BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Tocilizumab (Actemra)

File Name:	tocilizumab_actemra
Origination:	2/2010
Last CAP Review:	2/2019
Next CAP Review:	2/2020
Last Review:	2/2019

Description of Procedure or Service

Tocilizumab (Actemra®) is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ subclass with a typical H_2L_2 polypeptide structure approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have used one or more disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX), with inadequate response.

Tocilizumab subcutaneous injection is also approved for the treatment of adult patients with giant cell arteritis (GCA). In addition, tocilizumab is used as both the intravenous (IV) or subcutaneous formulations for patients two years of age and older with active polyarticular juvenile idiopathic arthritis (PJIA) and systemic juvenile idiopathic arthritis (SJIA), and as the IV formulation for chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS). Tocilizumab is not approved for subcutaneous use in patients with CRS. It is not known if tocilizumab is safe and effective in children with PJIA, SJIA or CRS under two years of age or in children with conditions other than PJIA, SJIA or CRS.

Related Policies:
Abatacept (Orencia)
Golimumab (Simponi Aria)
Infliximab (Remicade)
Rituximab for the Treatment of Rheumatoid Arthritis

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for Tocilizumab (Actemra®) for the treatment of rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis and cytokine release syndrome when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

Please refer to the Member's Benefit Booklet for availability of benefits. This policy relates only to the services or supplies described herein. Member's benefits may vary according to benefit design, therefore Member benefit language should be reviewed before applying the terms of this medical policy.

Coverage for Tocilizumab (Actemra®) requires prior review.

When Tocilizumab (Actemra®) is covered

Tocilizumab (Actemra®) may be medically necessary for the treatment of:

- Adult patients with moderately to severely active rheumatoid arthritis who have failed to respond adequately or are intolerant to Remicade® (infliximab) **OR** Simponi Aria® (golimumab).
- Adult patients with giant cell arteritis.
- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (pJIA) or with active systemic juvenile idiopathic arthritis (sJIA).
- 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.

When Tocilizumab (Actemra®) is not covered

Tocilizumab (Actemra®) is considered not medically necessary for the treatment of rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis and cytokine release syndrome when the criteria listed above are not met.

Tocilizumab (Actemra®) is considered not medically necessary when used for patients who at initiation have an absolute neutrophil count (ANC) below 2000/mm^3, platelet count below 100,000/mm^3, or who have ALT or AST above 1.5 times the upper limit of normal.

Tocilizumab (Actemra®) is considered not medically necessary for patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiation of Tocilizumab (Actemra®) in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of serious or opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or with underlying conditions that may predispose them to these infections;
- with recently active GI problems such as diverticulitis possibly placing them at risk of perforation

Tocilizumab (Actemra®) is considered not medically necessary when used in combination with biological DMARDs such as TNF antagonists, anakinra (Kineret®), rituximab (Rituxan®), and abatacept (Orencia®).

Tocilizumab (Actemra®) is considered investigational when used for conditions other than rheumatoid arthritis (RA), active systemic juvenile idiopathic arthritis (sJIA), polyarticular juvenile idiopathic arthritis (pJIA), and chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome. BCBSNC does not cover investigational services.

Policy Guidelines

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including tocilizumab for rheumatoid arthritis. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants.

For RA, pJIA, and sJIA, tocilizumab may be used alone or in combination with methotrexate; and in RA, other non-biologic DMARDs may be used.

The safety and effectiveness of tocilizumab in pregnant or nursing women has not been established.

According to the Food and Drug Administration (FDA) approved labeling for tocilizumab, the dose should not exceed 800 mg per infusion every 28 days for RA or CRS patients.

According to the Food and Drug Administration (FDA) approved labeling for tocilizumab, in children 2 years of age and older with active Systemic Juvenile Idiopathic Arthritis (sJIA), the dosing interval is every 2 weeks.

According to the Food and Drug Administration (FDA) approved labeling for tocilizumab, in children 2 years of age and older with active Polyarticular Juvenile Idiopathic Arthritis (pJIA), the dosing interval is every 4 weeks.

According to the Food and Drug Administration (FDA) approved labeling for tocilizumab, if no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of tocilizumab may be administered, with the interval between consecutive doses being at least 8 hours.

The safety and effectiveness of tocilizumab (Actemra®) in pediatric patients with conditions other than RA, pJIA, sJIA or CRS have not been studied.

The approved labeling does not describe circumstances in which dosages above this maximum would be considered safe and effective.

