aPolicy Title:	Tocilizumab: Actemra, Tofidence, Tyenne **NON-ONCOLOGY POLICY** (Intravenous)		
		Department:	PHA
Effective Date:	01/01/2020		
Review Date:	09/25/2019, 12/18/2019, 1/22/2020, 8/3/2020, 11/9/2020, 5/13/2021, 10/21/21, 4/14/2022, 8/10/23, 12/07/2023, 01/10/2024,12/18/2024		

Purpose: To support safe, effective, and appropriate use of tocilizumab

Scope: Medicaid, Commercial, Medicare Medicaid Plan (MMP)

Policy Statement:

Tocilizumab is covered under the Medical Benefit when used within the following guidelines for non-oncology indications. Use outside of these guidelines may result in non-payment unless approved under an exception process. **For oncology indications, please refer to NHPRI Oncology Policy**

Procedure:

Coverage of tocilizumab will be reviewed prospectively via the prior authorization process based on criteria below.

Summary of Evidence:

Tocilizumab is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs), adult patients with giant cell arteritis, slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD), patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis, patients 2 years of age and older with active systemic juvenile idiopathic arthritis. The efficacy and safety of intravenously administered Actemra was assessed in five randomized, double-blind, multicenter studies in patients greater than 18 years with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. The primary endpoint was the proportion of Actemra patients who achieved an ACR 20 response at Week 24. In all intravenous studies, patients treated with 8 mg per kg Actemra had higher ACR 20, ACR 50, and ACR 70 response rates versus MTX- or placebo-treated patients at week 24. During the 24 week-controlled portions of Studies I to V, patients treated with Actemra at a dose of 4 mg per kg in patients with inadequate response to DMARDs or TNF antagonist therapy had lower response rates compared to patients treated with Actemra 8 mg per kg. The clinical efficacy of Actemra was assessed in a phase 3 multicenter, randomized, double-blind, placebo-controlled study in patients with Systemic Sclerosis (SSc) (Study WA29767). Patients were not permitted to use biologic agents (such as TNF antagonists), alkylating agents, or cyclophosphamide. The primary efficacy endpoint was change from baseline at Week 48 in modified Rodnan skin score (mRSS). In the overall population of Study WA29767, there was not a statistically significant difference in the mean change from baseline to Week 48 in mRSS (primary endpoint) in patients receiving Actemra compared to placebo (difference: -1.73; 95% CI: -3.78, 0.32). The efficacy of Actemra was assessed in a three-part

study, WA19977 (NCT00988221), including an open-label extension in children 2 to 17 years of age with active polyarticular juvenile idiopathic arthritis (PJIA), who had an inadequate response to methotrexate or inability to tolerate methotrexate. Treatment with a stable dose of methotrexate was permitted but was not required during the study. Concurrent use of disease modifying antirheumatic drugs (DMARDs), other than methotrexate, or other biologics (e.g., TNF antagonists or T cell co-stimulation modulator) were not permitted in the study. Part I consisted of a 16-week active Actemra treatment lead-in period (n=188) followed by Part II, a 24-week randomized double-blind placebo-controlled withdrawal period, followed by Part III, a 64-week open-label period. The primary endpoint was the proportion of patients with a JIA ACR 30 flare at week 40 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%). During the withdrawal phase (Part II), more patients treated with Actemra showed JIA ACR 30/50/70 responses at Week 40 compared to patients withdrawn to placebo. The efficacy of Actemra for the treatment of active SJIA was assessed in WA18221 (NCT00642460), a 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study. The primary endpoint 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). The JIA ACE response rate with the absence of a fever in the Actemra treatment group had an 85% respond rate meanwhile placebo had a 24% response rate.

