 Approved Revision: Do Not Implement Until 4/2/21

Tocilizumab (Intravenous)

NDC CODE(S) 50242-0135-XX ACTEMRA 20MG/ML Solution (GENENTECH)
50242-0136-XX ACTEMRA 200MG/10ML Solution (GENENTECH)
50242-0137-XX ACTEMRA 400MG/20ML Solution (GENENTECH)

DESCRIPTION

Tocilizumab is a recombinant interleukin 6 (IL-6) receptor monoclonal antibody classified as a disease modifying antirheumatic drug. It binds specifically to soluble and membrane-bound IL-6 receptors and has been shown to block IL-6-mediated signaling through these receptors. IL-6 is a pro-inflammatory cytokine produced by a variety of cell types, including synovial and endothelial cells in joints affected by inflammatory processes.

POLICY

- Tocilizumab (Intravenous) for the treatment of the following is considered ***medically necessary*** if the medical appropriateness criteria are met: **(See Medical Appropriateness below.)**
  - Acute Graft Versus Host Disease
  - Castleman's disease
  - Cytokine Release Syndrome (CRS)
  - Neuromyelitis Optica Spectrum Disorder (NMOSD)
  - Rheumatoid arthritis (RA)
  - Juvenile idiopathic arthritis systemic (SJIA) or polyarticular (PJIA) disease
  - Immune Checkpoint Inhibitor Related Arthritis
- Tocilizumab (Intravenous) for the treatment of other conditions/diseases is considered ***investigational.***

MEDICAL APPROPRIATENESS

INITIAL APPROVAL

- Tocilizumab (Intravenous) for the treatment of the following is considered **medically appropriate** if **ALL** of the following:
  - Individual is 18 years of age or older (unless otherwise specified)
  - Individual has been evaluated and screened for the presence of latent tuberculosis (TB) infection prior to initiating treatment and will receive ongoing monitoring for presence of TB during treatment
  - Individual does not have an active infection, including clinically important localized infections
  - Will not be administered concurrently with live vaccines
  - Individual is not on concurrent treatment with a TNF inhibitor, other biologic response modifier or non-biologic agent, e.g., apremilast, tofacitinib, baricitinib, upadacitinib, etc., unless otherwise specified
  - Diagnosis of **ANY ONE** of the following:
    - Acute Graft Versus Host Disease (aGVHD) if individual has **ALL** of the following:
      - Received a hematopoietic stem cell transplant
      - Steroid-refractory acute GVHD
      - No response to first-line therapies (steroid-refractory disease) in combination with systemic corticosteroids as additional therapy
    - Castleman's Disease (NHL) if **ANY ONE** of the following:
      - Unicentric disease if **ALL** of the following:
        - Used as second-line single agent therapy
        - Disease is relapsed or refractory
        - Individual is human immunodeficiency virus (HIV)-negative and human herpesvirus-8 (HHV-8)-negative

- Multicentric disease if **ALL** of the following:
  - Used as subsequent single agent therapy
  - Relapsed, refractory or progressive disease

- Cytokine Release Syndrome (CRS) if **ALL** of the following:
  - Individual is 2 years of age or older
  - Individual has received or will be receiving chimeric antigen receptor T- cell therapy (CAR-T therapy) and **ANY ONE** of the following:
    - Tocilizumab is being ordered to have on-hand, prior to the administration of CAR-T therapy, if needed for the treatment of CRS
    - Individual has a confirmed diagnosis of chimeric antigen receptor T-cell (CAR-T) induced Grades 2-4 CRS
    - Individual has Grade 1-4 neurotoxicity with concurrent CRS
    - Used as supportive care for refractory CRS secondary to anti-CD19 therapy (i.e., blinatumomab)
- Management Immune Checkpoint Inhibitor Related Arthritis (immunotherapy-related inflammatory arthritis) if individual has **ALL** of the following:
  - Diagnosis of inflammatory arthritis related to immunotherapy with an immune checkpoint inhibitor (e.g. nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, cemiplimab, etc.)
  - Documented severe disease
  - Condition is refractory to high-dose corticosteroids (i.e., no improvement within 2 weeks of starting therapy)
- Juvenile idiopathic arthritis systemic (SJIA) or polyarticular (PJIA) disease if **ALL** of the following:
  - Individual is 2 years of age or older
  - Disease is active systemic (SJIA) or polyarticular (PJIA) disease
  - Physician has assessed baseline disease severity utilizing an objective measure/tool
  - Individual has had at least a one month trial and failure (unless contraindicated or intolerant) of previous therapy with either oral non-steroidal anti-inflammatory drugs (NSAIDs) **OR** an oral disease-modifying anti-rheumatic agent (DMARD) (e.g., methotrexate, leflunomide, sulfasalazine, etc.)
  - Administration is **ANY ONE** of the following:
    - As monotherapy
    - In combination therapy with methotrexate
- Neuromyelitis Optica Spectrum Disorder (NMOSD) if **ALL** of the following:
  - Used as a single agent or in combination with immunosuppressive therapy (e.g. azathioprine, methotrexate, mycophenolate, etc.)
  - Diagnosis confirmed by **ANY ONE** of the following:
    - Seropositive for aquaporin-4 (AQP4) IgG antibodies and **ALL** of the following:
      - Has **ANY ONE** of the NMO/NMOSD core clinical characteristics (***See Chart Part 1 below***)
      - Alternative diagnoses have been excluded (e.g., multiple sclerosis, sarcoidosis, cancer, chronic infection, etc.)
    - Seronegative for AQP-4 IgG antibodies **OR** unknown AQP-4-IgG status if individual has **ALL** of the following:
      - Minimum of **TWO** or more of the NMO/NMOSD core clinical characteristics (***See Chart - Part 1 below***) occurring as a result of one or more clinical attacks:
      - At least 1 core clinical characteristic must be **ANY ONE** of the following:
        - Optic neuritis
        - Acute myelitis with LETM (longitudinally extensive transverse myelitis lesions)
        - Area postrema syndrome
      - Dissemination in space (≥2 different core clinical characteristics)
      - Fulfillment of additional MRI requirements, as applicable (***See Chart - Part 2 below***)

