tocilizumab (Actemra®)

Policy # 00252
Original Effective Date: 07/21/2010
Current Effective Date: 01/01/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Rheumatoid Arthritis

Based on review of available data, the Company may consider the use of both intravenous and subcutaneous tocilizumab (Actemra®)‡ for the treatment of rheumatoid arthritis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility will be met:

- Patient is 18 years of age or older; AND
- Patient has a diagnosis of moderately to severely active rheumatoid arthritis; AND
- Patient has failed treatment to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDS); AND
- Requested drug is NOT given concomitantly with biologic DMARDs, such as adalimumab (Humira®‡ or etanercept (Enbrel®‡, or other drugs such as apremilast (Otezla®‡ or tofacitinib (Xeljanz/XR®‡; AND
- For tocilizumab (Actemra) subcutaneous requests ONLY (this criterion is NOT applicable to the intravenous version): Patient has failed treatment with adalimumab (Humira) after at least TWO months of therapy unless there is clinical evidence or patient history that suggests the use of adalimumab (Humira) will be ineffective or cause an adverse reaction to the patient; AND
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

- Patient has a negative tuberculosis (TB) test (e.g., purified protein derivative [PPD], blood test) prior to treatment.

Systemic Juvenile Idiopathic Arthritis

Based on review of available data, the Company may consider the use of both intravenous and subcutaneous tocilizumab (Actemra) for the treatment of systemic juvenile idiopathic arthritis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of both intravenous and subcutaneous tocilizumab (Actemra) for the treatment of active systemic juvenile idiopathic arthritis will be considered when all of the following patient selection criteria are met:

- Patient is 2 years of age and older; AND
- Patient has a diagnosis of active systemic juvenile idiopathic arthritis; AND
- Patient has inadequate clinical response to nonsteroidal anti-inflammatory drugs (NSAIDS) or corticosteroids; AND
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Requested drug is NOT given concomitantly with biologic DMARDs, such as adalimumab (Humira) or etanercept (Enbrel), or other drugs such as apremilast (Otezla) or tofacitinib (Xeljanz/XR); AND
- Patient has a negative TB test (e.g., PPD, blood test) prior to treatment.

Polyarticular Juvenile Idiopathic Arthritis

Based on review of available data, the Company may consider the use of both intravenous and subcutaneous tocilizumab (Actemra) for the treatment of active polyarticular juvenile idiopathic arthritis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of both intravenous and subcutaneous tocilizumab (Actemra) for the treatment of active polyarticular juvenile idiopathic arthritis will be considered when all of the following patient selection criteria are met:

- Patient is 2 years of age and older; AND

tocilizumab (Actemra®)

Policy # 00252
Original Effective Date: 07/21/2010
Current Effective Date: 01/01/2021

- Patient has a diagnosis of active polyarticular juvenile idiopathic arthritis; AND
- Patient has failed treatment to one or more DMARDS; AND
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- For tocilizumab (Actemra) subcutaneous requests ONLY (this criterion is NOT applicable to the intravenous version): Patient has failed treatment with adalimumab (Humira) after at least TWO months of therapy unless there is clinical evidence or patient history that suggests the use of adalimumab (Humira) will be ineffective or cause an adverse reaction to the patient; AND
- Requested drug is NOT given concomitantly with biologic DMARDs, such as adalimumab (Humira) or etanercept (Enbrel), or other drugs such as apremilast (Otezla) or tofacitinib (Xeljanz/XR); AND
- Patient has a negative TB test (e.g., PPD, blood test) prior to treatment.

