BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

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| **EVIDENCE-BASED CRITERIA** | **ORIGINAL EFFECTIVE DATE: 10/14/24** |
| **SECTION: SPECIALTY MEDICAL DRUGS** | **LAST REVIEW DATE: 08/15/24** |
| | **CURRENT EFFECTIVE DATE: 10/14/24** |
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| **NEXT ANNUAL REVIEW DATE: 3RD QTR 2025** | **ARCHIVE DATE:** |

# UPLIZNA™ (inebilizumab-cdon)

**Non-Discrimination Statement is located at the end of this document.**

**Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.**

**This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.**

**The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.**

**The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.**

**State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.**

**Evidence-Based Criteria are subject to change as new information becomes available.**

**For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.**

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# UPLIZNA™ (inebilizumab-cdon)

**Criteria:**

**Refer to FDA website for current indications and dosage.**

- **Criteria for initial therapy:** Uplizna (inebilizumab-cdon) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of neuromyelitis optica spectrum disorder (NMOSD) with **ALL** of the following:

   - Documentation of confirmed anti-aquaporin-4 (AQP4) antibody positive
   - History of at least 1 relapse in the last 12 months or two relapses in the last 2 years [Note: Criterion may be waived if individual has documented contraindication to rituximab]
   - Attacks of NMOSD consist of at least **ONE** of the following core clinical features:

     a. Optic neuritis
     b. Acute myelitis
     c. Area postrema syndrome (episodes unexplained intractable hiccups or nausea and vomiting)
     d. Acute brainstem syndrome
     e. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
     f. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

4. Individual has failure (trial of at least 3 months), contraindication per FDA label or intolerance, or is not a candidate for **rituximab** [Note: Criterion may be waived if individual has documented failure of Enspryng, Soliris, or Ultomiris, due to lack of efficacy]

5. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:

   - Hepatitis B screening (HB surface Ag, anti-HB surface Ab, anti-HB core Ab)
   - Tuberculosis screening
   - Serum immunoglobulins

6. There are **NO** contraindications including:

   - Life-threatening reaction to infusion of Uplizna
   - Active hepatitis B infection

- Active or untreated latent tuberculosis

7. Individual does **NOT** have **ANY** of the following:

   - Evidence of active infection
   - Will not receive live attenuated or live vaccines during treatment with Uplizna and after discontinuation, until B-cell repletion

8. Uplizna will not be used in combination with immunosuppressive drugs (e.g., Actemra, Enspryng, Kesimpta, Rinvoq, rituximab, Soliris, Ultomiris, etc.)

**Initial approval duration**: 6 months

- **Criteria for continuation of coverage (renewal request):** Uplizna (inebilizumab-cdon) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

2. Individual has a confirmed diagnosis of neuromyelitis optica spectrum disorder (NMOSD) and is anti-aquaporin-4 (AQP4) antibody positive

3. Individual's condition has responded while on therapy with response defined as **TWO** of the following:

   - Reduction in the number and/or severity of relapses
   - Decrease in concomitant corticosteroid or immunosuppressive therapy (e.g., azathioprine, mycophenolate, etc.)
   - Decrease in NMOSD symptoms (e.g., pain, fatigue, improvement in motor function)

4. Individual has been adherent with the medication

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:

   - Life-threatening reaction to infusion of Uplizna
   - Active hepatitis B infection
   - Active or untreated latent tuberculosis

6. Uplizna will not be used in combination with immunosuppressive drugs (e.g., Actemra, Enspryng, Kesimpta, Rinvoq, rituximab, Soliris, Ultomiris, etc.)

**Renewal duration**: 12 month

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- If the individual has one or more NMOSD relapse, consider changing disease modifying therapy

- Uplizna (inebilizumab-cdon) for all other indications not previously listed is considered ***experimental or investigational*** and will not be approved when any **ONE** or more of the following criteria are met:

  1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
  3. Insufficient evidence to support improvement of the net health outcome; or
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
  5. Insufficient evidence to support improvement outside the investigational setting.

  These indications include *but are not limited to:*

  - Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

## Description:

Uplizna (inebilizumab-cdon) is a CD19-ddirected cytolytic antibody indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

The precise mechanism by which inebilizumab-cdon exerts its therapeutic effects in NMOSD 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 results in antibody-dependent cellular cytolysis

NMOSD, previously known as Devic disease or neuromyelitis optica [NMO]) are inflammatory disorders of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting optic nerves and spinal cord.

NMOSD is distinguished from multiple sclerosis and other central nervous system inflammatory disorders by the presence of the disease-specific AQP4 antibody (also referred to as NMO-immunoglobulin G antibody). AQP4 is a water channel protein that is concentrated in the spinal cord gray matter, periaqueductal and periventricular regions, and astrocytic foot processes of the blood brain barrier. Studies have shown that serum anti-AQP4 titers correlate with disease activity, decrease after immunotherapy, and are low during remission.