- Alternative diagnoses have been excluded (e.g., multiple sclerosis, sarcoidosis, cancer, chronic infection, etc.)

Part 1 - Core Clinical Characteristics of NMOSD
▪ Optic neuritis ▪ Acute myelitis ▪ Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting ▪ Acute brainstem syndrome ▪ Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions ▪ Symptomatic cerebral syndrome with NMOSD-typical brain lesions
Part 2 - Additional MRI requirements - NMOSD without AQP4-IgG and NMOSD unknown AQP4-IgG status
Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm **Acute myelitis**: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM*) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis **Area postrema syndrome**: requires associated dorsal medulla/area postrema lesions **Acute brainstem syndrome**: requires associated peri-ependymal brainstem lesions
*LETM = longitudinally extensive transverse myelitis lesions

- Rheumatoid arthritis if **ALL** of the following:
  - Physician has assessed baseline disease severity utilizing an objective measure/tool
  - Documented moderate to severe active disease
  - Individual has had failure of or inadequate response to at least a 3 month trial of one or more oral DMARD (disease modifying anti-rheumatic drug) (e.g., methotrexate, azathioprine, auranofin, hydroxychloroquine, penicillamine, sulfasalazine, leflunomide, etc.)
  - May be used alone or in combination with methotrexate

RENEWAL CRITERIA

- Tocilizumab (Intravenous) is considered **medically appropriate** for renewal if **ALL** of the following criteria are met:
  - Individual continues to meet initial approval criteria
  - Individual is receiving ongoing monitoring for TB or other active infections
  - Absence of unacceptable toxicity from the agent, e.g., serious infection, severe neutropenia, severe thrombocytopenia, severe hepatotoxicity, gastrointestinal perforation, immunosuppression, severe hypersensitivity reactions, demyelinating disorders, etc.
  - For a diagnosis of **ANY ONE** of the following:
    - Acute Graft Versus Host Disease (aGVHD) if individual displayed a beneficial response to therapy (i.e., a complete or partial response) as determined by clinical assessment (e.g., International Bone Marrow Transplant Registry (IBMTR) scoring system, modified Glucksberg criteria, etc.)
    - Castleman's Disease (NHL) if ~~tumor~~ disease response as defined by stabilization of disease or decrease in size of tumor or tumor spread
    - Juvenile Idiopathic Arthritis (SJIA),(PJIA) with disease response as indicated by improvement in signs and compared to baseline such as the number of tender and swollen joint counts, reduction of C-reactive protein, improvement of patient global assessment, and/or an improvement on a disease activity scoring tool [e.g., an improvement on a composite scoring index such as Juvenile Arthritis Disease Activity Score (JADAS) or the American College of Rheumatology (ACR) Pediatric (ACR-Pedi 30) of at least 30% improvement from baseline in three of six variables]and/or an improvement on a disease activity scoring tool (e.g. an improvement on a composite scoring index such as Juvenile

Arthritis Disease Activity Score [JADAS] or the American College of Rheumatology [ACR] Pediatric [ACR-Pedi 30] of at least 30% improvement from baseline in three of six variables)
- NMOSD with disease response as indicated by stabilization/improvement in neurologic symptoms as evidenced by a decrease in acute relapses, stability reduced hospitalizations, reduction/discontinuation in plasma exchange treatments, and/or reduction/discontinuation of corticosteroids without relapse
- Rheumatoid arthritis (RA) with disease response as indicated by improvement in signs and compared to baseline such as the number of tender and swollen joint counts, reduction of C-reactive protein, improvement of patient global assessment, and/or an improvement on a disease activity scoring tool (e.g., an improvement on a composite scoring index such as Disease Activity Score-28 [DAS28] of 1.2 points or more or a ≥20% improvement on the American College of Rheumatology-20 [ACR20] criteria)
- Cytokine Release Syndrome may **NOT** be renewed after 4 doses total
- Management of Immune Checkpoint Inhibitor related Inflammatory Arthritis may not be renewed

