Medical Benefit Drug Policy

Uplizna (inebilizumab-cdon) injection, for intravenous use

Policy Number: MC/PC 048
Effective Date: July 1, 2025

Instructions for Use

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Related Policies

- N/A

Coverage Rationale

Neuromyelitis Optica Spectrum Disorder (NMOSD)

For initial coverage of Uplizna (inebilizumab-cdon) for Neuromyelitis Optica Spectrum Disorder (NMOSD), the following will be required:

- Diagnosis of neuromyelitis optica spectrum disorder (NMOSD) **and**
- Patient is anti-aquaporin-4 (AQP4) antibody positive **and**
- One of the following:
  - Trial and failure, contraindication, or intolerance to rituximab **or**
  - For continuation of prior therapy **and**
- Prescribed by or in consultation with one of the following:
  - Neurologist
  - Ophthalmologist

For reauthorization coverage of Uplizna (inebilizumab-cdon) for Neuromyelitis Optica Spectrum Disorder (NMOSD), the following will be required:

- Presence of positive clinical response to therapy

Immunoglobulin G4-Related Disease (IgG4-RD)

For initial coverage of Uplizna (inebilizumab-cdon) for Immunoglobulin G4-Related Disease (IgG4-RD), the following will be required:

- Diagnosis of Immunoglobulin G4-Related Disease (IgG4-RD) **and**
- Presence of disease involving two or more organ systems or sites (e.g., Pancreas, Submandibular gland, Lymph node(s), Kidneys, Bile Duct, Lungs or Lacrimal glands) **and**
- One of the following:

- Patient is currently being treatment with a glucocortic methylprednisolone) **or**
- Trial and failure, contraindication or intolerance to a glucocorticoid (e.g., prednisone, methylprednisolone).

For reauthorization coverage of Uplizna (inebilizumab-cdon) for Immunoglobulin G4-Related Disease (IgG4-RD), the following will be required:

- Presence of positive clinical response to therapy

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

ICD-10 Code	Description
G36.0	Neuromyelitis optica [Devic]
D89.84	Immunoglobulin G4-Related Disease (IgG4-RD)

Background

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a rare inflammatory, demyelinating autoimmune disorder of the central nervous system (CNS). Previously known as neuromyelitis optica (NMO) or Devic's Disease, NMOSD presents as acute attacks or relapses in which patients experience inflammation of the optic nerve (optic neuritis), spinal cord (transverse myelitis), or brainstem. The prevalence of NMOSD is from 0.37 to 10 per 100,000. The incidence of NMOSD in females is up to 7.6 times higher than males, and the median age of onset is 32 to 41 years. NMOSD may also present in children and older adults (*Glisson 2025*).

The treatment goals of NMOSD are to treat acute relapses, prevent relapses, and provide symptom management. NMOSD relapses can lead to permanent disability, poor prognosis, and overall high risk of mortality due to neurogenic respiratory failure (*Glisson 2025*). Acute relapses should be treated with corticosteroids; in corticosteroid-refractory cases, plasma exchange (PE) may be considered (*Sellner et al 2010*). Historically, the prevention of NMOSD relapses has consisted of off-label use of immunosuppressants including azathioprine, mycophenolate mofetil, tocilizumab, and rituximab (*Glisson 2025, Sellner et al 2010*). Since 2019, the FDA has approved eculizumab, inebilizumab, and satralizumab, each with a unique mechanism of action for the treatment of adults with NMOSD. Eculizumab, inebilizumab, and satralizumab received FDA-approval in 2019 and 2020, respectively, for the treatment of NMOSD in patients who are AQP4-IgG seropositive. All 3 agents have demonstrated a significant delay in time to the first adjudicated relapse in patients with NMOSD who are AQP4-IgG seropositive. Differences in the study designs, populations enrolled, and use of other concurrent immunosuppressants or as monotherapy make indirect comparisons of these 3 agents challenging. Eculizumab has only been studied in AQP4-IgG seropositive patients on stable immunosuppressant therapy such as azathioprine, corticosteroids, or mycophenolate mofetil. Inebilizumab, as monotherapy, reduced the risk of first relapse vs placebo over 6.5 months. Satralizumab has demonstrated benefit as

monotherapy and as add-on therapy in patients with NMOSD who are AQP4-Ig[illegible]been updated to include eculizumab, inebilizumab, and satralizumab.