Giant Cell Arteritis

Based on review of available data, the Company may consider the use of subcutaneous tocilizumab (Actemra) for the treatment of giant cell arteritis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of subcutaneous tocilizumab (Actemra) for the treatment of giant cell arteritis will be considered when the following patient selection criteria are met:

Initial:

- Patient has a diagnosis of giant cell arteritis (which is confirmed by the presence of unequivocal cranial symptoms of giant cell arteritis [severe headaches, jaw pain, or visual symptoms], AND a temporal artery biopsy, color doppler ultrasonography, computed tomography angiography [CTA], or magnetic resonance angiography [MRA] confirms evidence of large-vessel vasculitis AND presence of elevated erythrocyte sedimentation rate [ESR >50]/C-reactive protein [CRP 2.45 or greater]); AND
- Patient is 50 years of age or older; AND
  *(Note: This specific patient criterion is an additional Company requirement, based on clinical trials, for coverage eligibility and will be denied as not medically necessary** if not met).*

- Patient is using requested drug in combination with a tapering course of glucocorticoids; AND
- Patient has a negative TB test (e.g., PPD, blood test) prior to treatment; AND
- Requested drug is NOT given concomitantly with biologic DMARDs, such as adalimumab (Humira) or etanercept (Enbrel), or other drugs such as apremilast (Otezla) or tofacitinib (Xeljanz/XR); AND
- Patient is NOT having an adequate response after at least 4 weeks of glucocorticoids alone (e.g., NO signs of the following: ability to reduce glucocorticoid dose, normalization of acute phase reactants [e.g., erythrocyte sedimentation rate {ESR<30}, C-reactive protein {CRP<1}], reduction or resolution of signs or symptoms of giant cell arteritis) OR adequate glucocorticoid dose is not tolerated or symptoms progress despite adequate glucocorticoid dose prior to the 4 week mark.
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

Continuation:

- Patient received initial authorization for the requested drug; AND
- Patient has had a response (e.g., reduced glucocorticoid dose, normalization of acute phase reactants [e.g., ESR < 30, CRP < 1], reduction or resolution of signs or symptoms of giant cell arteritis), as determined by the prescriber
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

Cytokine Release Syndrome

Based on review of available data, the Company may consider the use of intravenous tocilizumab (Actemra) for the treatment of cytokine release syndrome to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of intravenous tocilizumab (Actemra) for the treatment of cytokine release syndrome will be considered when the following patient selection criteria are met:

- Patient is 2 years of age and older; AND
- Patient has a diagnosis of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome. Severe or life-threatening cytokine release syndrome

is defined as having either hemodynamic instability despite intravenous fluids and vasopressor support OR worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation OR rapid clinical deterioration; AND

- No more than 4 total doses of tocilizumab (Actemra) (to not exceed 800 mg per infusion) should be administered per event of cytokine release syndrome.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of tocilizumab (Actemra) when any of the following criteria for their respective disease listed below (and denoted in the patient selection criteria above) are not met to be **not medically necessary**:**

- For rheumatoid arthritis:
  - Patient has failed treatment with adalimumab (Humira) after at least TWO months of therapy (applicable to subcutaneous requests ONLY)
- For systemic juvenile idiopathic arthritis:
  - Patient has inadequate clinical response to NSAIDS or corticosteroids
- For polyarticular juvenile idiopathic arthritis:
  - Patient has failed treatment to one or more DMARDS
  - Patient has failed treatment with adalimumab (Humira) after at least TWO months of therapy (applicable to subcutaneous requests ONLY)
- For giant cell arteritis:
  - Initial: Patient is 50 years of age or older
  - Initial: Patient is NOT having an adequate response after at least 4 weeks of glucocorticoids alone (e.g. NO signs of the following: ability to reduce glucocorticoid dose, normalization of acute phase reactants [e.g., ESR < 30, CRP < 1], reduction or resolution of signs or symptoms of giant cell arteritis) OR adequate glucocorticoid dose is not tolerated or symptoms progress despite adequate glucocorticoid dose prior to the 4 week mark
  - Continuation: Patient has had a response (e.g., reduced glucocorticoid dose, normalization of acute phase reactants [e.g., ESR < 30, CRP < 1], reduction or resolution of signs or symptoms of giant cell arteritis), as determined by the prescriber.

