ for tocilizumab plus MTX vs MTX; $p = 0.0356$ for tocilizumab vs MTX). The authors concluded that immediate initiation of tocilizumab is more effective compared to initiation of MTX in early RA.

Tyenne (tocilizumab-aazg) was compared to European Union-approved tocilizumab in patients with moderate to severe active RA who had an inadequate prior response to ≥ 1 DMARD (Zubrzycka-Sienkiewicz et al 2024). Patients (N = 604) were randomized to receive weekly SQ injections of either 162 mg of Tyenne or European Union-approved tocilizumab for 24 weeks. The least squares mean difference between groups in the change from baseline in the DAS28-ESR score at Week 24 was 0.01 (95% CI, -0.19 to 0.22). Biosimilarity of Tyenne to reference tocilizumab was established.

Tofidence (tocilizumab-bavi) was compared to reference tocilizumab in a Phase 3, multicenter, double-blind, active-control, randomized trial in 621 patients with moderate to severe RA with inadequate response to MTX. For the primary endpoint at week 12, estimated ACR 20 response was 64.8% in the reference tocilizumab group vs 69% in the Tofidence

treated group (difference, 4.1%; 95% CI, -3.6 to 11.9). In addition to efficacy, comparable pharmacokinetic and immunogenicity profiles were observed for the reference tocilizumab and Tofidence (Leng et al 2024).

The focuSSced trial evaluated the safety and efficacy of tocilizumab in patients with systemic sclerosis (SSc) The focuSSced trial was a Phase 3, randomized, double-blind, placebo-controlled clinical study in 212 adults with SSc. Supportive information was also used from the faSScinate trial, a Phase 2/3, randomized, double-blind, placebo-controlled study in patients with SSc. The primary efficacy endpoint was change from baseline at week 48 in modified Rodnan Skin Score (mRSS). Change from baseline in percent predicted forced vital capacity (ppFVC) at week 48 was a key secondary endpoint. In the overall population of focuSSced, there was not a statistically significant difference in the mean change from baseline to week 48 in mRSS in patients receiving tocilizumab vs. placebo (difference: -1.73; 95% CI: -3.78, 0.32). There also was not a statistically significant effect on the primary endpoint of mRSS in the faSScinate trial. In the overall population of focuSSced, patients treated with tocilizumab, as compared to placebo treated patients, were observed to have less decline from baseline in ppFVC and observed FVC at 48 weeks. FVC results from faSScinate were similar. The ppFVC and observed FVC results in the overall population were primarily driven by results in the SSc-ILD subgroup. In the SSc-ILD subgroup, the differences in mean changes from baseline to week 48 for tocilizumab vs. placebo were 6.47% (95% CI: 3.43, 9.50) and 241 mL (95% CI: 124, 358) for ppFVC and observed FVC, respectively. The results of the key FVC secondary endpoints from focuSSced support a conclusion of effectiveness of tocilizumab in reducing the rate of progressive loss of lung function in the study population. (Khanna et al 2020).

The GiACTA trial was a phase III, global, randomized, double-blind, placebo-controlled trial investigating the efficacy and safety of Actemra as a novel treatment for GCA. In this trial 251 screened patients with new-onset or relapsing GCA were randomized to one of four treatment arms. Two subcutaneous doses of Actemra (162 mg every week and 162 mg every other week) were compared to two different placebo control groups (pre-specified prednisone-taper regimen over 26 weeks and 52 weeks) randomized 2:1:1:1. The study consisted of a 52-week blinded period, followed by a 104-week open-label extension. It this study, all patients received background glucocorticoid (prednisone) therapy. The primary efficacy endpoint was the proportion of patients achieving sustained remission from Week 12 through Week 52. Sustained remission was defined by a patient attaining a sustained (1) absence of GCA signs and symptoms from Week 12 through Week 52, (2) normalization of erythrocyte sedimentation rate (ESR) (to < 30 mm/hr without an elevation to ≥ 30 mm/hr attributable to GCA) from Week 12 through Week 52, (3) normalization of C-reactive protein (CRP) (to < 1 mg/dL, with an absence of successive elevations to ≥ 1mg/dL) from Week 12 through Week 52, and (4) successful adherence to the prednisone taper defined by not more than 100 mg of excess prednisone from Week 12 through Week 52. ACTEMRA 162 mg weekly and 162 mg every other week + 26 weeks prednisone taper both showed superiority in achieving sustained remission from Week 12 through Week 52 compared with placebo + 26 weeks prednisone taper. Both Actemra treatment arms also showed superiority compared to the placebo + 52 weeks prednisone taper. (Stone et al. 2017)