Immunoglobulin G4-Related Disease (IgG4-RD) is an immune-mediated fibroinflammatory condition that can affect multiple organs. IgG4-RD often present with subacute development of a mass in the affected organ or diffuse enlargement of an organ. Patients often feel well at the time of diagnosis. Lymphadenopathy is common, but patients are generally afebrile. However, symptoms of asthma or allergy are present in approximately 40 percent of patients. Additionally, patients with multiorgan disease often lose substantial amounts of weight (eg, 20 to 30 pounds), which may be due to IgG4-related autoimmune pancreatitis (*Moutsopoulos 2025 a*).

Common presentations include type 1 (IgG4-related) autoimmune pancreatitis (AIP); IgG4-related sclerosing cholangitis; major salivary gland enlargement or sclerosing sialadenitis; orbital disease, often with proptosis; and retroperitoneal fibrosis, frequently with chronic periaortitis. (Moutsopoulos 2025 b).

The overall incidence of IgG4-RD was estimated to be 0.78 to 1.39 per 100,000 person-years (*Wallace et al.,2023*).

Inebilizumab-cdon is a CD19-directed humanized afucosylated IgG1 monoclonal antibody; The precise mechanism by which inebilizumab-cdon exerts its therapeutic effects in NMOSD and IgG4-RD is unknown but is presumed to involve binding to CD19, a cell surface antigen presents on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, inebilizumab-cdon results in antibody-dependent cellular cytolysis.

Clinical Evidence

NMOSD

The N-MOmentum trial was a 28-week, Phase 2/3, double-blind, placebo controlled, multi-center, randomized controlled trial that evaluated the efficacy and safety of inebilizumab in patients with NMOSD (*Cree et al 2019*). A total of 230 adults with AQP4-IgG seropositive (n = 213) or seronegative (n = 17) NMOSD were randomized in a 3:1 fashion to inebilizumab 300 mg IV on Days 1 and 15 then 300 mg IV every 6 months or to placebo; no other immunosuppressants were permitted. All patients received oral prednisone or equivalent for the first 14 days followed by a 7-day taper. At baseline, the mean Expanded Disability Status Scale (EDSS) scores were 3.8 for the inebilizumab group and 4.2 for the placebo group. For the primary endpoint of time to first adjudicated relapse on or before Day 197, inebilizumab significantly reduced the risk of an NMOSD relapse by 73% compared with placebo in the overall population (HR, 0.272; 95% CI, 0.150 to 0.496; $p < 0.0001$). Relapses occurred in 12.1% and 39.3% of patients in the inebilizumab and placebo groups, respectively. In the AQP4-IgG seropositive group, inebilizumab significantly reduced the percentage of patients with relapses (11.2% vs 42.3%; HR, 0.227; 95% CI, 0.121 to 0.423; $p < 0.0001$). No difference in relapses was seen in the AQP4-IgG seronegative group with inebilizumab (23.1% vs 0%); the placebo group had a total of 4 patients and no reported relapses. The secondary endpoint, number of patients with worsening from baseline in EDSS, favored inebilizumab (16% vs 34%; HR, 0.370; 95% CI, 0.185 to 0.739; $p = 0.0049$); however, the FDA found that the EDSS findings were uninterpretable due to the variable observation periods between patients inherent in the time-to-event trial design (which also resulted in a significant amount of missing data), a consistent lack of relapse confirmation visits at an acceptable interval, and the protocol's inadequate approach to accounting for the impact of an acute relapse on EDSS changes from baseline (*Uplizna FDA Summary Review 2020*).

Place in Therapy

There are no U.S. based guidelines for NMOSD available at present. NMO acute relapses are treated with high-dose corticosteroids followed by an oral prednisone taper over several months (*Kimbrough et al 2012, Sellner et al 2010, Trebst et al 2014*). The European Federation of Neurological Societies (EFNS) guideline for the prevention of NMO relapses recommends oral azathioprine plus prednisone or rituximab as first-line therapy (*Sellner et al 2010*). Other groups recommend mycophenolate mofetil plus prednisone as an additional first-line choice. Other treatment options include oral methotrexate, mitoxantrone, IV cyclophosphamide, IVIG, or PE (*Kimbrough et al 2012, Sellner et al 2010*, *Trebst et al 2014*).