tocilizumab (Actemra®)

Policy # 00252
Original Effective Date: 07/21/2010
Current Effective Date: 01/01/2021

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of tocilizumab (Actemra) when patient selection criteria are not met to be **investigational*** (with the exception of those denoted above as **not medically necessary**).**

Based on review of available data, the Company considers the use of tocilizumab (Actemra) for indications other than those listed above to be **investigational.***

Based on review of available data, the Company considers the use of a dosage form of tocilizumab (Actemra) for indications in which it is not approved (e.g. intravenous form for giant cell arteritis) to be **investigational.***

Background/Overview

Actemra is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H2L2 polypeptide structure that is indicated for treating rheumatoid arthritis, systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, giant cell arteritis, and cytokine release syndrome. Single-use vials are available containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of Actemra. In October of 2013, a subcutaneous (SC) dosage form of Actemra was released for the rheumatoid arthritis indication. The SC form of Actemra contains 162 mg of Actemra in 0.9 mL. This 162 mg dosage can also be used for giant cell arteritis and both systemic and juvenile idiopathic arthritis.

Dosing for Actemra in rheumatoid arthritis is 4 mg/kg IV every 4 weeks following by an increase to 8 mg/kg IV every 4 weeks based on clinical response. The SC dosing is weight based. In patients less than 100 kg, the dosing is 162 mg administered SC every other week, followed by an increase to every week based on clinical response. For patients at or above 100 kg, the dosing is 162 mg SC every week. Dosing for polyarticular juvenile idiopathic arthritis is weight based. If a patient is less than 30 kg, the dose is 10 mg/kg IV every 4 weeks. If the patient is at or above 30 kg, the dose is 8 mg/kg IV every 4 weeks. As of late 2018, there is a subcutaneous option for dosing for this indication. The dosing for patients less than 30 kg is 162 mg SC every three weeks. For those at or

above 30 kg, the SC dose is 162 mg once every two weeks. For systemic juvenile idiopathic arthritis, the dosing is weight based as well. If the patient is less than 30 kg, the dose is 12 mg/kg IV every 2 weeks. If the patient's weight is at or above 30 kg, the dose is 8 mg/kg IV every 2 weeks. As of late 2018, there is a subcutaneous option for dosing for this indication. The dosing for patients less than 30 kg is 162 mg SC every two weeks. For those at or above 30 kg, the SC dose is 162 mg once every week. For giant cell arteritis, the dosing is 162 mg given once every week as a SC injection, in combination with a tapering course of glucocorticoids. A dose of 162 mg given once every other week can be considered. Dosing for cytokine release syndrome is weight based as well. The dose for patients less than 30 kg is 12 mg/kg. For those above 30 kg of weight is 8 mg/kg. The max dose per infusion for cytokine release syndrome is 800 mg/infusion. No more than 4 total infusions of Actemra should be used for cytokine release syndrome.

Rheumatoid Arthritis
Rheumatoid Arthritis is a chronic (long-term) disease that causes inflammation of the joints and surrounding tissues. It can also affect other organs. It is considered an autoimmune disease. In an autoimmune disease, the immune system confuses healthy tissue for foreign substances. Typically first line treatments such as DMARDs are used to treat this condition. An example of a DMARD would include methotrexate.

Polyarticular Juvenile Idiopathic Arthritis
Polyarticular juvenile idiopathic arthritis includes the inflammation of joints and presence of arthritis in children. Polyarticular juvenile idiopathic arthritis typically occurs in a symmetrical manner with knees, wrists, and ankles most frequently affected. However certain subgroups of children do have predominantly asymmetrical involvement. Typically, first line treatments such as DMARDs are used to treat this condition. An example of a DMARD would include methotrexate.

