Uplizna® (Inebilizumab-Cdon)

Policy Number: 2025D0091I
Effective Date: September 1, 2025

➲ Instructions for Use

Table of Contents **Page**

Related Commercial Policies
- Provider Administered Drugs – Site of Care

Community Plan Policy
- Uplizna® (Inebilizumab-Cdon)

Coverage Rationale

➲ See Benefit Considerations

Uplizna (inebilizumab-cdon) is proven for the treatment of neuromyelitis optica spectrum disorder (NMOSD).
Uplizna (inebilizumab-cdon) is medically necessary for the treatment of neuromyelitis optica spectrum disorder (NMOSD) when all the following criteria are met:

- For **initial therapy**, **all** of the following:
  - Diagnosis of neuromyelitis optica spectrum disorder (NMOSD) by a neurologist confirming **all** of the following:[1-4]
    - 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**
    - Diagnosis of multiple sclerosis or other diagnoses have been ruled out

    and
  - **One** of the following (for Medicare reviews, refer to the CMS section*):[7-14]
    - History of failure of rituximab therapy; **or**
    - **Both** of the following:
      - History of intolerance or contraindication to rituximab; **and**
      - Physician attests that, in their clinical opinion, the same intolerance or severe adverse event would not be expected to occur with Uplizna

    and
  - **One** of the following:[5]
    - History of one or more relapses that required rescue therapy during the previous 12 months prior to initiating Uplizna; **or**
    - History of two or more relapses that required rescue therapy during the previous 24 months, prior to initiating Uplizna

    and
  - Uplizna is initiated according to the U.S. FDA labeled dosing for NMOSD; **and**

- Prescribed by, or in consultation with, a neurologist; **and**
- Patient is **not** receiving Uplizna in combination with **any** of the following for treatment of the same indication:
  - Multiple sclerosis disease modifying therapies [e.g., dimethyl fumarate, fingolimod, Ocrevus (ocrelizumab), etc.]
  - Complement inhibitors [e.g., eculizumab, PiaSky (crovalimab), Ultomiris (ravulizumab)]
  - Anti-IL6 therapy [e.g., tocilizumab]
  - Anti-CD20 therapy [e.g., rituximab]

  and
- Initial authorization will be for no more than 12 months

- For **continuation of therapy**, **all** of the following:
  - Documentation of positive clinical response; **and**
  - Uplizna is dosed according to the U.S. FDA labeled dosing for NMOSD; **and**
  - Patient is **not** receiving Uplizna in combination with **any** of the following for treatment of the same indication:
    - Multiple sclerosis disease modifying therapies [e.g., dimethyl fumarate, fingolimod, Ocrevus (ocrelizumab), etc.]
    - Anti-IL6 therapy [e.g., tocilizumab]
    - Complement inhibitors [e.g., eculizumab, PiaSky (crovalimab), Ultomiris (ravulizumab)]
    - Anti-CD20 therapy [e.g., rituximab]

    and
  - Reauthorization will be for no more than 12 months

Uplizna (inebilizumab-cdon) is proven for the treatment of Immunoglobulin G4-related disease (IgG4-RD).
Uplizna (inebilizumab-cdon) is medically necessary for the treatment of Immunoglobulin G4-related disease (IgG4-RD) when all the following criteria are met:

- For **initial therapy**, **all** of the following:
  - Diagnosis of Immunoglobulin G4-related disease (IgG4-RD); **and**
  - Confirmation of IgG4-RD by a positive assessment using the ACR/EULAR classification criteria, demonstrated by **all** of the following:
    - Involvement of at least 1 or more organ(s) in a manner consistent with IgG4-RD; **and**
    - Exclusion criteria is negative and consistent with an IgG4-RD diagnosis (e.g., clinical findings, serologic results, radiology assessments, pathology interpretations); **and**
    - Inclusion criteria is positive and signifies a diagnosis of IgG4-RD (e.g., clinical findings, serologic results, radiology assessments, pathology interpretations)

