Policy Number	**RX501.127**
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Inebilizumab-cdon

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Inebilizumab-cdon (Uplizna®) **may be considered medically necessary** when **ALL** the following criteria are met, and the individual:

- Is 18 years of age or older; AND
- Has a diagnosis of neuromyelitis optica spectrum disorder (NMOSD); AND
- Is anti-aquaporin-4 (AQP4) antibody seropositive; AND
- Has a history of at least one relapse requiring rescue therapy during the previous 12 months **OR** at least two relapses requiring rescue therapy during the previous 24 months; AND
- Will not receive inebilizumab concurrently with other biologics used to treat NMOSD (e.g., eculizumab, rituximab, satralizumab).

Inebilizumab-cdon (Uplizna®) **is considered experimental, investigational and/or unproven** for all other indications.

Policy Guidelines

None.

Description

Inebilizumab-cdon (Uplizna®)
Inebilizumab-cdon (Uplizna) 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. The exact mechanism by which inebilizumab-cdon exerts its therapeutic effects in NMOSD is unknown, but it is presumed to involve binding to the CD19, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, inebilizumab-cdon results in antibody-dependent cellular cytolysis. (1)

Neuromyelitis Optica Spectrum Disorder
Neuromyelitis optica spectrum disorder (NMOSD, previously known as Devic disease or neuromyelitis optica [NMO]) is an inflammatory disorder of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage predominately targeting the optic nerves and spinal cord. NMOSD can be distinguished from multiple sclerosis and other central nervous system inflammatory disorders by the presence of the disease-specific serum NMO-immunoglobulin G (IgG) antibody that selectively binds to the aquaporin-4 (AQP4) antibody, which plays a direct role in the pathogenesis of NMOSD. AQP4, the target

antigen of NMO-IgG, is a water channel protein abundant in spinal cord gray matter, periaqueductal and periventricular regions, and astrocytic foot processes at the blood-brain barrier. (2)

The incidence of NMOSD in women is up to 10 times higher than in men. The median age of onset is 32 to 41 years, but cases are described in children and older adults. Comparatively, the medical age of onset for multiple sclerosis is 24 years.

Hallmark features of NMOSD include acute attacks of bilateral or rapidly sequential optic neuritis (leading to severe visual loss) or transverse myelitis (often causing limb weakness, sensory loss, and bladder dysfunction) with a typically relapsing course. Other suggestive symptoms include episodes of intractable nausea, vomiting, hiccups, excessive daytime somnolence or narcolepsy, reversible posterior leukoencephalopathy syndrome (PRES), neuroendocrine disorders, and (in children) seizures. While no clinical features are disease-specific, some are highly characteristic.

NMOSD has a relapsing course in 90 percent or more of cases. In some patients, optic neuritis and transverse myelitis occur concurrently; in others, clinical episodes are separated by a variable time delay. Relapse occurs within the first year following an initial event in 60 percent of patients and within three years in 90 percent. As a rule, severe residual deficits follow initial and subsequent attacks, leading to rapid development of disability due to blindness and paraplegia within five years. Unlike multiple sclerosis, a secondary progressive phase of the disease is rare, and disability is associated with specific attacks. Patients with cerebral presentations may have continued brain attacks without involvement of the optic nerves or spinal cord. (2)

Regulatory Status
Inebilizumab-cdon (Uplizna®) was approved by the U.S. Food and Drug Administration (FDA) in June 2020 for the treatment of adult patients with neuromyelitis optica spectrum disorder who are anti-aquaporin-4 antibody positive. (1)

Rationale

The efficacy of Uplizna® for the treatment of neuromyelitis optica spectrum disorders (NMOSD) was established in Study 1 (NCT02200770), a randomized (3:1), double-blind, placebo-controlled trial that enrolled 213 patients with NMOSD who were anti-AQP4 (aquaporin-4) antibody positive and 17 who were anti-AQP4 antibody negative.

Patients met the following eligibility criteria:

- A history of one or more relapses that required rescue therapy within the year prior to screening, or 2 or more relapses that required rescue therapy in 2 years prior to screening.
- Expanded Disability Status Scale (EDSS) score of 7.5 or less. Patients with an EDSS score of 8.0 were eligible if they were deemed capable of participating.

- Patients were excluded if previously treated with immunosuppressant therapies within an interval specified for each such therapy.