Systemic Juvenile Idiopathic Arthritis
Systemic juvenile idiopathic arthritis (formerly known as Still's disease or systemic juvenile rheumatoid arthritis) is a subset of juvenile idiopathic arthritis. Patients often have intermittent fever, rash, and arthritis. The diagnosis of this condition is very difficult due to the lack of specific diagnostic tests coupled with arthritis not being present in the early form of the disease. The diagnosis is typically made clinically based upon intermittent daily, high, spiking fevers for at least two weeks and arthritis. A salmon pink rash may also be present. Typical early treatments include corticosteroids or NSAID products prior to progressing to a biologic product.

tocilizumab (Actemra®)

Policy # 00252
Original Effective Date: 07/21/2010
Current Effective Date: 01/01/2021

Disease-Modifying Anti-Rheumatic Drugs
Disease-modifying anti-rheumatic drugs are typically used for the treatment of rheumatoid arthritis and polyarticular juvenile idiopathic arthritis. These drugs slow the disease process by modifying the immune system.

- methotrexate
- cyclosporine
- sulfasalazine
- mercaptopurine
- gold compounds

Giant Cell Arteritis
Giant cell (temporal) arteritis is the most common of the systemic vasculitides and most often, occurs in those age 50 years or older. Typical presentation could include headache, abrupt visual disturbances, jaw claudication, unexplained fever or anemia, as well as elevated ESR and/or CRP. The gold standard for the diagnosis of giant cell arteritis is temporal biopsy. Typically, only a suspicion of giant cell arteritis warrants treatment with a steroid, such as prednisone. The prednisone is often started at a dose of 60 mg/day and is tapered over an extended period of time. In this condition, it would seem that Actemra would be an add on option for those not maintaining control of giant cell arteritis manifestations on prednisone alone.

Cytokine Release Syndrome
T-cells can be genetically modified to target tumors through the expression of a chimeric antigen receptor. To date, the most prevalent adverse effect following infusion of CAR-T cells is the onset of immune activation, also known as cytokine release syndrome. Cytokine release syndrome has also been seen following the infusion of therapeutic monoclonal antibodies, interleukins, etc. The hallmark of cytokine release syndrome is immune activation resulting in elevated inflammatory cytokines. Clinical features include high fever, malaise, fatigue, myalgia, nausea, anorexia, tachycardia/hypotension, capillary leak, cardiac dysfunction, renal impairment, hepatic failure, and disseminated intravascular coagulation. One of the drugs that uses this technology is tisangenlecleucel (Kymriah®‡). Kymriah's package insert defines severe or life-threatening cytokine release syndrome as having either hemodynamic instability despite intravenous fluids and vasopressor support OR worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation OR rapid

clinical deterioration. Lower grades of cytokine release syndrome can be treated by antibiotics, symptom support (prodromal syndrome), antipyretics, oxygen, intravenous fluids and/or low dose vasopressors (overt cytokine release syndrome). This is the definition that will be used in the medical policy. Higher degrees of cytokine release syndrome (resistant type) can be treated with additional doses of Actemra, multiple vasopressors, oxygen, and/or methylprednisolone. Currently, the only FDA approved product to treat CAR-T associated cytokine release syndrome is Actemra. No more than 4 total doses should be administered for cytokine release syndrome. The interval should be at least 8 hours between infusions and no infusion should exceed 800 mg.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Actemra is an infused as well as SC injected monoclonal antibody that inhibits interleukin-6 receptors. It was approved in Jan. 2010 to treat adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist(s). The U.S. FDA approved Genentech's tocilizumab (Actemra) for the treatment of active systemic juvenile idiopathic arthritis, alone or in combination with methotrexate, in patients two years of age and older in April 2011.

October 2012, the FDA has now approved Actemra for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs.

April 2013, the FDA has now approved Actemra for the treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.

In October of 2013, the FDA approved a SC version of the drug for use in rheumatoid arthritis.

In May of 2017, the FDA approved Actemra for use in patients with giant cell arteritis as a SC dose.