    and
  - **Both** of the following (for Medicare reviews, refer to the CMS section*):
    - History of failure, contraindication, or intolerance to glucocorticoids; **and**
    - **One** of the following:
      - History of failure of rituximab therapy; **or**
      - **Both** of the following:
        - History of intolerance or contraindication to rituximab; **and**
        - Physician attests that, in their clinical opinion, the same intolerance or severe adverse event would not be expected to occur with Uplizna

    and
  - Uplizna is initiated according to the U.S. FDA labeled dosing for IgG4-RD; **and**
  - Prescribed by, or in consultation with, a specialist with expertise in the treatment of IgG4-RD; **and**
  - Patient is **not** receiving Uplizna in combination with a disease modifying therapy for the treatment of IgG4-related disease (e.g., rituximab); **and**
  - Initial authorization will be for no more than 12 months
- For **continuation of therapy**, **all** of the following:
  - Documentation of positive clinical response; **and**
  - Uplizna is dosed according to the U.S. FDA labeled dosing for IgG4-RD; **and**
  - Prescribed by, or in consultation with, a specialist with expertise in the treatment of IgG4-RD; **and**
  - Patient is **not** receiving Uplizna in combination with a disease modifying therapy for the treatment of IgG4-related disease (e.g., rituximab); **and**
  - Reauthorization will be for no more than 12 months

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1823	Injection, inebilizumab-cdon, 1 mg

Diagnosis Code	Description
D89.84	IgG4-related disease
G36.0	Neuromyelitis optica [Devic]

Background

Uplizna (inebilizumab-cdon) is a CD19-directed humanized afucosylated IgG1 monoclonal antibody. The exact mechanism of action by which inebilizumab exerts its therapeutic effects in neuromyelitis optica spectrum disorder (NMOSD) and immunoglobulin G4 related disease (IgG4-RD) is not known, but is presumed to involve binding to CD19, a cell surface antigen on pre-B and mature B lymphocytes. After cell surface binding to B lymphocytes, inebilizumab results in antibody-dependent cellular cytolysis.[5]

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Clinical Evidence

Proven

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Inebilizumab-cdon is indicated for the treatment of NMOSD.

Cree et al., evaluated the efficacy and safety of inebilizumab, in 230 patients with NMOSD over 44 months in a multicenter, double-blind, randomized placebo-controlled phase 2/3 study. 174 participants received inebilizumab and 56 participants received placebo. Eligible patients were adults (≥ 18 years old), an expanded disability status score (EDSS) of 8 or less, who required at least one rescue therapy treatment during the year prior to screening, or at least 2 attacks requiring rescue therapy in the 2 years before screening. Patients who were AQP4-IgG-seropositive and AQP4-IgG-seronegative were eligible; however, patients who were seronegative also needed to meet the criteria described by Wingerchuk and colleagues. 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. Participants were randomly allocated (3:1) to receive 300 mg intravenous inebilizumab or placebo on days 1 and 15, with a total dose of inebilizumab in the randomized controlled period of 600 mg. No further doses occurred after day 15 within the study period. All participants received oral corticosteroids to minimize the risk of an attack immediately following the first inebilizumab treatment. Primary endpoint was the time in days to the onset of an NMOSD attack, on or before day 197. Secondary endpoints included worsening of EDSS score from baseline, change from baseline in low-contrast visual acuity binocular score; cumulative total number of active MRI lesions, and number of NMOSD-related inpatient hospitalizations, longer than an overnight stay. The randomized controlled period was stopped prior to completion of enrollment, as there was a clear demonstration of efficacy: 12% of participants receiving inebilizumab had an attack, versus 39% of participants receiving placebo (RR 73%; HR 0.272 [95% CI 0.150-0.496]; $p < 0.0001$). In the anti-AQP4 antibody positive population, there was a 77.3% relative reduction (HR 0.227, $p < 0.0001$), whereas patients who were anti-AQP4 antibody negative had no evidence of benefit.[5] Adverse events occurred in 72% of participants receiving inebilizumab and 73% of participants receiving placebo. Service

adverse events occurred in 5% of participants receiving inebilizumab and 9% of participants receiving placebo. The authors concluded that compared to placebo, inebilizumab reduced the risk of an NMOSD attack.[6]

Immunoglobulin G4-Related Disease (IgG4-RD)

Inebilizumab-cdon is indicated for the treatment of IgG4-RD is adult patients.