The CHERISH trial evaluated the use of Actemra in children 2 to 17 years of age with polyarticular juvenile idiopathic arthritis (PJIA). The primary endpoint was the proportion of patients with a JIA ACR30 flare at Week 40 relative to Week 16. In part 1, 188 patients received tocilizumab (<30 kg: 10 mg/kg (n=35) or 8 mg/kg (n=34); ≥30 kg: n=119). In part 2, 163 patients received tocilizumab (n=82) or placebo (n=81). JIA flare occurred in 48.1% of patients on placebo versus 25.6% continuing tocilizumab (difference in means adjusted for stratification: −0.21; 95% CI −0.35 to −0.08; p=0.0024). At the end of part 2, 64.6% and 45.1% of patients receiving tocilizumab had JIA-ACR70 and JIA-ACR90 responses, respectively. Rates/100 patient-years (PY) of adverse events (AEs) and serious AEs (SAEs) were 480 and 12.5, respectively; infections were the most common SAE (4.9/100 PY). In this trial, tocilizumab treatment results in significant improvement, maintained over time, of pcJIA signs and symptoms and has a safety profile consistent with that for adults with rheumatoid arthritis. (Brunner et al. 2015)

The RECOVERY trial was a randomized, controlled, open-label, platform study and supported by the results from a randomized, double-blind, placebo-controlled study (EMPACTA). Results of two other randomized, double-blind, placebo-controlled studies, COVACTA and REMDACTA, were also utilized. About 5,500 hospitalized patients with COVID-19 were included in these four studies. Overall, the results of these four studies showed that Actemra may improve

outcomes in patients with COVID-19 receiving corticosteroids and requiring supplemental oxygen or breathing support (RECOVERY 2021).

The TENDER trial was a 5-year, 2-part, Phase III study of IV Actemra infusions in patients 2 to 17 years of age with active systemic juvenile idiopathic arthritis (SJIA) with an inadequate response to glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs). In this study, the primary endpoint: JIA ACR30 + absence of fever at 12 weeks. In Part I: 12-week, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of Actemra (n=75) compared with placebo (n=37). Patients were randomized to receive Actemra 8 mg/kg (patients ≥30 kg) and 12 mg/kg (patients <30 kg) or placebo intravenously every 2 weeks. At week 12, patients continuing Actemra (n=73) and all patients receiving placebo entered Part II of the study. Part 2 was a single-group (N=110), open-label extension study examining the safety and efficacy of long-term Actemra use. Part III was a single-group, open-label extension through week 260. Patients who maintained clinically inactive disease for 3 months after completing 2 years of Actemra treatment were given the option to receive Actemra by an alternative dosing schedule in which Actemra and concomitant medications were tapered and discontinued. Week 104 results were consistent with placebo-controlled period and overall profile of the drug (De Benedetti et al. 2012).

The FDA approval of the SQ formulation of Actemra (tocilizumab) was based on 1 multicenter, double-blind, randomized, controlled trial in patients (n = 1262) with RA. Weekly tocilizumab SQ 162 mg was found to be noninferior to tocilizumab IV 8 mg/kg every 4 weeks through 24 weeks. A higher incidence of injection-site reactions were reported with the SQ formulation (Burmester et al 2014a). In an open-label extension period, patients in both treatment arms were re-randomized to receive either IV or SQ tocilizumab through week 97. The proportions of patients who achieved ACR 20/50/70 responses, DAS28 remission, and improvement from baseline in HAQ-DI ≥ 0.3 were sustained through week 97 and comparable across arms. IV and SQ treatments had a comparable safety profile with the exception of higher injection-site reactions with the SQ formulation (Burmester et al 2016). A placebo-controlled trial in 656 patients further confirmed the efficacy of SQ Actemra administered every other week (Kivitz et al 2014).