In August of 2017, the FDA approved Actemra for use in the treatment of cytokine release syndrome in patients 2 years of age or older.

tocilizumab (Actemra®)

Policy # 00252
Original Effective Date: 07/21/2010
Current Effective Date: 01/01/2021

In mid to late 2018, the FDA approve Actemra to be used in SC form for polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis. Previously, there was only IV dosing available.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Rheumatoid Arthritis-Intravenous

The efficacy and safety of Actemra was assessed in five randomized, double-blind, multicenter studies in patients > 18 years with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least eight tender and six swollen joints at baseline. Actemra was given IV every four weeks as monotherapy (Study I), in combination with methotrexate (Studies II and III) or other DMARDs (Study IV) in patients with an inadequate response to those drugs, or in combination with methotrexate in patients with an inadequate response to TNF antagonists (Study V).

Study I evaluated patients with moderate to severe active rheumatoid arthritis who had not been treated with methotrexate within six months prior to randomization, or who had not discontinued previous methotrexate treatment as a result of clinically important toxic effects or lack of response. In this study, 67% of patients were methotrexate-naïve, and over 40% of patients had rheumatoid arthritis less than two years. Patients received Actemra 8 mg/kg monotherapy or methotrexate alone (dose titrated over eight weeks from 7.5 mg to a maximum of 20 mg weekly). The primary endpoint was the proportion of Actemra patients who achieved an ACR20 response at Week 24.

Study II is an ongoing 2-year study with a planned interim analysis at week 24 that evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to methotrexate. Patients received Actemra 8 mg/kg, Actemra 4 mg/kg, or placebo every 4 weeks, in

combination with methotrexate (10 to 25 mg weekly). The primary endpoint at week 24 was the proportion of patients who achieved an ACR20 response.

Study III evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to methotrexate. Patients received Actemra 8 mg/kg, Actemra 4 mg/kg, or placebo every 4 weeks, in combination with methotrexate (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study IV evaluated patients who had an inadequate response to their existing therapy, including one or more DMARDs. Patients received Actemra 8 mg/kg or placebo every 4 weeks, in combination with the stable DMARDs. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study V evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy was discontinued prior to randomization. Patients received Actemra 8 mg/kg, Actemra 4 mg/kg, or placebo every 4 weeks, in combination with methotrexate (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Clinical Response
In all studies, patients treated with 8 mg/kg Actemra had statistically significant ACR20, ACR50, and ACR70 response rates versus methotrexate- or placebo-treated patients at week 24.

Patients treated with Actemra at a dose of 4 mg/kg in patients with inadequate response to DMARDs or TNF antagonist therapy had lower response rates compared to patients treated with Actemra 8 mg/kg.

Rheumatoid Arthritis-Subcutaneous
The efficacy and safety of SC administered Actemra was assessed in two double-blind, controlled, multicenter studies in patients with active rheumatoid arthritis. One study (SC-I) was a non-inferiority study that compared the efficacy and safety of Actemra 162 mg administered every week SC to 8 mg per kg IV every four weeks. The second study (SC-II) was a placebo-controlled superiority study that evaluated the safety and efficacy of Actemra 162 mg administered every other week SC to placebo. Both SC-I and SC-II required patients to be > 18 years of age with moderate to

severe active rheumatoid arthritis diagnosed according to ACR criteria who had at least 4 tender and 4 swollen joints at baseline (SC-I) or at least 8 tender and 6 swollen joints at baseline (SC-II), and an inadequate response to their existing DMARD therapy, where approximately 20% also had a history of inadequate response to at least one TNF inhibitor. All patients in both SC studies received background non-biologic DMARD(s). In SC-I, 1262 patients were randomized 1:1 to receive Actemra SC 162 mg every week or Actemra IV 8 mg/kg every four weeks in combination with DMARD(s). In SC-II, 656 patients were randomized 2:1 to Actemra SC 162 mg every other week or placebo, in combination with DMARD(s). The primary endpoint in both studies was the proportion of patients who achieved an ACR20 response at Week 24. In SC-I, the primary outcome measure was ACR20 at Week 24. The pre-specified non-inferiority margin was a treatment difference of 12%. The study demonstrated non-inferiority of Actemra with respect to ACR20 at Week 24; ACR50, ACR70, and DAS28 responses are also shown in Table 7. In SC-II, a greater portion of patients treated with Actemra 162 mg SC every other week achieved ACR20, ACR50, and ACR70 responses compared to placebo-treated patients. Further, a greater proportion of patients treated with Actemra 162 mg SC every other week achieved a low level of disease activity as measured by a DAS28-ESR less than 2.6 at Week 24 compared to those treated with placebo.