IgG4-RD is a fibroinflammatory condition that is brought about by an immune-mediated process. IgG4-RD is considered a variable condition that mirrors malignancies, infections, and other inflammatory disorders. It is a heterogeneous disease that can have unpredictable flares, tissue fibrosis, tumor-like masses, and affect single organs as well as span multiple organ systems. Involved organ systems most often include the lacrimal glands, major salivary glands (submandibular, parotid), thyroid gland, lungs, aorta, liver, bile ducts, pancreas, kidneys, retroperitoneal tissues, meninges, and lymph nodes. Unique to this disease, there are consistent histologic and immunologic findings within the affected organs that include plasma cells and lymphocyte infiltration, fibrosis in a storiform pattern, luminal obliteration of venules, and disproportionate IgG class-switching to IgG4. IgG4-RD is therefore a discrete, unique multiorgan disease that is thought to be mediated through autoimmune mechanisms including aberrant CD19 B-cell activity. Prevalence is considered to around 5 patients per 100,000. Hallmarks of the disease include an indolent phase and a period of time where flares occur. Often IgG4-RD progress undetected for months or years and the majority of patients have irreversible organ damage at the time of their initial diagnosis. Permanent damage can occur at any point in the course of the disease, but more frequent disease flares and incomplete disease control can increase the risk for permanent organ damage over time. The goal of the disease treatment is to reduct inflammation and stop any ongoing flare, as well as reducing the risk of future disease flares with maintenance therapy. The efficacy of inebilizumab for the treatment of IgG4-RD was established in a randomized, double-blind, placebo-controlled trial that enrolled 135 adult patients with a 52-week duration. Eligibility criteria was a newly diagnosed IgG4-RD requiring glucocorticoid treatment during screening, and a history of organ involvement at any time during the course of the disease. Other biologics or non-biologic immunosuppressive agents were prohibited during the blinded portion of the study. Enrolled individuals were randomized into a 1:1 ratio of those receiving placebo or inebilizumab. Glucocorticoids (GC) were tapered off once the trial period commenced and were only allowed for premedication of investigational treatment, treatment for a relapse, or in other conditions not related to 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 inebilizumab group, compared with the placebo group (Figure 2). Inebilizumab reduced the risk of treated and AC-determined IgG4-RD flare by 87%, compared with placebo (hazard ratio: 0.13; $p < 0.0001$). A key secondary endpoint was the proportion of patients who were in complete remission at week 52 and had no AC-determined flares or steroid treatment for flares during the randomized clinical trial period (RCP). 40 out of 68 patients on UPLIZNA (58.8%) achieved steroid-free, flare-free complete remission vs 15 out of 67 patients on placebo (22.4%) at week 52 (difference: 36.45% [95% CI: 21.0%, 51.9%]; $p < 0.0001$). Additionally, the mean (SD) total GC use for IgG4-RD control per patient other than the planned GC taper was lower in the inebilizumab-treated group compared with the placebo-treated group, with a mean (SD) of 118.25 (438.97) mg prednisone equivalent versus 1384.53 (1723.26) mg prednisone equivalent, respectively during the RCP. Forty-two (62.7%) placebo-treated patients and 7 (10.3%) UPLIZNA-treated patients received GC for IgG4-RD control other than the planned GC taper. The mean (SD) total GC use per patient for the 42 placebo -reated patients was 2202.76 (1709) mg prednisone equivalent and for the 7 UPLIZNA-treated patients was 1148.71 (878) mg prednisone equivalent.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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 and for the treatment of Immunoglobulin G4-related disease (IgG4-RD) in adult patients.[5]

Centers for Medicare and Medicaid Services (CMS)

Medicare does not have a National Coverage Determination (NCD) for Uplizna® (inebilizumab-cdon). Local Coverage Determinations (LCDs)/Local Coverage Articles (LCAs) do not exist.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals. (Accessed June 13, 2023)
*Preferred therapy criteria is not applicable for Medicare Advantage members.