Clinical Guidelines

Rheumatoid Arthritis:

- The America College of Rheumatology (ACR) recommends the use of conventional DMARDs, a TNF inhibitor, a non-TNF inhibitor biologic (tocilizumab, sarilumab, abatacept, or rituximab [only in patients that have had an inadequate response to TNF inhibitors or have a history of lymphoproliferative disorder]), or a JAK inhibitor (tofacitinib, baricitinib, upadacitinib). For patients who are not at target, switching to a medication in a different class is conditionally recommended over switching to a medication in the same class for patients receiving a biologic or JAK inhibitor. Biosimilars are considered equivalent to FDA-approved originator biologics. Anakinra was excluded from the ACR guideline because of its low use and lack of new data. (*Fraenkel et al 2021*).
- EULAR guidelines for RA management were recently updated (*Smolen et al 2023*). EULAR recommends that therapy with DMARDs should be initiated as soon as the RA diagnosis is made with treatment aimed at reaching a target of sustained remission or low disease activity in every patient. If the treatment target is not achieved with the first conventional synthetic DMARD (csDMARD) strategy, in the absence of poor prognostic factors, other csDMARDs should be considered. If poor prognostic factors are present with csDMARD failure, a biological DMARD should be added; JAK inhibitors may be considered, but pertinent risk factors should be taken into account. In patients who cannot use csDMARDs as a comedication, IL-6 inhibitors and targeted synthetic DMARDs may have some advantages compared with other biologic DMARDs. If a biological or targeted synthetic DMARD has failed, treatment with another should be considered. If one TNF or IL-6 inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF or IL-6 inhibitor.
- The ACR released a position statement on biosimilars, which stated that the decision to substitute a biosimilar product for a reference drug should only be made by the prescriber. The ACR does not endorse switching stable patients to a different medication (including a biosimilar) of the same class for cost saving reasons without advance consent from the prescriber and knowledge of the patient (*ACR 2021*). Similarly, the Task Force on the

Use of Biosimilars to Treat Rheumatological Disorders recommends that both healthcare providers and patients should take part in the decision-making process for switching amongst biosimilars (*Kay et al 2018*).

- EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).
- The ACR/Arthritis Foundation guidelines for the management of osteoarthritis of the hand, hip, and knee strongly recommends against the use of biologics (eg, TNF inhibitors, IL-1 receptor antagonists) for any form of osteoarthritis (*Kolasinski et al 2020*).

Juvenile Idiopathic Arthritis:

- The ACR and Arthritis Foundation published a guideline for the treatment of JIA in 2019 focusing on therapy for non-systemic polyarthritis, sacroiliitis, and enthesitis. In children and adolescents with JIA and polyarthritis with moderate to high disease activity, addition of a biologic (TNF inhibitor, abatacept, or tocilizumab) is conditionally recommended. Patients with continued disease activity and primary TNF inhibitor failure are conditionally recommended to receive abatacept or tocilizumab over a second TNF inhibitor. Children and adolescents with JIA and active sacroiliitis despite treatment with NSAIDs are strongly recommended to add TNF inhibitor therapy over continuing NSAID monotherapy (*Ringold et al 2019*).
- A 2021 guideline from the ACR addresses the treatment of oligoarthritis, temporomandibular joint arthritis, and SJIA (*Onel et al 2022*). For SJIA, an IL-1 inhibitor or IL-6 inhibitor is conditionally recommended for initial treatment; no specific agent is preferred. Monotherapy with an NSAID may also be considered for initial treatment of SJIA without macrophage activation syndrome. Systemic glucocorticoids are conditionally recommended as part of initial therapy for patients with macrophage activation syndrome. If residual arthritis is present despite these therapies, a conventional synthetic DMARD may be added or a different biologic therapy may be tried. Patients without macrophage activation syndrome who experience incomplete response or intolerance to an initial IL-1 or IL-6 inhibitor may be switched to an alternative IL-1 or IL-6 inhibitor.

Giant Cell Arteritis

- The 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis (GCA) and Takayasu Arteritis (TAK) provide guidance regarding the evaluation and management of patients with GCA and TAK, including diagnostic strategies, use of pharmacologic agents, and surgical interventions.
- Recommendation: For patients with newly diagnosed GCA, we conditionally recommend the use of oral GCs with tocilizumab over oral GCs alone
- For patients with GCA with active extracranial large vessel involvement, we conditionally recommend treatment with oral glucocorticoids combined with a nonglucocorticoid immunosuppressive agents, such as biologic agents (e.g., tocilizumab) as well as oral therapies (e.g., methotrexate), over oral glucocorticoids alone.
- Recommendation: For patients with GCA who experience disease relapse with symptoms of cranial ischemia while receiving GCs, we conditionally recommend adding tocilizumab and increasing the dose of GCs over adding methotrexate and increasing the dose of GCs (Maz et al 2021).