Polyarticular Juvenile Idiopathic Arthriitis - Intravenous
Actemra was assessed for polyarticular juvenile idiopathic arthritis in a three part study in patients who had an inadequate response to methotrexate or inability to tolerate methotrexate. The primary endpoint was the proportion of patients with a juvenile idiopathic arthriitis ACR30 flare at week 40 relative to week 16. Juvenile idiopathic arthriitis IA ACR 30 flare was defined as 3 or more of the 6 core outcome variables worsening by at least 30% with no more than 1 of the remaining variables improving by more than 30% relative to Week 16. Actemra treated patients experienced significantly fewer disease flares compared to placebo-treated patients (26% [21/82] versus 48% [39/81]; adjusted difference in proportions -21%, 95% CI: -35%, -8%).

Polyarticular Juvenile Idiopathic Arthriitis - Subcutaneous
Actemra SC in polyarticular juvenile idiopathic arthritis was assessed in a 52-week, open-label, multicenter, pharmacokinetic/pharmacodynamic (PK/PD) and safety study to determine the appropriate SC dose of Actemra that achieved comparable PK/PD profiles to the Actemra IV regimen. Polyarticular juvenile idiopathic arthritis patients aged 1 to 17 years with an inadequate response or inability to tolerate methotrexate, including patients with well-controlled disease on treatment with Actemra IV and Actemra-naïve patients with active disease, were treated with

Actemra SC based on body weight. Patients weighing at or above 30 kg (n = 25) were treated with 162 mg of Actemra SC every 2 weeks and patients weighing less than 30 kg (n = 27) received 162 mg of Actemra SC every 3 weeks for 52 weeks. The efficacy of subcutaneous Actemra in children 2 to 17 years of age is based on pharmacokinetic exposure and extrapolation of the established efficacy of intravenous Actemra in polyarticular juvenile idiopathic arthritis patients and subcutaneous Actemra in patients with rheumatoid arthritis.

Systemic Juvenile Idiopathic Arthritis - Intravenous
The efficacy of Actemra for the treatment of systemic juvenile idiopathic arthritis was assessed in a 12 week randomized, double blind, placebo controlled trial. The primary endpoint of the trial was the proportion of patients with at least 30% improvement in JIA ACR core set (JIA ACR 30 response) at Week 12 and absence of fever (no temperature at or above 37.5°C in the preceding 7 days. Eighty-five percent (85%) of patients in the Actemra group met the primary endpoint vs. 24% in the placebo group.

Systemic Juvenile Idiopathic Arthritis - Subcutaneous
Actemra SC in pediatric patients with systemic juvenile idiopathic arthritis was assessed in a 52-week, open-label, multicenter, PK-PD and safety study to determine the appropriate subcutaneous dose of Actemra that achieved comparable PK/PD profiles to the Actemra IV regimen. Eligible patients received Actemra SC dosed according to body weight, with patients weighing at or above 30 kg (n = 26) dosed with 162 mg of Actemra every week and patients weighing below 30 kg (n = 25) dosed with 162 mg of Actemra every 10 days (n=8) or every 2 weeks (n=17) for 52 weeks. The efficacy of subcutaneous Actemra in children 2 to 17 years of age is based on pharmacokinetic exposure and extrapolation of the established efficacy of intravenous Actemra in systemic juvenile idiopathic arthritis patients.