References

1. Trebst C, Jarius S, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: Recommendations of the Neuromyelitis Optica Study Group (NEMOS). J Neurol. 2014 Jan;261(1):1-16. doi: 10.1007/s00415-013-7169-7. Epub 2013 Nov 23.
2. Scott TF, Frohman EM, DeSeze J, et al. Evidence-based guideline: Clinical evaluation and treatment of transverse myelitis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2011 Dec 13;77(24):2128-34.
3. Sellner J1, Boggild M, Clanet M, et al. EFNS guidelines on diagnosis and management of neuromyelitis optica. Eur J Neurol. 2010 Aug;17(8):1019-32.
4. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015 Jul 14;85(2):177-89.
5. Uplizna [prescribing information]. Gaithersburg, MD: Viela Bio, Inc.; April 2025.
6. Cree B, Bennett J, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. The Lancet. 2019 Oct;394(10206): 1352-1363.
7. Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019 May 3.
8. Kim SH, Huh SY, Lee SJ, et al. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. JAMA Neurol. 2013 Sep 1;70(9):1110-7.
9. Mealy MA, Wingerchuk DM, Palace J, et al. Comparison of Relapse and Treatment Failure Rates Among Patients With Neuromyelitis Optica: Multicenter Study of Treatment Efficacy. JAMA Neurol. 2014 Mar;71(3):324-30.
10. Sato D, Callegaro D, Lana-Peixoto MA, Fujihara K. Treatment of neuromyelitis optica: an evidence based review. Arq Neuropsiquiatr 2012;70(1);59-66.
11. Ciron J, Audoin B, Bourre B, et al. Recommendations for the use of Rituximab in neuromyelitis optica spectrum disorders. Rev Neurol (Paris). 2018 Apr;174(4):255-264.
12. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015 Jul 14;85(2):177-89.
13. Nikoo Z, Badihian S, Shaygannejad V, et al. Comparison of the efficacy of azathioprine and rituximab in neuromyelitis optica spectrum disorder: a randomized clinical trial. J Neurol. 2017 Sep;264(9):2003-2009.
14. Gao F, Chai B, Gu C, et al. Effectiveness of rituximab in neuromyelitis optica: a meta-analysis. BMC Neurol. 2019 Mar 6;19(1):36.
15. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25(9):1181–92.
16. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. 2012;366:539-551.
17. Perugino CA, Stone JH. IgG4-related disease: an update on pathophysiology and implications for clinical care. Nat Rev Rheumatol. 2020;16:702-714.
18. Wallace ZS, Mattoo H, Mahajan VS, et al. Predictors of disease relapse in IgG4-related disease following rituximab. *Rheumatology (Oxford)*. 2016;55(6):1000-1008. doi:10.1093/rheumatology/kev438.
19. Wallace ZS, Katz G, Hernandez-Barco YG, Baker MC. Current and future advances in practice: IgG4-related disease. *Rheumatol Adv Pract*. 2024;8(2):rkae020. Published 2024 Apr 10. doi:10.1093/rap/rkae020.
20. Wallace ZS, Miles G, Smolkina E, et al. Incidence, prevalence and mortality of IgG4-related disease in the USA: a claims-based analysis of commercially insured adults. *Ann Rheum Dis*. 2023;82(7):957-962. doi:10.1136/ard-2023-223950.
21. Khosroshahi A, Stone JH. Treatment approaches to IgG4-related systemic disease. Curr Opin Rheumatol 2011; 23:67.
22. Khosroshahi A, Bloch DB, Deshpande V, Stone JH. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. Arthritis Rheum 2010; 62:1755.
23. Khosroshahi A, Carruthers MN, Deshpande V, et al. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. Medicine (Baltimore) 2012; 91:57.

