UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Uplizna Utilization Management Medical Policy
- Uplizna® (inebilizumab-cdon intravenous infusion – Amgen/Horizon)

REVIEW DATE: 04/02/2025; selected revision 05/21/2025, 06/04/2025

OVERVIEW

Uplizna, a CD19-directed cytolytic antibody, is indicated for the following uses:[1]
- **Immunoglobulin G4-related disease** (IgG4-RD) in adults.
- **Neuromyelitis optica spectrum disorder** (NMOSD) in adults who are anti-aquaporin-4 antibody-positive.

Dosing

For both the IgG4-RD and NMOSD indications, the recommended dose of Uplizna is an initial dose of 300 mg administered as an intravenous (IV) infusion, followed by a second 300 mg IV infusion 2 weeks after the first dose. Subsequent doses, starting 6 months after the first infusion, are single 300 mg IV infusions every 6 months.

Disease Overview

IgG4-RD

IgG4-RD (also known as IgG4-related systemic disease, hyper-IgG4 disease, IgG4-related autoimmune disease, IgG4-associated disease, IgG4-related sclerosing disease, and IgG4-syndrome) is a rare, progressive, highly destructive, autoimmune, fibroinflammatory disease.[5,6] The incidence rate was estimated to be 1.39 per 100,000 person-years in 2019 and the point prevalence was 5.3 persons per 100,0000. The disease can affect nearly any organ system and typically, multiple organs are affected simultaneously. Approximately 40% of patients present with clinically evident disease in a single organ and approximately 60% to 90% of patients present with disease in more than one organ. Although any organ can be affected; the most commonly affected organs include the aorta, bile ducts, kidneys, lacrimal glands, orbits, pachymeninges, pancreas, retroperitoneum, major salivary glands (submandibular, parotid, sublingual), thyroid gland (Riedel's thyroiditis).[7]

The disease course is unpredictable with recurrent flares that cause functional and structural damage in the affected organs.[5,6] If IgG4-RD is not treated, major organ dysfunction and failure can result. Diagnosis of IgG4-RD is challenging as there is no single definitive diagnostic test; therefore, accurate diagnosis relies on a combination of clinical and serological features as well as radiological and histological findings.[5-7] The 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for IgG4-RD note that the presence of an elevated serum immunoglobulin G4 (IgG4) levels is no longer considered essential for diagnosis of the disease.[7] In addition, clinical diagnosis can be made without a biopsy; a representative biopsy sample may be difficult to obtain. Since patients may present with a wide range of clinical manifestations and symptoms, a multidisciplinary approach may be needed to accurately identify the condition.[5-7]

NMOSD

NMOSD is a rare, relapsing, autoimmune central nervous system inflammatory disorder that can lead to significant morbidity and mortality.[2,3] The predominant symptoms are inflammation of the optic nerve (optic neuritis) and inflammation of the spinal cord (myelitis). Optic neuritis may lead to pain inside the eye and can progress to blindness. Myelitis tends to affect some, and often all, motor, sensory, and

autonomic functions (bladder and bowel). Affected patients may experience pain in the spine or limbs, mild to severe paralysis of the lower limbs, and loss of bowel and bladder control.

Recommendations

IgG4-RD

There are no formal guidelines for the diagnosis and treatment of IgG4-RD.[9] The The 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteira for IgG4-RD note that all patients with the disease had involvement of one or more organs.[7], Treatment is needed to sustain remission and to prevent further organ damage or failure.[5,6] Systemic corticosteroids (used off-label) are the mainstay of treatment. Objective measures of response include tapering or reduction in the corticosteroid dose, reduction in the number of disease flares, increase in the duration of flare-free period, and absence of disease activity.[8,9] Although most patients respond quickly to systemic corticosteroids, disease control is not maintained following corticosteroid taper or discontinuation.[5,6,9] Other therapies that are used off-label to manage patients with IgG4-RD include conventional, synthetic disease-modifying antirheumatic drugs (DMARDs) [including azathioprine, mycophenolate mofetil, methotrexate, leflunomide, and cyclosporine] and anti-CD20 monoclonal antibodies, such as rituximab. Support for these therapies are mostly from case series, retrospective chart analyses, or single-center tirals with an open-label, single-arm design.