Giant Cell Arteritis
The safety and efficacy of Actemra SC was evaluated in a single, randomized, double-blind, multicenter study in patients with active giant cell arteritis. Patients were placed in four treatment arms. Two doses of Actemra (162 mg once weekly and every other week) were compared to placebo (prednisone taper over 26 weeks and 52 weeks). The study consisted of a 52 week blinded period, followed by a 104 week open label extension. All patients received background prednisone therapy. The primary efficacy endpoint was the proportion of patients achieving sustained remission from week 12 thru week 52. This was defined as 1.) absence of giant cell arteritis signs and symptoms

from week 12 thru week 52, 2.) normalization of erythrocyte sedimentation rate (to less than 30 mm/hr without an elevation to greater than or equal to 30 mm/hr attributable to giant cell arteritis) from week 12 to week 52, 3.) normalization of C-reactive protein to less than 1 mg/dL with an absence of successive elevations greater than or equal to 1 mg/dL from week 12 to 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. Both arms of the Actemra treated patients showed superiority in achieving sustained remission from week 12 to week 52 compared with placebo plus 26 weeks of prednisone. Both Actemra arms also achieved superiority as compared to the placebo plus 52 weeks of prednisone arm. Percent responders were 14%, 17.6%, 56%, and 53.1% in the placebo plus 26 week prednisone taper, placebo plus 52 week prednisone taper, Actemra once weekly plus prednisone taper, and Actemra every other week plus prednisone taper groups.

Cytokine Release Syndrome
The efficacy or Actemra for the treatment of cytokine release syndrome was assessed in a retrospective analysis of pooled outcome data from clinical trials of CAR-T (chimeric antigen receptor T) cell therapies for hematological malignancies. Patients were given Actemra with or without additional high dose steroids. Resolution of cytokine release syndrome was defined as a lack of fever and off vasopressors for at least 24 hours. Sixty-nine percent (69%) of patients (31), achieved a response.

References

1. Food and Drug Administration (FDA). Center for Drug Evaluation and Research (CDER). Drug Information. Tocilizumab (Actemra). Information. Approved 10/2012. Available at: http://www.fda.gov.
2. An MM, Zou Z, Shen H, Zhang JD, Cao YB, Jiang YY; The addition of tocilizumab to DMARD therapy for rheumatoid arthritis: a meta-analysis of randomized controlled trials. EUR J Clin Pharmacol. 2009 Nov 21.
3. Garnero P, Thompson E, Woodworth T, Smolen JS. Rapid and sustained improvement in bone and cartilage turnover markers with the anti-interleukin-6 receptor inhibitor tocilizumab plus methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate: Results from a substudy of the multicenter double-blind, placebo-controlled trial of tocilizumab in inadequate responders to methotrexate alone. Arthritis Rheum. 2009:62(1):33-43.

4. Kawashiri SY, Kawakami A, Yamasaki S, Imazato T, et al; Effects of the anti-interleukin-6 receptor antibody, tocilizumab, on serum lipid levels in patients with rheumatoid arthritis. Rheumatol Int. 2009 Dec 19.
5. Kawashiri SY, Kawakami A, Iwamoto N, Fujikawa K, et al.; Switching to the anti-interleukin-6 receptor antibody tocilizumab in rheumatoid arthritis patients refractory to antitumor necrosis factor biologics. Mod Rheumatol. 2009 Oct 3.
6. Tanaka T, Kuwahara Y, Shima Y, Hirano T, et al.; Successful treatment of reactive arthritis with a humanized anti-interleukin-6 receptor antibody, tocilizumab. Arthritis Rheum. 2009; 61(12):1762-4.
7. Actemra [Package Insert]. Updated September 2018. Genentech. San Francisco, CA.
8. Bonifant CL, Jackson HJ, Brentjens RJ, et al. Toxicity and management in CAR-T cell therapy. Molecular Therapy Oncolytics. 2016.
9. Kymriah [package insert]. Novartis Pharmaceuticals Corporation. Easy Hanover, New Jersey. Updated August 2017.

