Medical Policy Bulletin

Title:
Inebilizumab-cdon (Uplizna)
Policy #:
MA08.126c

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

In the absence of coverage criteria from applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals, or other Medicare coverage documents, this policy uses internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, and/or regulatory status.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

MEDICALLY NECESSARY

Inebilizumab-cdon (Uplizna®) is considered medically necessary and, therefore, covered for the treatment of adult individuals for the indications listed below:

NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)
Inebilizumab-cdon (Uplizna) is considered medically necessary and, therefore, covered for the treatment of adult individuals with neuromyelitis optica spectrum disorder (NMOSD), when all of the following criteria are met, including dosing and frequency:

- The individual has a diagnosis of NMOSD.
- The individual is anti-aquaporin-4 (AQP4) antibody seropositive.
- The individual has a history of one or more relapses that required rescue therapy within the year or two or more relapses that required rescue therapy in the past 2 years.
- Dosing and frequency for inebilizumab-cdon (Uplizna):
    - Initial dose: 300-mg intravenous infusion followed 2 weeks later by a second 300-mg intravenous infusion
    - Subsequent doses (starting 6 months from the first infusion): single 300-mg intravenous infusion every 6 months

IMMUNOGLOBULIN G4-RELATED–DISEASE (IgG4-RD)

Inebilizumab-cdon (Uplizna) is considered medically necessary and, therefore, covered for the treatment of adult individuals with immunoglobulin G4–related disease (IgG4-RD), when all of the following criteria are met, including dosing and frequency:

- The individual has a diagnosis of IgG4-RD
- Newly diagnosed or recurrent IgG4-RD that requires glucocorticoid (GC) treatment
- Confirmed history of least two organs/sites involvement at any time in the course of disease.
- Dosing and frequency for inebilizumab-cdon (Uplizna):
    - Initial dose: 300 mg intravenous infusion followed two weeks later by a second 300 mg intravenous infusion
    - Subsequent doses (starting six months from the first infusion): single 300 mg intravenous infusion every six months

GENERALIZED MYASTHENIA GRAVIS (gMG)

Inebilizumab-cdon (Uplizna) is considered medically necessary and, therefore, covered for the treatment of adult individuals with Myasthenia Gravis, when all of the following criteria are met, including dosing and frequency:

- The individual has a diagnosis of gMG
- Presence of autoantibodies against AChR or MuSK
- Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV
- Myasthenia Gravis-Activities of Daily Living (MG-ADL) score between 6 and 10 with > 50% of this score attributed to non-ocular items or an MG-ADL score ≥ 11
- Quantitative Myasthenia Gravis (QMG) score of ≥ 11
- On a stable dose of a corticosteroid or a specified non-steroidal immunosuppressive therapy, or a combination of both
- Dosing and frequency for inebilizumab-cdon (Uplizna):
    - Initial dose: 300-mg intravenous infusion followed 2 weeks later by a second 300-mg intravenous infusion
    - Subsequent doses (starting 6 months from the first infusion): single 300-mg intravenous infusion every 6 months

EXPERIMENTAL/INVESTIGATIONAL

All other uses for inebilizumab-cdon (Uplizna) are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

DOSING AND FREQUENCY REQUIREMENTS

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of inebilizumab-cdon (Uplizna). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the US Food and Drug Administration (FDA); Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of inebilizumab-cdon (Uplizna) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the utilization management activities. The Company reserves the right to conduct post-payment review and audit procedures for any claims submitted for inebilizumab-cdon (Uplizna).

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may

include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

PEDIATRIC USE

The safety and effectiveness have not been established in the pediatric population for inebilizumab-cdon (Uplizna).

Guidelines

There is no Medicare coverage determination addressing inebilizumab-cdon (Uplizna™); therefore, the Company policy is applicable.

DRUG INFORMATION

In accordance with US Food and Drug Administration (FDA) prescribing information, inebilizumab-cdon (Uplizna) is administered as an intravenous infusion titrated to completion, approximately 90 minutes. The recommended initial dose: 300-mg intravenous infusion followed 2 weeks later by a second 300-mg intravenous infusion. Subsequent doses (starting 6 months from the first infusion): single 300-mg intravenous infusion every 6 months**.**

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable Evidence of Coverage, inebilizumab-cdon (Uplizna) is covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria listed in this medical policy are met.

MYASTHENIA GRAVIS FOUNDATION OF AMERICA (MGFA) CLINICAL CLASSIFICATION

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.

> **A**. IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
> **B**. 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.

> A. IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
> B. 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.

> A. IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
> B. 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 individual in class IVb.

MG Activities of Daily Living (MG-ADL) Profile

Grade	**Score**			
Activities of Daily Living (ADL)	**0**	**1**	**2**	**3**
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed.	Rest periods needed	Cannot do one of these functions
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant

The Quantitative Myasthenia Gravis (QMG) total score calculation

- The total QMG score can range from 0 to 39.
- A higher score indicates worse disease severity.
- The scoring can also be categorized into ocular (0–23) and generalized (0–16) components, allowing for a more detailed assessment of the patient's condition.