NMOSD

The Neuromyelitis Optica Study Group (NEMOS) published revised recommendations for the treatment of NMOSD in 2024.[4] The standard of care for the treatment of NMOSD attacks (for both AQP4-IgG-positive and double-negative cases) are high-dose glucocorticoids and/or apheresis therapy. Long term immunotherapy is recommended for patients with AQP4-IgG-positive NMOSD. NEMOS notes the first-choice therapies for the treatment of AQP4-IgG-positive NMOSD are Uplizna, Enspryng® (satralizumab-mwge subcutaneous injection), eculizumab intravenous infusion (Soliris®, biosimilars), Ultomiris® (ravulizumab-cwvz intravenous infusion), and rituximab. The order of preference for these therapies is unclear and further comparative trials and real-world data are needed. The choice of treatment is dependent on several factors, including disease activity and severity, mode and onset of action, possibility to combine it with immunosuppressive drugs, effect on autoimmune and other comorbidities, gender (family planning issues), frequency and route of administration, side effect profile as well as patient and physician preference. In general, if a patient fails a first-choice treatment, another first-choice treatment should be tried; other options include use of a second-choice treatment (azathioprine, mycophenolate mofetil, low-dose oral glucocorticoids) or the addition of a second-choice treatment to the regimen.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Uplizna. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Uplizna as well as the monitoring required for adverse events and long-term efficacy, approval requires Uplizna to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Uplizna is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Immunoglobulin G4-Related Disease.** Approve if the patient meets ONE of the following (A or B):
   Note: Immunoglobulin G4-related disease (IgG4-RD) can be referred as the following: IgG4-related systemic disease, hyper-IgG4 disease, IgG4-related autoimmune disease, IgG4-associated disease, IgG4-related sclerosing disease, and IgG4-syndrome.
   - **A.** Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has had a history of involvement of at least one organ; AND
       Note: Examples of organs that are involved include the aorta, bile ducts, kidneys, lacrimal glands, orbits, pachymeninges, pancreas, retroperitoneum, major salivary glands (submandibular, parotid, sublingual), thyroid gland (Riedel's thyroiditis).
     - **iii.** Patient meets ONE of the following (a or b):
       - **a)** Patient has received or is currently receiving a systemic corticosteroid; OR
       - **b)** Patient has had inadequate efficacy, a contraindication, or significant intolerance to a systemic corticosteroid; AND
     - **iv.** The medication is being prescribed by or in consultation with an endocrinologist, gastroenterologist, immunologist, nephrologist, neurologist, pulmonologist, rheumatologist, or a physician who specializes in treating immune-mediated disorders; OR
   - **B.** Patient is Currently Receiving Uplizna. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** According to the prescriber, patient has had clinical benefit from the use of Uplizna; AND
       Note: Examples of clinical benefit include reduction in the corticosteroid dose, reduction in the number of disease flares, increase in the duration of flare-free period, and absence of disease activity.
     - **iii.** The medication is being prescribed by or in consultation with an endocrinologist, gastroenterologist, immunologist, nephrologist, neurologist, pulmonologist, rheumatologist, or a physician who specializes in treating immune-mediated disorders.

   Dosing. Approve ONE of the following dosing regimens (A or B):
   - **A)** Initial Therapy. Approve the following dosage regimens (i and ii):
     - **i.** Initial dose: 300 mg administered by intravenous infusion, followed by a second 300 mg administered by IV infusion 2 weeeks after the first infusion; AND
     - **ii.** Subsequent doses, starting 6 months after the initial infusion, are single 300 mg administered by intravenous infusion every 6 months; OR
   - **B)** Patient is Currently Receiving Uplizna: Approve a single 300 mg administered by intravenous infusion every 6 months.