NMOSD acute attacks are characterized by bilateral or rapidly sequential optic neuritis (leading to visual loss), acute transverse myelitis (often causing limb weakness and bladder dysfunction), and the area postrema syndrome (with intractable hiccups or nausea and vomiting). The acute attacks may occur over

days with variable degrees of recovery that can be weeks to months. It has a relapsing course and management is directed at treating an acute attack and then preventing another attack or prolonging the time to a relapse.

The natural history of NMOSD is a stepwise deterioration from accumulating visual, motor, sensory, and bladder deficits from recurrent attacks. Mortality rate is high in NMOSD, and it is often due to neurogenic respiratory failure, that occurs with extension of cervical lesions into the brainstem or from primary brainstem lesions.

**Definitions:**

**Neuromyelitis optica spectrum disorder (NMOSD):**

**Diagnostic criteria for NMOSD with AQP4-IgG**
1. At least one core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses

**Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status**
1. At least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
a. At least one core clinical characteristic must be optic neuritis, acute myelitis with longitudinally extensive transverse myelitis (LETM), or area postrema syndrome
b. Dissemination in space (two or more different core clinical characteristics)
c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses

**Core clinical characteristics**
1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: Episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

**Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status**
1. Acute optic neuritis: Requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, **or** (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium enhancing lesion extending over more than one-half the optic nerve length or involving optic chiasm

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2. Acute myelitis: Requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) **or** ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis
3. Area postrema syndrome: Requires associated dorsal medulla/area postrema lesions
4. Acute brainstem syndrome: Requires associated periependymal brainstem lesions

**Biologic NMOSD therapies:**

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| Interleukn-6 Receptor Antagonist | ENSPRYNG (satralizumab) |
| Compliment 5 inhibitor (C5i) | SOLIRIS (eculizumab) |
| Compliment 5 inhibitor (C5i) | ULTOMIRIS (ravulizumab) |
| Anti-CD19 Monoclonal Antibody | UPLIZNA (inebilizumab) |
| Anti-CD20 Monoclonal Antibody | RIABNI* (rituximab) (off-label) |
| Anti-CD20 Monoclonal Antibody | RITUXAN (rituximab) (off-label) |
| Anti-CD20 Monoclonal Antibody | RUXIENCE* (rituximab)* (off-label) |
| Anti-CD20 Monoclonal Antibody | TRUXIMA* (rituximab)* (off-label) |

** Biosimilar to Rituxan*

| **History**: | **Date**: | **Activity**: |
|---|---|---|
| Pharmacy and Therapeutics Committee | 08/15/24 | Approved guideline (effective 10/14/24) |
| Clinical Pharmacist | 05/17/24 | Development |

**Coding**:

HCPCS: J1823

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**Resources:**

**Literature reviewed 08/15/24. We do not include marketing materials, poster boards and non-published literature in our review.**

1. Damato V, Evoli A, Iorio R. Efficacy and Safety of Rituximab Therapy in Neuromyelitis Optica Spectrum Disorders: A Systematic Review and Meta-analysis. *JAMA Neurol*. 2016 Nov 1;73(11):1342-1348. doi: 10.1001/jamaneurol.2016.1637.

2. Glisson CC. Neuromyelitis optica spectrum disorder (NMOSD): Clinical features and diagnosis. In: UpToDate, González-Scarano F, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2024. Topic last updated August 30, 2022. May 17, 2024.

3. Glisson CC. Neuromyelitis optica spectrum disorder (NMOSD): Treatment and prognosis. In: UpToDate, González-Scarano F, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2024. Topic last updated April 11, 2024. Accessed May 17, 2024.

4. Ongphichetmetha T, Jitprapaikulsan J, Siritho S, et al. Efficacy and safety of rituximab in multiple sclerosis and neuromyelitis optica spectrum disorder. *Sci Rep.* 2024;14(1):3503. doi: 10.1038/s41598-024-53838-y.

5. Tania Kümpfel, Katrin Giglhuber, Orhan Aktas, et al. Update on the diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD) – revised recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part II: attack therapy and long-term management. *J Neurol*. 2023; 270(7):3341-3368. doi: 10.1007/s00415-023-11634-0.

6. 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; 261:1-16.

7. Uplizna (inebilizumab-cdon) product information revised by Horizon Therapeutics USA, Inc. 07/2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 21, 2024.

8. Wang Y, Chang H, Zhang X, Yin L. Efficacy of rituximab in the treatment of neuromyelitis optica spectrum disorders: An update systematic review and meta-analysis. *Mult Scler Relat Disord*. 2021 May;50:102843. doi: 10.1016/j.msard.2021.102843.

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**Non-Discrimination Statement:**

**Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.**

**If you believe that BCBSAZ 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: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights 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, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html**