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Inebilizumab-cdon (Uplizna) injection for intravenous use, was approved by the FDA on June 11, 2020, for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult individuals who are anti-aquaporin-4 (AQP4) antibody positive.

PEDIATRIC USE

The safety and effectiveness of inebilizumab-cdon (Uplizna) for the treatment of NMOSD in pediatric individuals have not been established.

Description

Inebilizumab-cdon (UpliznaTM) is a CD19-directed humanized afucosylated IgG1 monoclonal antibody produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture. The molecular weight is approximately 149 kilodaltons (kDa). Inebilizumab-cdon (Uplizna) depletes the B cells in the body that produce autoantibodies against aquaporin-4 (AQP4). This reduces the frequency of attacks and the severity of symptoms. Inebilizumab-cdon (Uplizna) was approved by the US Food and Drug Administration (FDA) for neuromyelitis optica spectrum disorder (NMOSD) on June 11, 2020. Data from the end-of-study analysis of the N-MOmentum (A Clinical Research Study of Inebilizumab in Neuromyelitis Optica Spectrum Disorders) trial showed continued and sustained clinical benefits of long-term inebilizumab treatment in individuals with NMOSD.

NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)

Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing, autoimmune, inflammatory disorder that typically affects the optic nerves and spinal cord. At least two thirds of cases are associated with aquaporin-4 antibodies (AQP4-IgG) and complement-mediated damage to the central nervous system.

The safety and efficacy of inebilizumab-cdon (Uplizna) for the treatment of individuals with AQP4-IgG–positive neuromyelitis optica were evaluated in a Study 1, in which 161 individuals were exposed to inebilizumab-cdon (Uplizna) at the recommended dosage regimen during the randomized, controlled treatment period, during which 52 individuals received placebo. Subsequently, 198 individuals were exposed to inebilizumab-cdon (Uplizna) during an open-label treatment period. A total of 208 individuals in the randomized and open-label treatment periods had a total of 324 person-years of exposure to inebilizumab-cdon (Uplizna), including 165 individuals with exposure for at least 6 months and 128 with exposure for 1 year or more. The Study 1 included AQP4-IgG antibody-positive and AQP4-IgG antibody-negative individuals. During the 197-day study, the risk of an NMOSD relapse in the 161 anti-AQP4 antibody–positive individuals who were treated with inebilizumab-cdon (Uplizna) was reduced by 77% when compared to the placebo treatment group. There was no evidence of a benefit in anti-AQP4 antibody–negative individuals. The most common adverse reactions in the NMOSD clinical trial were urinary tract infection, headache, joint pain (arthralgia), nausea, and back pain.

IMMUNOGLOBULIN G4–RELATED DISEASE (IgG4-RD)

Immunoglobulin G4–related disease (IgG4-RD) is a rare, chronic autoimmune condition in which the immune system attacks healthy organs, causing inflammation, fibrosis (scarring), and often tumor-like masses that can mimic cancer, affecting organs like the pancreas, salivary glands, kidneys, and aorta. The disease is characterized by high levels of IgG4 antibodies, dense inflammation with IgG4 plasma cells, and typically responds well to steroid treatment, although early diagnosis is crucial to prevent organ damage.

The pathology of IgG4-RD is very specific and looks similar in all organs. Therefore it is considered to be analogous to systemic sarcoidosis. IgG4-RD–affected individuals are often misdiagnosed as having a malignancy because the lesions can mimic tumors, infections, or immune-mediated diseases. This disease is underdiagnosed due to the lack of a systemic approach. IgG4-RD–affected individuals usually have a good recovery after being treated with systemic glucocorticosteroids. The response to steroids is so dramatic that it is has been suggested as one diagnostic criterion for the disease.

The safety and efficacy of inebilizumab-cdon (Uplizna) for the treatment of individuals with IgG4-related disease was evaluated in randomized, double-blind, placebo-controlled Phase 3 trial. The MITIGATE (A Study of Inebilizumab Efficacy and Safety in IgG4- Related Disease) trial is the first placebo-controlled Phase 3 trial in this disease. This trial enrolled 135 adults with active IgG4-RD, multiorgan involvement, and a recent flare requiring glucocorticoids. The study was conducted across 80 sites in 22 countries. The primary endpoint was the time to first adjudicated, investigator-treated IgG4-RD flare. Secondary endpoints included annualized flare rate; flare-free, treatment-free complete remission; glucocorticoid-free remission; and safety and tolerability. Inebilizumab reduced risk of flare by 87% to 90% versus placebo over 52 weeks. Flares occured in 10% to 10.3% (inebilizumab) versus 59.7% to 60% (placebo). Flare-free, treatment-free complete remission at Week 52 was 57% (inebilizumab) versus 22% (placebo). Ninety percent of individuals receiving inebilizumab fully discontinued glucocorticoids compared with 37% for placebo.