Initial Criteria:

- Patient has been evaluated and screened for the presence of latent TB infection prior to initiating treatment; **AND**
- Patient does not have an active infection, including clinically important localized infections; **AND**
- Must not be administered concurrently with live vaccines; **AND**
- Patient is not on concurrent treatment with another biologic therapy (e.g, IL-inhibitor, TNF-inhibitor, integrin receptor antagonist, T cell costimulation modulator, etc.) or targeted synthetic therapy (e.g., Otezla (apremilast), Cibinqo (abrocitinib), Xeljanz/Xeljanz XR (tofacitinib), Rinvoq (Upadacitinib), Jakafi(ruxolitinib), Velsipity (etrasimod), etc.); **AND**
- If requesting Actemra (tocilizumab) or Tofidence (tocilizumab-bavi), the patient must have an inadequate response or intolerance to at least a 3-month trial of Tyenne (tocilizumab-aazg)
- Medicare members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements

Rheumatoid Arthritis

- Patient is 18 years or older; **AND**
- Physician has assessed baseline disease severity utilizing an objective measure/tool; **AND**
- Documented moderate to severe active disease; **AND**
    - Patient has had at least a 3-month trial and failed previous therapy with ONE conventional synthetic disease modifying anti-rheumatic drug (csDMARD) such as methotrexate, azathioprine, hydroxychloroquine, sulfasalazine, leflunomide, etc.;

AND has had an inadequate response, intolerance or contraindication to at least a 3-month trial of adalimumab at maximum tolerated doses; OR
    - Patient is already established on biologic or targeted synthetic therapy for the treatment of RA; AND
- May be used as a single agent or in combination with csDMARD (e.g., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine, etc.);

Systemic Juvenile Idiopathic Arthritis (sJIA) / Polyarticular Juvenile Idiopathic Arthritis pJIA)

- Patient is at least 2 years of age; **AND**
- Physician has assessed baseline disease severity utilizing an objective measure/tool;
- Patient has active systemic juvenile idiopathic arthritis (sJIA) or polyarticular juvenile idiopathic arthritis (pJIA); **AND**
    - Patient has had at least a 1-month trial and failure (unless contraindicated or intolerant) of previous therapy with either oral non-steroidal anti-inflammatory drugs (NSAIDs);OR conventional synthetic disease modifying anti-rheumatic drugs (csDMARDS) e.g., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine, etc.; AND has had an inadequate response, intolerance or contraindication to at least a 3-month trial of adalimumab at maximum tolerated doses; OR
    - Patient is already established on biologic or targeted synthetic therapy for the treatment of sJIA or pJIA; AND
- May be used alone or in combination with methotrexate;

Management of Immune Checkpoint Inhibitor Related Toxicities

- Patient has been receiving therapy with an immune checkpoint inhibitor (e.g. nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, cemiplimab, ipilimumab, dostarlimab, nivolumab/relatlimab-rmbw, retifanlimab, tislelizumab, toripalimab etc.); AND
    - Used as additional disease modifying antirheumatic therapy (DMARD) for any of the following immunotherapy-related toxicities:
        - Giant cell arteritis; OR
        - Moderate or severe inflammatory arthritis; **AND**
            - Patient's symptoms have not improved after holding immunotherapy; **AND**
                - Patient has not responded to oral corticosteroids; **OR**
                - Patient is unable to taper corticosteroids; **OR**
        - Polymyalgia rheumatica and is unable to taper prednisone OR has no improvement in symptoms from prednisone; OR
    - Used as additional corticosteroid-sparing immunosuppression for management of any of the following immunotherapy related toxicities:
        - G2 elevated alanine transaminase/aspartate transaminase (ALT/AST); **AND**

- Liver enzymes suggest worsening or no improvement after 3-7 days of prednisone; **OR**
- G3 or G4 elevated ALT/AST; **AND**
  - AST/ALT does not improve after 1-2 days of prednisone/methylprednisolone; **OR**
- G2 elevated alkaline phosphatase **AND**
  - Alkaline phosphatase worsens or does not improve within 3 days after initiating corticosteroids; **OR**
- G3 or G4 elevated alkaline phosphatase; **AND**

Alkaline phosphatase does not improve after 1-2 days of prednisone/methylprednisolone

