BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Tocilizumab (Actemra®)

Policy # 00252
Original Effective Date: 07/21/2010
Current Effective Date: 01/01/2014

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

Patient Selection Criteria
Coverage eligibility for the use of tocilizumab (Actemra) for the treatment of rheumatoid arthritis (RA) will be considered when all of the following patient selection criteria are met:

- Patient is 18 years of age or older; and
- Patient has a diagnosis of moderately to severely active rheumatoid arthritis (RA); and
- Patient has failed treatment to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDS); and
- For Actemra subcutaneous (SC) requests: Patient has failed treatment with adalimumab (Humira) AND etanercept (Enbrel) after at least two months of therapy with each product (unless there is clinical evidence or patient history that suggests that these products 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 purified protein derivative (PPD) test prior to treatment.

Systemic Juvenile Idiopathic Arthritis (SJIA)
Based on review of available data, the Company may consider the use of tocilizumab (Actemra) for the treatment of systemic juvenile idiopathic arthritis (SJIA) to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for the use of tocilizumab (Actemra) for the treatment of active systemic juvenile idiopathic arthritis (SJIA) 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 (SJIA); 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*)
- Patient has a negative purified protein derivative (PPD) test prior to treatment.

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Polyarticular Juvenile Idiopathic Arthritis (PJIA)
Based on review of available data, the Company may consider the use of tocilizumab (Actemra) for the treatment of active polyarticular juvenile idiopathic arthritis (PJIA) to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for the use of tocilizumab (Actemra) for the treatment of active polyarticular juvenile idiopathic arthritis (PJIA) 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 polyarticular juvenile idiopathic arthritis (PJIA); and
- Patient has failed treatment to one or more Disease-Modifying Anti-Rheumatic Drugs (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).*
- Patient has a negative purified protein derivative (PPD) test prior to treatment.

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.***

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 (RA):
  - For Actemra subcutaneous (SC) requests: Patient has failed treatment with adalimumab (Humira) AND etanercept (Enbrel) after at least two months of therapy with each product
- For systemic juvenile idiopathic arthritis (SJIA):
  - Patient has inadequate clinical response to nonsteroidal anti-inflammatory drugs (NSAIDS) or corticosteroids
- For polyarticular juvenile idiopathic arthritis (PJIA):
  - Patient has failed treatment to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDS)

Background/Overview

Tocilizumab (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 RA, SJIA, and PJIA. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. Actemra has a molecular weight of approximately 148kDa.

Actemra is supplied as a sterile, preservative-free solution for intravenous (IV) infusion at a concentration of 20 mg/mL. Actemra is a colorless to pale yellow liquid, with a pH of about 6.5. Single-use vials are available containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of Actemra. Injectable solutions of Actemra are formulated in an aqueous solution containing disodium phosphate dodecahydrate and sodium dihydrogen phosphate dehydrate (as a 15 mmol/L phosphate buffer), polysorbate 80 (0.5 mg/ml), and sucrose (50 mg/mL). In October of 2013, a SC dosage form of Actemra was released for the RA indication. The SC form of Actemra contains 162 mg of Actemra in 0.9 mL.

Dosing for Actemra in RA is 4mg/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 PJIA is weight based. If a patient is less than 30 kg, the dose in 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. For SJIA, 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.

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 RA 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 SJIA, alone or in combination with methotrexate (MTX), in patients two years of age and older in April 2011. Full prescribing information can be found at: www.actemra.com.

October 2012, the FDA has now approved Actemra for the treatment of adult patients with moderately to severely active RA 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 PJIA.

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

Rationale/Source

Rheumatoid Arthritis-Intravenous
The efficacy and safety of Actemra was assessed in five randomized, double-blind, multicenter studies in patients > 18 years with active RA 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 MTX (Studies II and III) or other DMARDs (Study

IV) in patients with an inadequate response to those drugs, or in combination with MTX in patients with an inadequate response to TNF antagonists (Study V).

Study I evaluated patients with moderate to severe active RA who had not been treated with MTX within six months prior to randomization, or who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response. In this study, 67% of patients were MTX-naïve, and over 40% of patients had RA less than two years. Patients received Actemra 8 mg/kg monotherapy or MTX 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 RA who had an inadequate clinical response to MTX. Patients received Actemra 8 mg/kg, Actemra 4 mg/kg, or placebo every 4 weeks, in combination with MTX (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 RA who had an inadequate clinical response to MTX. Patients received Actemra 8 mg/kg, Actemra 4 mg/kg, or placebo every 4 weeks, in combination with MTX (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 RA 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 MTX (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 MTX- 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 RA. 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 RA 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
Actemra was assessed for PJIA in a three part study in patients who had an inadequate response to MTX or inability to tolerate MTX. The primary endpoint was the proportion of patients with a juvenile idiopathic arthriitis (JIA) ACR 30 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%).

Systemic Juvenile Idiopathic Arthritis
The efficacy of Actemra for the treatment of SJIA 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.

References

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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.

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7. Actemra [Package Insert]. Updated October 2013. Genentech. San Francisco, CA.

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines (BCBSLAMPCG) are obtained from Current Procedural Terminology (CPT®)‡, copyright 2012 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.

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CPT is a registered trademark of the American Medical Association.

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-9 Diagnosis	714.0, 714.30 thru 714.33
ICD-9 Procedure	No code

Policy History

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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.

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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.

Next Scheduled Review Date: 12/2014

*****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.

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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.