IgG4-RD

Initial treatment of IgG4-RD is prednisone, usually at a dose of 0.6 mg/kg (typic ll patients demonstrate a response to prednisone 40 mg daily within two to four weeks, many patients respond even earlier (*Moutsopoulos 2025b*). Glucocorticoids are the first-line agent for remission induction in all patients with active, untreated IgG4-RD, unless contraindications to such treatment are present. Control of disease with glucocorticoids alone, glucocorticoid monotherapy will often fail to produce sustained disease control.

In some patients with multi-organ disease (eg, three or more organs) or a high serum IgG4 concentration (eg, >5 times the upper limit of normal), starting treatment with the combination of glucocorticoids plus rituximab or inebilizumab is beneficial (*Moutsopoulos 2025b*).

A retrospective nationwide study in France showed that rituximab was effective as both induction and maintenance treatment. Relapses occurred when rituximab was discontinued. Systematic rituximab infusion (before evidence of relapse) was associated with longer relapse-free survival (*Ebbo et al.,2017*). In addition, in an open-label trial, 30 patients with IgG4-RD were treated with two doses of rituximab, most without concomitant use of glucocorticoids (Carruthers et al.,2015). The disease responded in 97 percent of the patients, and 40 percent remained at complete remission at 12 months. In a meta-analysis examining efficacy and safety of rituximab in IgG4-RD with pancreato-biliary manifestations, it was found that the pooled rate of complete response at six months was 88.9 percent (95% CI 80.5-93.9), while the relapse rate was 21 percent (95% CI 10.5-40.3) (*Lanzillotta et al. 2021*). Relapses were more frequent in patients who had multiorgan disease.

Inebilizumab has been approved by the US Food and Drug Administration (FDA) for the treatment of IgG4-RD based on a randomized trial of 135 patients with IgG4-RD that randomly assigned patients to receive inebilizumab (300 mg intravenous infusions on days 1 and 15 and week 26) or placebo (*Stone et al., 2025*). At the end of 52 weeks of observation, patients treated with inebilizumab had fewer flares than patients treated with placebo (10 versus 60 percent). Patients assigned to inebilizumab were also more likely to have a flare-free, glucocorticoid-free, complete remission than patients treated with placebo (odds ratio 5.0).

Head-to-head comparisons of inebilizumab and rituximab have not been performed. In theory, because CD19 is expressed on a broader spectrum of B cells than CD20, inebilizumab may be more effective at depleting B cells and even some plasma cells, some of which retain CD19. Moreover, because inebilizumab is a humanized monoclonal antibody and rituximab is chimeric, inebilizumab may be associated with a lower rate of infusion reactions and serum sickness episodes. The clinical implications of these differences in the molecules for both efficacy and safety are not clear at this time (*Moutsopoulos 2025b*).

Place in Therapy

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have developed comprehensive guidelines published in 2019 for the classification and treatment of IgG4-related disease (IgG4-RD). The treatment guidelines emphasize that the initial therapy is Glucocorticoids are used as first-line treatment for inducing remission. The maintenance therapy is to immunosuppressive agents like rituximab may be used for long-term management. They haven't been updated to included inebilizumab (*Wallace et al., 2019*).

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.

Uplizna is indicated for the treatment of Immunoglobulin G4-related disease (IgG4-RD) in adult patients.

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Policy History/Revision Information

Date	Summary of Changes
12/13/2023	Approved by OptumRx P&T Committee
6/19/2024	Annual review. Updated references.
6/18/2025	Annual review. Added Immunoglobulin G4-Related Disease (IgG4-RD) indication for Uplizna, clinical content, and references.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting 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. The insurance 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.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx 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.

Archived Policy Versions (Internal Only)

Effective Date	Policy Number	Policy Title
mm/dd/yyyy – mm/dd/yyyy	######	Title of Policy Hyperlinked to KL or Other Internal Location

Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

Hindi: _यान द_: य_द आप ि हंदी बोलते ह_ तो आपके ि लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_।1-800-332-6501 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

Korean: 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다.1-800-332-6501 (TTY: 711)번으로 전화해 주십시오.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer1-800-332-6501 (TTY: 711).

Russian: ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода.Звоните 1-800-332-6501 (телетайп: 711).

Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al1-800-332-6501 (TTY: 711).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1-800-332-6501 (TTY: 711).

Traditional Chinese: 注意：如果您使用繁體中文， 您可以免費獲得語言援助服務。請 致電 1-800-332-6501 (TTY: 711)

Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-800-332-6501 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-800-332-6501 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-800-332-6501 (TTY: 711).