Neuromyelitis Optica Spectrum Disorder (NMOSD)

- Patient has a confirmed diagnosis based on the following:
  - Patient is seropositive for aquaporin-4 (AQP4) IgG antibodies; **AND**
    - Patient has at least one core clinical characteristic §; **AND**
    - Alternative diagnoses have been excluded (e.g., myelin oligodendrocyte glycoprotein (MOG) antibody disease (MOGAD), multiple sclerosis, sarcoidosis, cancer, chronic infection, etc.); OR
  - Patient is seronegative for AQP-4 IgG antibodies OR has unknown AQP-4-IgG status; **AND**
    - Patient has at least two core clinical characteristics § occurring as a result of one or more clinical attacks; **AND**
    - Patient experienced ALL of the following:
      - At least 1 core clinical characteristic must be acute optic neuritis, acute myelitis with, or area postrema syndrome; **AND**
      - Fulfillment of additional typical MRI finding requirements for each area affected, ψ; **AND**
    - Alternative diagnoses have been excluded (e.g., myelin oligodendrocyte glycoprotein (MOG) antibody disease (MOGAD multiple sclerosis, sarcoidosis, cancer, chronic infection, etc.); **AND**
- Used as a single agent or in combination with immunosuppressive therapy (e.g. azathioprine, methotrexate, mycophenolate, etc.)

Giant Cell Arteritis (GCA) †

- Patient has large vessel arteritis that has at some point been verified with biopsy or with imaging of the large vessels (color Doppler ultrasound [CDUS], MRI, PET-CT, or CT angiography); **AND**
- Patient has active disease and an elevated c-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR); **AND**

- Patient has had an inadequate response, contraindication, or intolerance to glucocorticoid therapy alone; **AND**
- Used in combination with a tapering course of glucocorticoids *(NOTE: tocilizumab can be used alone following discontinuation of glucocorticoids.)*

§ Core Clinical Characteristics of NMOSD: ▪ Acute Optic neuritis ▪ Acute myelitis ▪ Area postrema syndrome (APS): episode of otherwise unexplained hiccups and/or nausea and vomiting (lasting for at least 48 hours or with MRI evidence of a dorsal brainstem lesion) ▪ Acute brainstem syndrome other than APS ▪ Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions ▪ Acute cerebral syndrome with NMOSD-typical brain lesions
ψ Typical MRI findings in NMOSD related to clinical presentation (T2 unless noted otherwise) ▪ Optic neuritis: Normal cerebral MRI (or only nonspecific white matter lesions) OR longitudinally extensive optic nerve lesion (≥ half of the length of the optic nerve or involving optic chiasm; T2 or T1/Gd) ▪ Myelitis: Intramedullary lesion ≥ 3 contiguous VS (LETM) OR focal atrophy ≥ 3 contiguous VS in patients with a history of acute myelitis ▪ Area postrema syndrome (APS): Lesion in the dorsal medulla oblongata/area postrema ▪ Other brainstem syndrome: Periependymal brainstem lesion (4th ventricle) ▪ ¥ Diencephalic syndrome: Periependymal lesion (3rd ventricle) OR hypothalamic/thalamic lesion ▪ § Cerebral syndrome: Extensive periependymal lesion (lateral ventricle; often with Gd) OR long (> 1⁄2 length), diffuse, heterogeneous or edematous corpus callosum lesion OR long corticospinal tract lesion (unilateral or bilateral, contiguously involving internal capsule and cerebral peduncle) OR large, confluent (unilateral or bilateral) subcortical or deep white matter lesion

LETM = *longitudinally extensive transverse myelitis lesions*

VS=vertebral segments

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

Continuation of Therapy Criteria:

- Patient continues to meet initial criteria; AND
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: serious infection, severe neutropenia, severe thrombocytopenia, severe hepatotoxicity,

gastrointestinal perforation, immunosuppression, severe hypersensitivity reactions, demyelinating disorders, etc.;

Non-Oncology Indications

Rheumatoid arthritis (RA)

- Disease response as indicated by improvement in signs and symptoms 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, an improvement of disease severity on RAPID3 assessment, etc]

Juvenile Idiopathic Arthritis (SJIA/PJIA)

- Disease response as indicated by improvement in signs and symptoms 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 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].