NCCN Recommended Uses

The NCCN Drugs & Biologics Compendium recommends (2A) tocilizumab for the treatment of:

- Hematopoietic Cell Transplantation - Hematopoietic Cell Transplantation
    - For acute graft-versus-host disease (GVHD) as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options

- Management of Immunotherapy-Related Toxicities - Immune Checkpoint Inhibitor-Related Toxicities
  Consider as
  - additional disease modifying antirheumatic therapy for the management of moderate or severe immunotherapy-related inflammatory arthritis if no improvement after holding immunotherapy and treating with oral corticosteroids or if unable to taper corticosteroids
  - additional disease modifying antirheumatic therapy for polymyalgia rheumatica if unable to taper prednisone or no improvement in symptoms
  - additional therapy for management of immunotherapy-related giant cell arteritis (urgent referral to rheumatology even in mild cases)
- Management of Immunotherapy-Related Toxicities - CAR T-Cell-Related Toxicities
  Consider for management of
  - prolonged (>3 days) G1 cytokine release syndrome (CRS) in patients with significant symptoms, comorbidities, and/or in elderly patients
  - CRS symptoms that persist >24 hours in patients who have been treated with axicabtagene ciloleucel or brexucabtagene autoleucel
  - G1 CRS that develops <72 hours after infusion in patients who have been treated with lisocabtagene maraleucel
- Management of Immunotherapy-Related Toxicities - CAR T-Cell-Related Toxicities
  Used for management of
  - G2-4 cytokine release syndrome (CRS)
  - G1-4 neurotoxicity as additional single-dose therapy if concurrent CRS
- Acute Lymphoblastic Leukemia - Acute Lymphoblastic Leukemia
  - Consider as supportive care for patients with severe cytokine release syndrome (CRS) related to blinatumomab therapy
- B-Cell Lymphomas - Castleman Disease
  - Second-line therapy as a single agent for relapsed or refractory unicentric CD for disease that is human immunodeficiency virus-negative and human herpesvirus-8-negative
- B-Cell Lymphomas - Castleman Disease
  - Subsequent therapy as a single agent for multicentric CD that has progressed following treatment of relapsed/refractory or progressive disease

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Actemra (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of:

- Rheumatoid Arthritis (RA) Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
- Giant Cell Arteritis (GCA) Adult patients with giant cell arteritis.
- Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD) Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD)
- Polyarticular Juvenile Idiopathic Arthritis (PJIA) Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.
- Systemic Juvenile Idiopathic Arthritis (SJIA) Patients 2 years of age and older with active systemic juvenile idiopathic arthritis. Cytokine Release Syndrome (CRS)
- Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell induced severe or life-threatening cytokine release syndrome.
- Coronavirus Disease 2019 (COVID-19) Hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Tofidence (tocilizumab-bavi) is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of:

- Rheumatoid Arthritis (RA) (Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
- Giant Cell Arteritis (GCA) Adult patients with giant cell arteritis.
- Polyarticular Juvenile Idiopathic Arthritis (PJIA) Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.
- Systemic Juvenile Idiopathic Arthritis (SJIA) Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.
- Coronavirus Disease 2019 (COVID-19) Hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)

Tyenne (tocilizumab-aazg) is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of:

- Rheumatoid Arthritis (RA) Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs)
- Giant Cell Arteritis (GCA) Adult patients with giant cell arteritis.
- Polyarticular Juvenile Idiopathic Arthritis (PJIA) Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.
- Systemic Juvenile Idiopathic Arthritis (SJIA) Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

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Policy History/Revision Information

Date	Summary of Changes
10/18/2023	Approved by OptumRx P&T Committee
05/16/2024	Annual review. Updated codes and references only.
05/15/2025	Annual review. Addition of Tofidence and Tyenne, leading to change of name in policy. Updated language in coverage rationale section and Updated references.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Archived Policy Versions (Internal Only)

Effective Date	Policy Number	Policy Title
mm/dd/yyyy – mm/dd/yyyy	######	Title of Policy Hyperlinked to KL or Other Internal Location

Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

Hindi: _यान द_: य_द आप ि हंदी बोलते ह_ तो आपके ि लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_।1-800-332-6501 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

Korean: 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다.1-800-332-6501 (TTY: 711)번으로 전화해 주십시오.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer1-800-332-6501 (TTY: 711).

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Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al1-800-332-6501 (TTY: 711).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1-800-332-6501 (TTY: 711).

Traditional Chinese: 注意：如果您使用繁體中文， 您可以免費獲得語言援助服務。請 致電 1-800-332-6501 (TTY: 711)

Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-800-332-6501 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-800-332-6501 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-800-332-6501 (TTY: 711).

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