Administration of UPLIZNA® (inebilizumab-cdon)

ICD-10 C&M Meeting

Horizon Therapeutics
March 2022

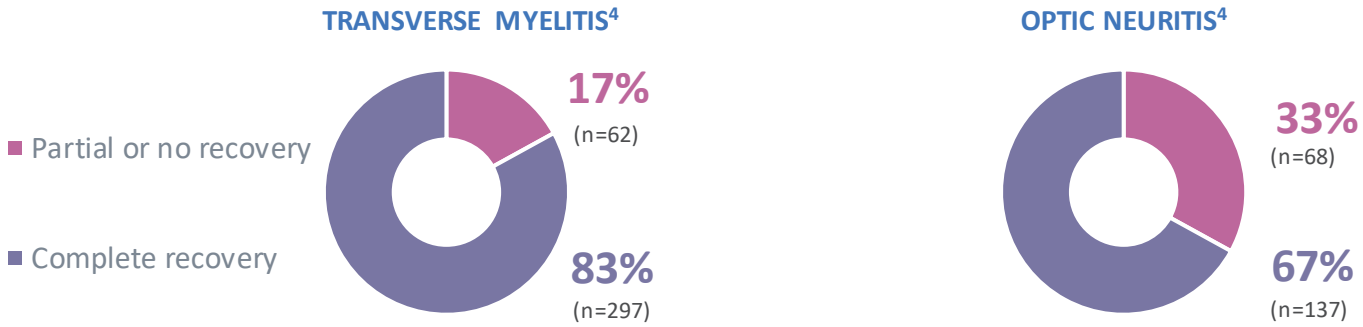
Neuromyelitis Optica Spectrum Disorder (NMOSD) is a Rare and Debilitating Autoimmune-Mediated Neurological Condition

NMOSD is characterized by recurrent CNS attacks that can result in blindness, paralysis and death[2a]

22% of patients with NMOSD may **require a walker** at five years after disease onset[3]

41% of patients with NMOSD may become **legally blind in at least one eye** at five years after disease onset[3]

Damage from NMOSD attacks is often irreversible



[a]Accumulation of disability resulting from severe attacks (>3 on EDSS).

CNS, central nervous system; EDSS, expanded disability status scale; NMOSD, neuromyelitis optica spectrum disorder.

1. Borisow N, Mori M, Kuwabara S, Scheel M, Paul F. Diagnosis and Treatment of NMO Spectrum Disorder and MOG-Encephalomyelitis. Front Neurol. 2018;9:888.
2. Ajmera MR, Boscoe A, Mauskopf J, Candrilli SD, Levy M. Evaluation of comorbidities and health care resource use among patients with highly active neuromyelitis optica. J Neurol Sci. 2018;384:96-103.
3.Jiao Y, Fryer JP, Lenon VA, et al. Updated estimate of AQP4-IgG serostatus and disability outcome in neuromyelitis optica. Neurology. 2013;81(14):1197-1204.
4. Jarius S, Ruprecht K, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A multicenter study of 175 patients. J Neuroinflammation. 2012;9:14.

NMOSD is Relapse Dependent, with Attacks Driving Cumulative Disability

Without treatment, a repeat attack is nearly inevitable over time

- 60% of patients with AQP4 autoantibodies relapse within one year[1]
- More than 1/3 of attacks require hospitalization[2]
- Cumulative attack-related neurological disability necessitates prompt initiation of immunosuppressive therapy