24. Ebbo M, Grados A, Samson M, et al. Long-term efficacy and safety of rituximab in IgG4-related disease: Data from a French nationwide study of thirty-three patients. PLoS One 2017; 12:e0183844.
25. Carruthers MN, Topazian MD, Khosroshahi A, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. Ann Rheum Dis 2015; 74:1171.
26. Lanzillotta M, Della-Torre E, Wallace ZS, et al. Efficacy and safety of rituximab for IgG4-related pancreato-biliary disease: A systematic review and meta-analysis. Pancreatology 2021; 21:1395.
27. Zhang W, Stone JH. Management of IgG4-related disease. *Lancet Rheumatol*. 2019;1(1):e55-e65. doi:10.1016/S2665-9913(19)30017-7.
28. Löhr JM, Beuers U, Vujasinovic M, et al. European Guideline on IgG4-related digestive disease - UEG and SGF evidence-based recommendations. *United European Gastroenterol J*. 2020;8(6):637-666. doi:10.1177/2050640620934911.
29. Haldar D, Cockwell P, Richter AG, Roberts KJ, Hirschfield GM. An overview of the diagnosis and management of immunoglobulin G4-related disease. CMAJ. 2016;188(13):953-961. doi:10.1503/cmaj.151402.
30. Wallace ZS, Naden RP, Chari S, et al. The 2019 American College of Rheumatology/European League against rheumatism classification criteria for IgG4-related disease. Arthritis Rheumatol. 2020;72(1):7–19.

Policy History/Revision Information

Date	Summary of Changes
09/01/2025	**Coverage Rationale** ***Neuromyelitis Optica Spectrum Disorder (NMOSD)*** • Replaced language indicating "Uplizna (inebilizumab-cdon) is proven for the treatment of NMOSD *when all the [listed] criteria are met*" with "Uplizna (inebilizumab-cdon) is proven for the treatment of NMOSD" • Revised coverage criteria; replaced criterion requiring "the patient is not receiving any of [the listed therapies] in combination with Uplizna" with "the patient is not receiving any of [the listed therapies] in combination with Uplizna *for treatment of the same indication*" ***Immunoglobulin G4-Related Disease (IgG4-RD)*** • Added language to indicate Uplizna (inebilizumab-cdon) is proven for the treatment of IgG4-RD; Uplizna (inebilizumab-cdon) is medically necessary for the treatment of IgG4-RD when all the following criteria are met: ***Initial Therapy*** ○ Diagnosis of IgG4-RD ○ Confirmation of IgG4-RD by a positive assessment using the ACR/EULAR classification criteria, demonstrated by all of the following: ▪ Involvement of at least 1 or more organ(s) in a manner consistent with IgG4-RD ▪ Exclusion criteria is negative and consistent with an IgG4-RD diagnosis (e.g., clinical findings, serologic results, radiology assessments, pathology interpretations) ▪ Inclusion criteria is positive and signifies a diagnosis of IgG4-RD (e.g., clinical findings, serologic results, radiology assessments, pathology interpretations) ○ Both of the following: ▪ History of failure, contraindication, or intolerance to glucocorticoids ▪ One of the following: – History of failure of rituximab therapy – Both of the following: • History of intolerance or contraindication to rituximab • Physician attests that, in their clinical opinion, the same intolerance or severe adverse event would not be expected to occur with Uplizna ○ Uplizna is initiated according to the U.S. FDA labeled dosing for IgG4-RD ○ Prescribed by, or in consultation with, a specialist with expertise in the treatment of IgG4-RD ○ Patient is not receiving Uplizna in combination with a disease modifying therapy for the treatment of IgG4-related disease (e.g., rituximab) ○ Initial authorization will be for no more than 12 months ***Continuation of Therapy*** ○ Documentation of positive clinical response

Date	Summary of Changes
	○ Uplizna is dosed according to the U.S. FDA labeled dosing for IgG4-RD ○ Prescribed by, or in consultation with, a specialist with expertise in the treatment of IgG4-RD ○ Patient is not receiving Uplizna in combination with a disease modifying therapy for the treatment of IgG4-related disease (e.g., rituximab) ○ Reauthorization will be for no more than 12 months **Applicable Codes** • Added ICD-10 diagnosis code D89.84 **Supporting Information** • Updated *Background*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version 2025D0091H

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.