INDICATION(S)	DOSAGE & ADMINISTRATION Doses exceeding 800 mg per infusion are not recommended
Acute GVHD	Administer 8 mg/kg intravenously, every 2-4 weeks until disease progression or unacceptable toxicity
Adult Rheumatoid Arthritis	Administer 4 mg/kg intravenously every 4 weeks May increase to 8 mg/kg every 4 weeks based on clinical response, up to a maximum of 800 mg per dose
Polyarticular Juvenile Idiopathic Arthritis	Weight ≥ 30 kg - Administer 8 mg/kg intravenously every 4 weeks Weight < 30 kg - Administer 10 mg/kg intravenously IV every 4 weeks
Systemic Juvenile Idiopathic Arthritis	Weight ≥ 30 kg - 8 mg/kg IV every 2 weeks Weight < 30 kg - 12 mg/kg IV every 2 weeks
Castleman's Disease (NHL)	Administer 8 mg/kg intravenously every 2 weeks for 16 weeks (8 doses total)
Cytokine Release Syndrome (CRS)	Weight ≥ 30 kg - Administer 8 mg/kg intravenously every 8 hours, if needed, up to a maximum of 4 total doses* Weight < 30 kg - Administer 12 mg/kg intravenously every 8 hours, if needed, up to a maximum of 4 total doses* **If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses may be administered. The interval between consecutive doses should be at least 8 hours. May be used with or without corticosteroids. Doses exceeding 800 mg per infusion are not recommended in CRS patients.*
Immune-Checkpoint Inhibitor Related Inflammatory Arthritis	Administer 4 mg/kg intravenously **ONE TIME ONLY**
NMOSD	Administer 8 mg/kg intravenously, every 4 weeks

LENGTH OF AUTHORIZATION

Coverage will be provided for Castleman's Disease for 4 months and may be renewed;
Coverage will be provided for Cytokine Release Syndrome for 4 doses only and may not be renewed;
Coverage will be provided for Immune Checkpoint Inhibitor related arthritis for 1 dose only and may not be renewed;
All other indications, coverage will be provided for 6 months and may be renewed.

Click here to view **DOSAGE LIMITS**

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with **Tennessee** Code Annotated **Section 56-7-2352** regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

SOURCES

Lexi-Comp Online. (2020). AHFS DI. *Tocilizumab*. Retrieved December 7, 2020 from Lexi-Comp Online with AHFS.

MICROMEDEX Healthcare Series. Drugdex Evaluations. (2020, September). *Tocilizumab*. Retrieved December 7, 2020 from MICROMEDEX Healthcare Series.

National Comprehensive Cancer Network. (2020). NCCN Drugs & Biologics Compendium®. *Tocilizumab*. Retrieved December 7, 2020 from the National Comprehensive Cancer Network.

Ringelstein, M., Ayzenberg, I., Harmel, J., Lauenstein, A. S., Lensch, E., Stögbauer, F., et al. (2015, July). Long-term therapy with interleukin 6 receptor blockade in highly active neuromyelitis optica spectrum disorder. *JAMA Neurology*. 2015; 72(7):756-763. doi:10.1001/jamaneurol.2015.0533.

Ringold, S., Weiss P.F., Beukelman T., DeWitt, E.M., Ilowite, N.T., Kimura, Y., et al. (2013, October). 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis & Rheumatism* 65(10), 2499-512. Retrieved June 1, 2017 from https://www.rheumatology.org/Portals/0/Files/2013%20Update%20of%20the%202011%20ACR%20Recommendations%20for%20the%20Treatment%20of%20Juvenile%20Idiopathic%20Arthritis.pdf.

Trebst, C., Jarius, S., Berthele, A., Friedemann, P., Schippling, S., Wildemann, B., et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). Journal of Neurology 2014; 261:1.

U. S. Food and Drug Administration. (2020, May). Center for Drug Evaluation and Research. *Actemra® (tocilizumab) injection, for intravenous or subcutaneous use*. Retrieved December 7, 2020 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125276s129,125472s042lbl.pdf.

Wingerchuk, D. M., Banwell, B., Bennett, J. L., Cabre, P., Carroll, W., Chitnis, T., et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015 Jul; 85(2):177-89.

Zhang, C., Zhang, M., Qiu, W., Ma, H., Zhang, X., Zhu, Z., et al, TANGO Study Investigators. Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial. *Lancet Neurology*, 2020; 19 (5):391.

EFFECTIVE DATE 4/2/21

ID_MRx