Prevalence Summary Statistics

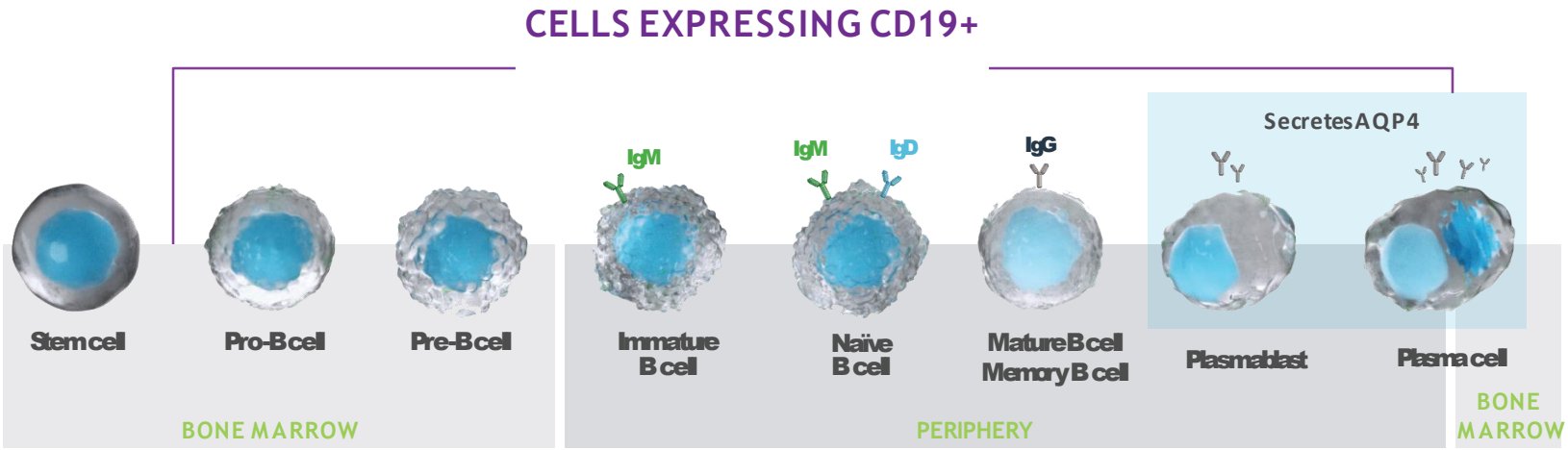
In the U.S., approximately
10-15k people
are affected by NMOSD

Prevalence data are limited but suggest NMOSD occurs in **< 5/100,000** with well-recognized ethnic, geographic and gender disparities[3,4,5]

Pathogenic auto **antibodies against aquaporin 4** (AQP4-IgG) found in **~75% of patients**[5,6]

1. Sherman E, Han MH. Acute and Chronic Management of Neuromyelitis Optica Spectrum Disorder. Curr Treat Options Neurol. 2015;17(11):48.
2. Royston M, Kielhorn A, Weycker D, Shaff M, Houde L, Tanvir I, Bhattacharyya S, Levy M. Neuromyelitis Optica Spectrum Disorder: Clinical Burden and Cost of Relapses and Disease-Related Care in US Clinical Practice. Neurol Ther. 2021 Dec;10(2):767-783.
3. Flanagan EP, Cabre P, Weinshenker BG, et al. Epidemiology of aquaporin-4 autoimmunity and neuromyelitis optica spectrum. Ann Neurol. 2016;79(5):775-783.
4. Pandit L, Asgari N, Apiwattanakul M, et al. Demographic and clinical features of neuromyelitis optica: A review. Mult Scler. 2015;21(7):845-853.
5. Wingerchuk DM. Neuromyelitis optica: Effect of gender. J Neurol Sci. 2009;286(1-2):18-23.
6. Borisow N, Mori M, Kuwabara S, Scheel M and Paul F. Diagnosis and Treatment of NMO Spectrum Disorder and MOG-Encephalomyelitis. Front Neurol. 2018;9:888.

CD19 is a Specific Marker of B Cells and is Broadly Expressed Across the B-cell Lineage



- B cells play a fundamental role in NMOSD immunopathology, with multiple proposed mechanisms contributing to disease pathogenesis including Anti-AQP4 antibody production[1]
- CD19 is widely expressed on a broader array of surfaces on B cells, including on plasmablasts and plasma cells that produce AQP4 antibodies[1,2]

1. Bennett JL, O'Connor KC, Bar-Or A, et al. B lymphocytes in neuromyelitis optica. Neurol Neuroimmunol Neuroinflamm. 2015;2(3):e104.
2. Forsthuber TG, Cimbora DM, Ratchford JN, Katz E, Stve O. B cell-based therapies in CNS autoimmunity: differentiating CD19 and CD20 as therapeutic targets. Ther Adv Neurol Disord. 2018;11:1756286418761697.