Tocilizumab Site of Care Eligibility

1. Tocilizumab administration may be given in an inpatient setting if the inpatient setting is medically necessary. An inpatient admission for the sole purpose of Tocilizumab infusion is not medically necessary, OR
2. Tocilizumab administration in a hospital outpatient setting is considered medically necessary if the following criteria are met:
    a. History of mild adverse events that have not been successfully managed through mild pre-medication (diphenhydramine, acetaminophen, steroids, fluids, etc.), OR
    b. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity, OR
    c. First infusion, OR
    d. Less than 3 months since first Tocilizumab infusion, OR
    e. First infusion after six months of no Tocilizumab infusions, OR
    f. Requirement of a change in Tocilizumab product.
3. Members who do not meet the criteria above are appropriate for Tocilizumab administration in a **home-based infusion** or physician office setting with or without supervision by a certified healthcare professional. Inpatient and hospital outpatient infusion, in the absence of the criteria in #1 or #2 above is considered not medically necessary.

DEFINITIONS

Biologic DMARDs: A class of drugs thought to work by targeting components of the immune system by blocking specific immune cytokines, blocking other cytokines, binding with cytokines suppressing Il-12 and IL-23, or by directly suppressing lymphocytes; includes the anti-CD20 monoclonal antibodies (e.g. rituximab), interleukin-1 receptor antagonists (IL-1Ra) (e.g. anakinra), interleukin-6 (IL-6) receptor antagonists (e.g. tocilizumab), interleukin-(IL)-12 and IL- 23 antagonists (e.g. ustekinumab), selective co-stimulation modulators (e.g. abatacept), and the tumor necrosis factor (TNF) antagonists (inhibitors).

Nonbiologic DMARDs: A class of drugs, also referred to as synthetic DMARDs, thought to work by altering the immune system function to halt the underlying processes that cause certain forms of inflammatory conditions, although their exact mechanisms of action are unknown. Drugs in this class include azathioprine, hydroxychloroquine, leflunomide, methotrexate (MTX), minocycline, organic gold compounds, penicillamine, and sulfasalazine.

Tumor Necrosis Factor (TNF) antagonists: A class of biologic DMARDs designed to neutralize inflammatory cytokines that target specific pathways of the immune system and either enhance or inhibit immune response. Drugs in this class include adalimumab (Humira®, Abbott Laboratories, North Chicago, IL), certolizumab pegol (Cimzia®, UCB, Inc., Smyrna, GA), etanercept (Enbrel®, Immunex Corporation, Thousand Oaks, CA), golimumab (Simponi®, Centocor Ortho Biotech Inc., Horsham, PA), and infliximab (Remicade®, Centocor Ortho Biotech Inc., Horsham, PA).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *J3262*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

U.S. Food and Drug Administration. BLA Approval letter dated January 8, 2010. BL 1215276.

U.S. Food and Drug Administration. Actemra® Prescribing Information. Retrieved 2/1/10 from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

Specialty Matched Consultant Advisory Panel Review 2/2011

U.S. Food and Drug Administration. Prescribing information. Retrieved 6/23/11 from http://www.fda.gov/downloads/Drugs/DrugSafety/UCM197463.pdf

FDA website. Retrieved 6/23/11 from http://www.fda.gov/downloads/Drugs/DrugSafety/UCM197463.pdf

Specialty Matched Consultant Advisory Panel Review 2/2012

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2011/ucm251572.htm

FDA website. Retrieved 1/11/12 from http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM202044.pdf

FDA website. Retrieved 2/4/2013 from http://www.fda.gov/downloads/Drugs/DrugSafety/UCM197463.pdf

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FDA website. Retrieved 1/2014 from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm352022.htm

http://www.gene.com/download/pdf/actemra_prescribing.pdf

Specialty Matched Consultant Advisory Panel Review 2/2014

Specialty Matched Consultant Advisory Panel Review 2/2015

Specialty Matched Consultant Advisory Panel Review 2/2016

National Institute for Health and Clinical Excellence (NICE). Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. Technology Appraisal Guidance 375. London, UK: NICE; 2016

Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016; 68(1):1-26. Available at: http://www.rheumatology.org/Portals/0/Files/ACR%202015%20RA%20Guideline.pdf

FDA Prescribing information available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s114lbl.pdf

Specialty Matched Consultant Advisory Panel Review 2/2018

Genentech, Inc. Actemra (tocilizumab) injection, for intravenous or subcutaneous use. Highlights of prescribing information. December 2018. Available at: https://www.gene.com/download/pdf/actemra_prescribing.pdf. Accessed January 2019.

