Policy Title:	Uplizna (inebilizumab-cdon) (Intravenous)		
		Department:	PHA
Effective Date:	12/01/2020		
Review Date:	11/2/2020, 7/15/2021, 7/7/2022, 4/27/2023, 12/14/2023, 01/04/2024, 05/21/2025, 04/07/2026		

Purpose: To support safe, effective, and appropriate use of Uplizna (inebilizumab-cdon).

Scope: Medicaid, Commercial, Medicare

Policy Statement:
Uplizna (inebilizumab-cdon) is covered under the Medical Benefit when used within the following guidelines. Use outside of these guidelines may result in non-payment unless approved under an exception process.

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

Summary of Evidence:
Uplinza (inebilizumab-cdon) is a CD19-directed cytolytic antibody indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive, Immunoglobulin G4-related disease (IgG4-RD) in adult patients, and generalized Myasthenia Gravis (gMG) in adult patients. The N-MOmentum trial demonstrated that Uplinza reduced the risk of NMOSD relapse by 77% compared to placebo over a 197-week period. Additionally, Uplinza showed efficacy in reducing the risk of disability worsening by 50% compared to placebo. The approval of Uplizna for IgG4-RD was based on a Phase 3 multicenter, double-blind, randomized, placebo-controlled MITIGATE trial, which evaluated the safety and efficacy of Uplizna compared with placebo in adults with active IgG4-RD. The primary efficacy endpoint was the time to First Treated and Adjudication Committee (AC)-determined IgG4-RD flare within the 52-week RCP. The time to the First Treated and AC determined IgG4-RD flare was significantly longer in the Uplinza group, compared with the placebo group. Uplizna reduced the risk of treated and AC-determined IgG4-RD flare by 87%, compared with placebo (hazard ratio: 0.13; $p < 0.0001$). In a randoamized, placebo-controlled trial, Uplizna significantly improved outcomes in adults with gMC, with greater reductions in MG-ADL scores at 26 weeks (-4.2 vs -2.2; difference, $p < 0.0001$) compared with placebo. It also produced significant improvements in muscle strength as measured by QMG scores (-4.8 vs -2.3, $p = 0.0002$).Common adverse events include urinary tract infections, headache, infusion-related reactions, lymphopenia, and arthralgia.

Initial Criteria:

Medicare members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements.

- Member is 18 years or older; AND
- Prescribed by, or in consultation with, a neurologist; AND
- Member has been evaluated and screened for the presence of hepatitis B virus (HBV) prior to initiating treatment and confirmed negative for active HBV; AND
- Member has had baseline serum immunoglobulin measured prior to the start of therapy; AND
- Member does not have an underlying immunodeficiency disorder (i.e., acquired/congenital primary immunodeficiency, HIV, etc.); AND
- Live or live-attenuated vaccinations will not be administered within the 4-weeks prior to the start of therapy, and will not be administered concurrently while on therapy; AND
- Member has been evaluated and screened for the presence of latent TB infection prior to initiating treatment and will receive ongoing monitoring for presence of TB during treatment; AND
- Member does not have an active infection, including clinically important localized infections; AND
- The member will NOT be using the requested agent in combination with Soliris (eculizumab), Bkemv (eculizumab-aeeb), Epysqli (eculizumab-aagh), Ultomiris (ravulizumab-cwvz), Vyvgart (efgartigimod),Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), Zilbrysq (zilucoplan), Imaavy (nipocalimab-aahu), or Rystiggo (rozanolixizumab-noli); **AND**

Neuromyelitis Optica Spectrum Disorder (NMOSD)

- Submission of medical records (e.g., chart notes, laboratory values, etc.) to support the diagnosis of neuromyelitis optica spectrum disorder (NMOSD) by a neurologist confirming all the following:
    - Past medical history of one of the following:
        - 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; AND
    - Positive serologic test for anti-aquaporin-4 immunoglobulin G (AQP4-IgG)/NMO-IgG antibodies; AND
    - The member has had at least one discrete clinical attack of CNS symptoms; AND
    - Alternative diagnoses (e.g., multiple sclerosis, ischemic optic neuropathy) have been ruled out; AND

- Member has experienced failure, contraindication, or intolerance to Enspryng (satralizumab)*
- The member will not be using the requested agent in combination with Enspryng, Rituximab, Soliris, Bkemv, Epysqli, or Ultomiris

* This requirement **ONLY** applies to **Medicaid** Members

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

Immunoglobulin G4-Related Disease (IgG4-RD) † [1,7-10]

- Member has a confirmed diagnosis of IgG4-RD (e.g., physical exam findings, imaging results, laboratory tests, pathological findings in involved organ/sites, etc.); AND
- Alternative diagnoses have been ruled out (e.g., malignancy, infection, other autoimmune disorders, etc.); AND
- Member is experiencing (or recently experienced) an IgG4-RD flare that required corticosteroid treatment; AND
    - Member has disease that is refractory to corticosteroids; OR
    - Member has a contraindication or intolerance to corticosteroid treatment; AND
- Member is at high risk of recurrent disease flares based on a history of disease in ≥2 organs/sites; AND
- At least one of the following organs are affected:
    - Pancreas, bile ducts/biliary tree, orbits, lungs, kidneys, lacrimal glands, major salivary glands, retroperitoneum, aorta, pachymeninges, and/or thyroid gland

Generalized Myasthenia Gravis (gMG) † Φ [1,11-15]