GENERALIZED MYASTHENIA GRAVIS

Generalized myasthenia gravis (gMG) is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles. The muscle weakness usually worsens after periods of activity and improves after periods of rest. Muscles that control movements of the eye and eyelid, facial expression, chewing, talking, and swallowing are often

involved, but those that control breathing and neck and limb movements may also be involved. This weakness is a result of an antibody-mediated, T-cell dependent, immunological attack directed at proteins in the postsynaptic membrane of the neuromuscular junction. MG has an annual incidence of about seven to 23 cases per million. It most often begins before the age of 40 in women and after age 60 in men.

The safety and efficacy of inebilizumab-cdon (Uplizna) for the treatment of individuals with gMG was studied in a late-phase randomized, double-blind, placebo-controlled clinical study called MINT (A Randomized, Double-blind, Multicenter, Placebo-controlled Phase 3 Study With Open-label Period to Evaluate the Efficacy and Safety of Inebilizumab in Adults With Myasthenia Gravis), designed to determine whether a CD19-targeting monoclonal antibody can meaningfully improve symptoms and disease control in people living with gMG. Participants were adults with confirmed generalized MG who carried one of the two major MG-associated autoantibodies: acetylcholine receptor (AChR) antibodies or muscle-specific kinase (MuSK) antibodies.

Participants were randomly assigned in equal numbers to receive either the investigational therapy or placebo. Dosing occurred on a fixed schedule and differed slightly depending on antibody subtype. A key feature of the study was a structured glucocorticoid taper, which began early in treatment. Individuals who entered on prednisone or an equivalent medication were gradually reduced to a low daily dose by the middle of the trial. This allowed investigators to see whether the study medication could maintain disease control despite decreasing steroid exposure.

The primary end point was change in Myasthenia Gravis Activities of Daily Living (MG-ADL) at Week 26, assessed across the entire antibody-positive participant population. Secondary end points were changes in Quantitative Myasthenia Gravis (QMG) score, another widely accepted measure of MG severity, individual assessments of treatment response within AChR-positive and MuSK-positive subgroups and additional measures related to function, strength, and disease stability. Overall adverse events (AE) were similar between groups (approximately 81% vs 73%), suggesting no major increase in overall adverse events with inebilizumab. Common AEs (>10%) included headache, and mild infections (including COVID-19) were most frequent in the active arm. Serious AEs were numerically lower in the inebilizumab group (8.4%) compared with that in the placebo group (13.4%); there was no anaphylaxis or severe hypersensitivity.

OFF-LABEL INDICATION

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

References

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)

N/A

ICD - 10 Procedure Code Number(s)

N/A

ICD - 10 Diagnosis Code Number(s)

Report the most appropriate diagnosis code in support of medically necessary criteria as listed in the policy.

HCPCS Level II Code Number(s)

THE FOLLOWING CODES ARE USED TO REPRESENT

Inebilizumab-cdon (Uplizna™)

J1823 Injection, inebilizumab-cdon, 1 mg

Revenue Code Number(s)
N/A

Policy History

Revisions From MA08.126c:

06/18/2026	This policy has been updated to communicate the new medical necessity criteria, which reflect the US Food and Drug Administration (FDA) labeling for adult individuals with immunoglobulin G4–related disease (IgG4-RD) and myasthenia gravis. All of the ICD-10 CM codes have been removed from this policy, because they are informational. Report the most appropriate diagnosis code in support of medically necessary criteria as listed in the policy.

Revision From MA08.126b

03/28/2025	This policy has been reissued in accordance with the Company's annual review process.
05/07/2024	This policy has been reissued in accordance with the Company's annual review process.
09/05/2023	This policy has been reissued in accordance with the Company's annual review process.
05/04/2022	This policy has been reissued in accordance with the Company's annual review process.
08/09/2021	This version of the policy will become effective 08/09/2021. The criteria section has been updated to include dosing and frequency for inebilizumab-cdon (UpliznaTM).

Revisions From MA08.126a:

01/01/2021	This policy has been identified for the HCPCS code update, effective 01/01/2021. The following NOC code has been **removed** from this policy and is replaced by the following HCPCS code: **REMOVED:** C9399 Unclassified drugs or biologicals J3590 Unclassified biologics **REPLACED WITH:** **J1823 Injection, inebilizumab-cdon, 1 mg**

Revisions From MA08.126:

09/14/2020	This version of the policy will become effective 09/14/2020. This new policy has been developed to communicate the Company's coverage criteria for Inebilizumab-cdon (Uplizna™).

Version Effective Date:
06/18/2026
Version Issued Date:
06/18/2026
Version Reissued Date:
N/A