Specialty Matched Consultant Advisory Panel Review 2/2019

Policy Implementation/Update Information

3/2/10 New medical policy issued. Tocilizumab (Actemra®) may be medically necessary for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. Notification date 3/02/10 for effective date of 6/08/10. (adn)

1/4/11 Added new HCPCS code J3262 to Billing/Coding section. Removed J3590. (lpr)

3/15/11 Specialty Matched Consultant Advisory Panel Review 2/2011. Added "these infections" to end of last bullet statement which reads "who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or with underlying conditions that may predispose them to these infections." (lpr)

7/1/11 Added quantity limitations to Policy Guidelines. Medical director review 6/2011. Notification date 7/1/11 for effective date of 10/1/11. (lpr)

3/20/12 Added new approval guidelines from the FDA on use in patients 2 years old and older under "When Covered" and Policy Guidelines. Under "When Not Covered" changed first statement to read: Tocilizumab (Actemra) is considered not medically necessary patients when used for patients with an absolute neutrophil count (ANC) below 2000/mm^3, platelet count below 100,000/mm^3, or who have ALT or AST above 1.5 times the upper limit of normal. Changed the second statement under "When Not Covered" to read: Tocilizumab (Actemra) is considered not medically necessary for patients with an active infection, including localized infections and also added a fifth bullet that reads: "with recently active GI problems such as diverticulitis possibly placing them at risk of perforation." Added the following investigational statement under "When Not Covered": Tocilizumab (Actemra®) is considered investigational when used for conditions

other than rheumatoid arthritis (RA) and active systemic juvenile idiopathic arthritis (sJIA). Specialty Matched Consultant Advisory Panel review 2/29/2012. (lpr)

12/1/12 "When Covered" section modified to revise medical necessity criteria from "Tocilizumab (Actemra®) may be medically necessary for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies." to "Tocilizumab (Actemra®) may be medically necessary for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have failed to respond adequately or are intolerant to Remicade ® (infliximab)."; and from "Tocilizumab (Actemra®) may be medically necessary for the treatment of patients 2 years of age and older with active systemic juvenile idiopathic arthritis (sJIA)." to "Tocilizumab (Actemra®) may be medically necessary for the treatment of patients between 2 and 6 years of age with active systemic juvenile idiopathic arthritis (sJIA). Tocilizumab (Actemra®) may be medically necessary for the treatment of patients 6 years of age and older with active systemic juvenile idiopathic arthritis (sJIA) who have failed to respond adequately or are intolerant to Remicade ® (infliximab)." Notice 12/1/12, effective 2/1/13.

3/12/13 Specialty Matched Consultant Advisory panel review meeting 2/20/2013. No change to policy statement. Reference added. (lpr)

5/28/13 Under "When Covered" section: added medically necessary indication for polyarticular juvenile idiopathic arthritis (pJIA) since now FDA approved. Under Policy Guidelines, added dosing interval of every 4 weeks. Reference added. Medical director review. (lpr)

10/15/13 Added trial of Simponi Aria (golimumab) to statement # 1 under When Covered section. Medical director review 10/2013. (lpr)

3/11/14 Reference updated. Specialty Matched consultant advisory panel meeting 2/25/2014. No change to policy statement. (lpr)

5/27/14 Under "When Covered" section, revised statement #2 to read: Tocilizumab (Actemra®) may be medically necessary for the treatment of patients **2 years of age and older** with active systemic juvenile idiopathic arthritis (sJIA). Removed/deleted statement #4 which read: Tocilizumab (Actemra®) may be medically necessary for the treatment of patients 6 years of age and older with active systemic juvenile idiopathic arthritis (sJIA) who have failed to respond adequately or are intolerant to Remicade ® (infliximab). (lpr)

3/10/15 Specialty Matched Consultant Advisory Panel review meeting 2/25/2015. No change to policy statement. (lpr)

4/1/16 Specialty Matched Consultant Advisory Panel review meeting 2/24/2016. No change to policy. (an)

3/31/17 Updated Description section. Added definitions to Policy Guidelines. Added References. Specialty Matched Consultant Advisory Panel review meeting 2/22/17. No change to policy statement. (an)

12/15/17 Description section updated. Policy Statement revised to read: BCBSNC will provide coverage for Tocilizumab (Actemra®) for the treatment of rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis and cytokine release syndrome when it is determined to be medically necessary because the medical criteria and guidelines shown below are met. New indications added to "When Covered" section. Reference added. (an)

12/29/17 Site of care criteria added to Policy Guidelines. Notification given 12/29/17 for policy effective date of 4/1/2018. (an)

1/26/18 Policy name "Nononcologic Uses of Rituximab" replaced with correct policy name "Rituximab for the Treatment of Rheumatoid Arthritis" in the Description section. Policy remains on notice for effective date 4/1/2018. (an)

4/27/18 Updated the following statement in "When Not Covered" section from "when used for patients with" to "when used for patients who at initiation have" for clarity. Reference added. Specialty Matched Consultant Advisory Panel review 2/28/18. No change to policy intent. (krc)

3/12/19 Minor edits and additions made to "Description" and "Policy Guidelines" sections for clarity. Added "chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome" to investigational statement as an acceptable indication in "When not covered" section. Reference added. Specialty Matched Consultant Advisory Panel review 2/20/2019. (krc)