Management of Immune Checkpoint Inhibitor Related Toxicities

- May not be renewed

NMOSD

- Disease response as indicated by stabilization/improvement in any of the following: neurologic symptoms as evidenced by a decrease in acute relapses or improvement of stability, reduced hospitalizations, reduction/discontinuation in plasma exchange treatments, and/or reduction/discontinuation of corticosteroids without relapse

Giant Cell Arteritis

- Disease response as indicated by improvement in signs and compared to baseline such as headache, temporal artery tenderness, visual symptoms, inflammatory parameters, (e.g., erythrocyte sedimentation rate [ESR], C-reactive protein), improvement of periodic imaging studies (color Doppler ultrasound [CDUS], MRI, PET-CT, or CT angiography), etc.

Coverage durations:

Indication	Duration of initial approval	Continuation of therapy coverage
Adult Rheumatoid Arthritis	6 months	6 months
Polyarticular Juvenile Idiopathic Arthritis	6 months	6 months
Systemic Juvenile Idiopathic Arthritis	6 months	6 months
Immune Checkpoint Inhibitor Related Toxicities	1 dose	Cannot be renewed
NMOSD	6 months	6 months
Giant Cell Arteritis	6 months	6 months, up to a maximum of 18 months of therapy

Per §§ 42 CFR 422.101, this clinical medical policy only applies to INTEGRITY in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD).

Policy Rationale:
Tocilizumab was reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use Actemra according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For INTEGRITY (Medicare-Medicaid Plan) members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.

Dosage/Administration:

Indication	Dose	Maximum dose (1 billable unit = 1 mg)
Adult Rheumatoid Arthritis	4 mg/kg IV every 4 weeks May increase to 8 mg/kg every 4 weeks based on clinical response	800 units every 28 days

Polyarticular Juvenile Idiopathic Arthritis	Weight ≥ 30 kg: 8 mg/kg IV every 4 weeks Weight < 30 kg: 10 mg/kg IV every 4 weeks	800 units every 28 days
Systemic Juvenile Idiopathic Arthritis	Weight ≥ 30 kg 8 mg/kg IV every 2 weeks Weight < 30 kg 12 mg/kg IV every 2 weeks	800 units every 14 days
Management of Immune Checkpoint Inhibitor Related Toxicities	4 mg/kg IV once	3200 units for one course of therapy
NMOSD	8 mg/kg intravenously, every 4 weeks	800 units every 28 days
Giant Cell Arteritis	6 mg/kg intravenously, every 4 weeks Doses exceeding 600 mg per infusion are not recommended	600 units every 28 days

Investigational use: All therapies are considered investigational when used at a dose or for a condition other than those that are recognized as medically accepted indications as defined in any one of the following standard reference compendia: American Hospital Formulary Service Drug information (AHFS-DI), Thomson Micromedex DrugDex, Clinical Pharmacology, Wolters Kluwer Lexi-Drugs, or Peer-reviewed published medical literature indicating that sufficient evidence exists to support use. Neighborhood does not provide coverage for drugs when used for investigational purposes.

Applicable Codes:
Below is a list of billing codes applicable for covered treatment options. The below tables are provided for reference purposes and may not be all-inclusive. Requests received with codes from tables below do not guarantee coverage. Requests must meet all criteria provided in the procedure section.

The following HCPCS/CPT code is:

HCPCS/CPT Code	Description
J3262	Injection, tocilizumab, 1 mg (Actemra)
Q5133	Injection, tocilizumab-bavi (tofidence), biosimilar, 1 mg

Q5135	Injection, tocilizumab-aazg (tyenne), biosimilar, 1 mg

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