The use of immunosuppressants during the blinded phase of the trial was prohibited. The use of oral or intravenous corticosteroids during the blinded phase of the trial was prohibited, with the exception of premedication for investigational treatment and treatment for a relapse.

Of the 213 enrolled anti-AQP4 antibody positive patients, a total of 161 were randomized to receive treatment with Uplizna, and 52 were randomized to receive a placebo.

The baseline demographic and disease characteristics were balanced between the treatment groups. Females accounted for 94% of the study population. Fifty-two percent of patients were White, 21% Asian, and 9% Black or African American. The mean age was 43 years (range 18 to 74 years). The mean EDSS score was 4.0. The number of relapses in the two years prior to randomization was 2 or more in 83% of the patients.

Uplizna® was administered according to the recommended dosage regimen.

All potential relapses were evaluated by a blinded, independent, adjudication committee, who determined whether the relapse met protocol-defined criteria. Patients who experienced an adjudicated relapse in the randomized-controlled period (RCP), or who completed the day 197 visit without a relapse, exited the RCP.

The primary efficacy endpoint was the time to the onset of the first adjudicated relapse on or before day 197.

The time to the first adjudicated relapse was significantly longer in patients treated with Uplizna® compared to patients who received placebo (relative risk reduction 73%; hazard ratio: 0.272; $p < 0.0001$). In the anti-AQP4 antibody positive population there was a 77.3% relative reduction (hazard ratio: 0.227, $p < 0.0001$). There was no evidence of a benefit in patients who were anti-AQP4 antibody negative.

Table 1. Efficacy Results in Study 1 in anti-AQP4 Antibody Positive NMOSD Patients

	Treatment Group	
	Uplizna N=161	**Placebo N=52**
Time to Adjudication Committee-Determined Relapse (Primary Efficacy Endpoint)		
Number (%) of patients with relapse	18 (11.2%)	22 (42.3%)
Hazard ratio (95% CI)	0.227 (0.121, 0.423)	
p-value[a]	<0.0001	

NMOSD: neuromyelitis optica spectrum disorder; CI: confidence interval; AQP4: aquaporin-4 antibody.
[a] Cox regression method, with placebo as the reference group.

Compared to placebo-treated patients, patients treated with Uplizna® who were anti-AQP4 antibody positive had reduced annualized rates of hospitalizations (0.11 for UP versus

0.50 for placebo).

Summary of Evidence

Based on the study provided to the U.S. Food and Drug Administration for the approval process, inebilizumab-cdon (Uplizna®) may be considered medically necessary for patients who are 18 years of age or older; have a diagnosis of neuromyelitis optica spectrum disorder (NMOSD); are anti-aquaporin-4 antibody seropositive; have a history of at least one relapse requiring rescue therapy during the previous 12 months or at least two relapses requiring rescue therapy during the previous 24 months; and will not receive concurrent treatment with other biologics used to treat NMOSD, such as eculizumab, rituximab or satralizumab. Inebilizumab-cdon (Uplizna) is considered experimental, investigational and/or unproven for all other indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1823

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

1. Uplizna® Product Label. (July 2021). Available at: <https://uplinzahcp.com> (accessed January 17, 2025).
2. Glisson CC. Neuromyelitis optica spectrum disorders. In: UpToDate, Gonzalez-Scarano F (Ed), UpToDate, Waltham, MA. Available at: <https://www.uptodate.com> (accessed January 17, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
03/15/2025	Document updated with literature review. Coverage unchanged. References updated.
03/15/2024	Reviewed. No changes.
04/01/2023	Documents updated with literature review. Coverage unchanged. No new references added.
12/01/2022	Reviewed. No changes.
11/01/2021	Document updated with literature review. Coverage unchanged. References updated.
03/01/2021	New medical document. Inebilizumab-cdon (Uplizna™ is considered medically necessary when all the criteria are met and the patient: is 18 years of age or older; and has a diagnosis of neuromyelitis optica spectrum disorder; and is anti-aquaporin-4 antibody seropositive; and has a history of at least one relapse requiring rescue therapy during the previous 12 months or at least two relapses requiring rescue therapy during the previous 24 months; and will not receive concurrent treatment with other biologics used to treat NMOSD, such as eculizumab, rituximab or satralizumab. Inebilizumab-cdon (Uplizna™ is considered experimental, investigational and/or unproven for all other indications.