Policy History

Original Effective Date: 07/21/2010
Current Effective Date: 01/01/2021

07/01/2010	Medical Policy Committee review
07/21/2010	Medical Policy Implementation Committee approval. New policy.
06/02/2011	Medical Policy Committee review
06/15/2011	Medical Policy Implementation Committee approval. Added new FDA indication for systemic juvenile idiopathic arthritis.
06/14/2012	Medical Policy Committee review
06/20/2012	Medical Policy Implementation Committee approval. Added a Note to the criteria for systemic juvenile idiopathic arthritis stating that patients must have had an inadequate clinical response to therapies such as nonsteroidal anti-inflammatory drugs (NSAIDS) or corticosteroids before using tocilizumab (Actemra). The reason for denial will be not medically necessary if this criterion is not met. The not medically necessary denial statement is also incorporated into the Investigational and Not Medically Necessary coverage sections. Deleted the investigational statement regarding non-FDA approved indications, since it is duplicative given the additions to the coverage section.

tocilizumab (Actemra®)

Policy # 00252
Original Effective Date: 07/21/2010
Current Effective Date: 01/01/2021

11/01/2012	Medical Policy Committee review
11/28/2012	Medical Policy Implementation Committee approval. Added new FDA approved indication.
06/06/2013	Medical Policy Committee review
06/25/2013	Medical Policy Implementation Committee approval. Changed some wording to match other similar policies. Added a new indication of polyarticular juvenile idiopathic arthritis with similar criteria as other drugs. Relocated PPD to each indication instead of a note. Reworded the Investigational and Not Medically Necessary sections. Updated some background info.
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. Added requirements for Actemra SubQ requests to have tried both Humira and Enbrel. Updated Investigational and Not Medically Necessary sections to reflect change. Updated Background/Overview info and Rationale/Source sections to reflect new subQ dosage form of Actemra.
12/04/2014	Medical Policy Committee review
12/17/2014	Medical Policy Implementation Committee approval. No change to coverage.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. No change to coverage.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. Added indication and information for Giant Cell Arteritis. Clarified TB test. Updated language for combo use of biologics.
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. Removed requirement for Humira and Enbrel prior to Actemra for RA. Added the new FDA approved indication for cytokine release syndrome and subsequent background info and updates.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Updated to reflect the new availability of subcutaneous dosing for both systemic and polyarticular juvenile

	idiopathic arthritis. For the polyarticular variety, the use of Humira will be required first. Updated background information and rationale/source to reflect the new dosage.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/01/2020	Medical Policy Committee review
10/07/2020	Medical Policy Implementation Committee approval. For rheumatoid arthritis subcutaneous Actemra requests, added a requirement for Humira failure first.
10/01/2021	Coding update

Next Scheduled Review Date: 10/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

tocilizumab (Actemra®)

Policy # 00252
Original Effective Date: 07/21/2010
Current Effective Date: 01/01/2021

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J3262
ICD-10 Diagnosis	M05.40-M05.479, M05.49, M05.50-M05.579, M05.59, M05.70-M05.779, M05.79, M05.80-M05.879, M05.89, M05.9, M06.00-M06.079, M06.08, M06.09, M06.20-M06.279, M06.28-M06.29, M06.30-M06.379, M06.28-M06.29, M06.30-M06.379, M06.38-M06.39, M06.80-M06.879, M06.88-M06.89, M06.9, M08.00-M08.079, M08.08-M08.09, M08.20-M08.279, M08.28-M08.29, M08.3, M08.40-M08.479, M08.48, M08.80-M08.879, M08.88-M08.89, M08.90-M08.979, M08.98-M08.99, M31.5-M31.6 Adding codes eff 10/1/2021: M31.10-M31.19

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);

2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.