- Submission of medical records (e.g., chart notes, laboratory values, etc.) to support the diagnosis of generalized myasthenia gravis (gMG); **AND**
- Member has a positive serologic test for anti-acetylcholine receptor (AChR) antibodies OR the member has a positive serological test for anti-MuSK antibodies; **AND**
- Member has Myasthenia Gravis Foundation of America (MGFA) Clinical Classification of Class II to IVb disease§; **AND**
- Physician has assessed objective signs of neurological weakness and fatigability on a baseline neurological examination (e.g., including, but not limited to, the Quantitative Myasthenia Gravis (QMG) score or the MG-Activities of Daily Living (MG-ADL) score, etc.); **AND**

- Member has a baseline MG-Activities of Daily Living (MG-ADL) total score of greater than or equal to 6; **AND**
- The member meets one of the following:
    - The member has tried and had an inadequate response to at least ONE conventional agent used for the treatment of myasthenia gravis (i.e., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide); **OR**
    - The member has an intolerance or hypersensitivity to ONE conventional agent used for the treatment of myasthenia gravis (i.e., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide); **OR**
    - The member has an FDA labeled contraindication to ALL conventional agents used for the treatment of myasthenia gravis (i.e., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide); **OR**
    - The member required chronic intravenous immunoglobulin (IVIG); **OR**
    - The member required chronic plasmapheresis/plasma exchange; **AND**
- The member's current medications have been assessed and any medications known to exacerbate myasthenia gravis (e.g., beta blockers, procainamide, quinidine, magnesium, anti-programmed death receptor-1 monoclonal antibodies, hydroxychloroquine, aminoglycosides) have been discontinued OR discontinuation of the offending agent is NOT clinically appropriate.

† FDA approved indication(s); ‡ Compendia recommended indication(s); Φ Orphan Drug

§ Myasthenia Gravis Foundation of America (MGFA) Disease Classifications[11,12]:

- Class I: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
- Class II: Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
    - IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
    - IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- Class III: Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
    - IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
    - IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
    - IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
    - IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- Class V: Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the member in class IVb.

Continuation of Therapy Criteria:

- The member was previously approved for the requested drug through the plan's Pharmacy Drug Review process (Note: patients not previously approved for the requested agent will require initial evaluation review); **AND**
- The requested agent continues to be prescribed by, or in consultation with, a neurologist; **AND**
- The member will not be using the requested agent in combination with other immunomodulatory biologic therapies (e.g., Imaavy (nipocalimab), Rystiggo (rozanolixizumab), Zilbrysq (zilucoplan), Soliris/Epysqli/Bkemv (eculizumab), Ultomiris (ravulizumab), etc.)**;AND**
- The member does NOT have any FDA labeled contraindications to the requested agent; **AND**
- The requested quantity (dose) is within FDA labeled dosing for the requested indication; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: serious or life-threatening infusion related reactions, serious infections including PML, hypogammaglobulinemia necessitation IVIG or leading to recurrent infections, etc.; **AND**

Neuromyelitis Optica Spectrum Disorder (NMOSD)

- Disease response as indicated by stabilization/improvement in any of the following:
  - Neurologic symptoms as evidenced by a decrease in acute relapses, stability or improvement in EDSS
  - Reduced hospitalizations
  - Reduction/discontinuation in plasma exchange treatments
- The member will not be using the requested agent in combination with Enspryng, Rituximab, Soliris, Bkemv, Epysqli, or Ultomiris

Immunoglobulin G4-Related Disease (IgG4-RD)

- Disease response as indicated by one or more of the following:
  - Reduction in corticosteroid requirement for IgG4-RD flare treatment from baseline
  - Reduction in IgG4-RD flares from baseline
  - Stabilization/improvement in symptoms, physical exam findings, imaging results, laboratory tests, and/or pathological findings in IgG4-RD involved organ/sites compared to baseline

Generalized myasthenia gravis (gMG)

- Documentation that member demonstrates a positive response to therapy by an improvement (i.e., reduction) of at least 2-points from baseline in the Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL) total score sustained for at least 4-weeks ***Δ***
- Documentation of improvement in muscle strength testing with fatigue maneuvers as evidenced on neurologic examination when compared to baseline

- Member requires continuous treatment, after an initial beneficial response, due to new or worsening disease activity (Note: Subsequent treatment cycles were administered NO sooner than 28 days from the last administration of the previous treatment cycle)

(Δ May substitute an improvement of at least 3-points from baseline in the Quantitative Myasthenia Gravis (QMG total score sustained for at least 4-weeks, if available)

Coverage durations:

- Initial coverage: 6 months
- Continuation of therapy coverage: 12 months

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

Policy Rationale:
Uplizna 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 Uplizna 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 Medicare 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)**
All Indications	Uplizna is administered as an intravenous infusion, as follows: • Initial dose: 300 mg IV infusion followed 2 weeks later by a second 300 mg IV infusion. • Subsequent doses (starting 6 months from the first infusion): single 300 mg IV infusion every 6 months.	300 units on days 1, 15 and then 300 units every 6 months thereafter

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.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
G70.00	**Myasthenia gravis without (acute) exacerbation**
G70.01	**Myasthenia gravis with (acute) exacerbation**
G36.0	**Neuromyelitis optica [Devic]**
D89.84	**IgG4-related disease**

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 codes are:

HCPCS/CPT Code	Description
J1823	injection, inebilizumab-cdon, 1mg

References:

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