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2. **Neuromyelitis Optica Spectrum Disorder**. Approve if the patient meets ONE of the following (A or B):
   - **A.** Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Diagnosis of neuromyelitis optica spectrum disorder was confirmed by blood serum test for anti-aquaporin-4 antibody positive disease; AND
     - **iii.** The medication is being prescribed by or in consultation with a neurologist; OR

B. Patient is Currently Receiving Uplizna. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Diagnosis of neuromyelitis optica spectrum disorder was confirmed by blood serum test for anti-aquaporin-4 antibody positive disease; AND
- **iii.** According to the prescriber, patient has had clinical benefit from the use of Uplizna; AND
  Note: Examples of clinical benefit include reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing progression in symptoms.
- **iv.** The medication is being prescribed by or in consultation with a neurologist.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) Initial Therapy. Approve the following dosage regimens (i and ii):
- **iii.** Initial dose: 300 mg administered by intravenous infusion, followed by a second 300 mg administered by IV infusion 2 weeeks after the first infusion; AND
- **iv.** Subsequent doses, starting 6 months after the initial infusion, are single 300 mg administered by intravenous infusion every 6 months; OR

B) Patient is Currently Receiving Uplizna: Approve a single 300 mg administered by intravenous infusion every 6 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Uplizna is not recommended in the following situations:

1. **Concomitant Use With a Rituximab Product, Enspryng (satralizumab-mwge subcutaneous injection), Eculizumab Intravenous Infusion (Soliris, biosimilars), or Ultomiris (ravulizumab-cwvz intravenous infusion).** There is no evidence to support additive efficacy of combining Uplizna with rituximab, eculizumab, Enspryng, or Ultomiris.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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5. Nambiar S, Oliver TI. IgG4-related disease. Available at: IgG4-Related Disease - StatPearls - NCBI Bookshelf. Accessed on May 9, 2025.
6. Uplizna AMCP Dossier – Amgen. Version 1 (April 2025). Received on May 16, 2025.
7. 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;72:7-19.
8. Stone JH, Khosroshahi A, Zhang W, et al. Inebilizumab for treatment of IgG4-related disease. *N Engl J Med*. 2025;392: 1168-1177.
9. Umehara H, Okazaki K, Kawa S. The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD. *Mod Rheumatol*. 2021 May;31(3):529-533

HISTORY

Type of Revision	Summary of Changes	Review Date

Annual Revision	No criteria changes.	07/12/2023
Selected Revision	**Neuromyelitis Optica Spectrum Disorder – Initial Therapy:** Removed criterion that required prior use of two systemic therapies and criterion that patient has had a history of at least one relapse in the last 12 months or two relapses in the last 2 years. Uplizna is listed as a first-line treatment option in the Neuromyelitis Optica Study Group (NEMOS) recommendations for the treatment of Neuromyelitis Optica Spectrum Disorder (2024).	03/27/2024
Early Annual Revision	**Conditions Not Recommended for Approval:** Ultomiris (ravulizumab-cwvz intravenous infusion) received FDA approval for treatment of NMOSD and was added to the criterion "Concomitant Use with a Rituximab Product, Enspryng (satralizumab-mwge subcutaneous injection), or Soliris (eculizumab intravenous infusion)".	04/10/2024
Annual Revision	**Conditions Not Recommended for Approval:** Soliris (eculizumab intravenous infusion) was changed to add biosimilars; new verbiage reads "eculizumab intravenous infusion (Soliris, biosimilars)".	04/02/2025
Selected Revision	**Immunoglobulin G4-Related Disease:** This condition and criteria for approval were added to the policy. **Neuromyelitis Optica Spectrum Disorder:** The dosing section was revised to clarify dosing recommendations for initial treatment and for patients continuing treatment.	05/21/2025
Selected Revision	**Immunoglobulin G4-Related Disease:** Initial Therapy: Criterion that required patient to have serum IgG level > 135 mg/dL or two of the following three criteria (dense lymphocyte and plasma cell infiltration with fibrosis, ratio of IgG4-positive plasma cells/ IgG-positive cells > 40% and the number of IgG4-positive plasma cells > 10 per high powered field, and typical tissue fibrosis, particularly storiform fibrosis, or obliterative phlebitis) was removed. Regarding the Note of examples of organs that are involved, "orbital adnexal structures" was removed; the qualifier "major" was added to "salivary glands" along with examples "(submandibular, parotid, sublingual)"; and "bile ducts, orbits, lacrimal glands, aorta, pachymeninges, thyroid gland (Reidel's thyroiditis" were added. Neurologist and pulmonologist were added to the list of specialists. Patient is Currently Receiving Uplizna: Neurologist and pulmonologist were added to the list of specialists.	06/04/2025