UPLIZNA is the First Anti-CD19 B Cell Depleter Indicated for Adults Diagnosed With AQP4+ NMOSD[1]

UPLIZNA is a highly specific B-cell depleter that targets a wide spectrum of B-cells that play a role in NMOSD. [2,3]

How it works:

- In NMOSD, AQP4 autoantibodies bind astrocytes, leading to cell death and inflammation
- A sub-population of B-lineage cells, CD19+ plasmablasts/plasma cells produce AQP4 autoantibodies. Certain CD19+ B-cells are increased in the blood of AQP4-IgG seropositive individuals with NMOSD, with the highest levels observed during an attack
- UPLIZNA binds specifically to CD19, targeting an extended range of the B-cell lineage that contributes to the multi-mechanistic disease activity of NMOSD, including plasmablasts and some plasma cells[4]

Naming convention:

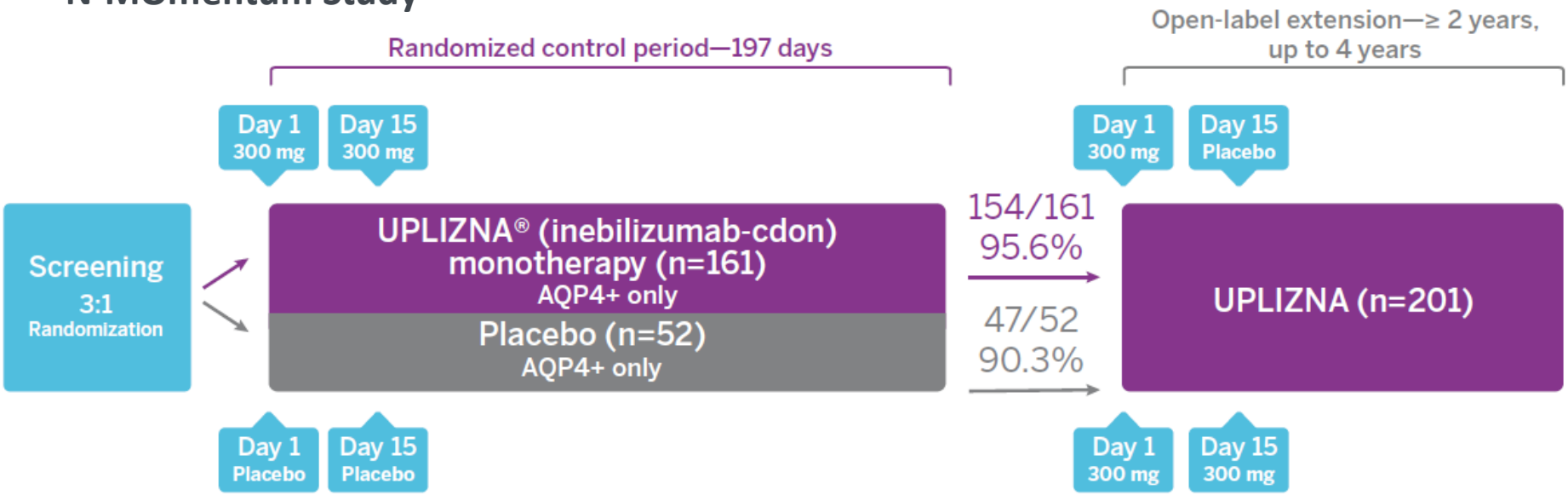
Proprietary name: UPLIZNA

Non proprietary name: Inebilizumab cdon

1. UPLIZNA (inebilizumab-cdon) [prescribing information] Horizon.
2. Schiopu E, Chatterjee S, Hsu V, et al. Safety and tolerability of an anti-CD19 monoclonal antibody, Medi-551, in subjects with systemic sclerosis: A phase I, randomized, placebo-controlled, escalating single-dose study. Arthritis Research & Therapy. Arthritis Res Ther. 2016; 18 (1):13 1.
3. Herbst R, Wang Y, Gallagher S, et al. B-cell depletion in vitro and in vivo with an afucosylated anti-CD19 antibody. Pharmacol Exp Ther. 20 10; 335(1) 213-222.
4. Forsthuber TG, Cimbora DM, Ratchford JN, Katz E, Stuve O. B cell-based therapies in CNS autoimmunity: differentiating CD19 and CD20 as therapeutic targets. Ther Adv Neurol Disord. 2018; 11:1756286418761697.

UPLIZNA Was Studied in the Largest Randomized Controlled Trial for NMOSD Monotherapy

N-MOmentum Study



n = 165 from inebilizumab arm plus n = 51 from the placebo arm in the RCP.
Participants received study drug according to their randomized allocation on days 1 and 15 of the RCP. To preserve masking in the OLP, participants randomized to inebilizumab received inebilizumab on day 1 and placebo on day 15, and those randomized to placebo received inebilizumab on both days 1 and 15. Thereafter, all participants received inebilizumab every 26 weeks.1
AQP4+, aquaporin-4 immunoglobulin G-seropositive
1. Cree BAC et al. Poster A-21-00375 presented at the 7th Congress of the European Academy of Neurology (virtual), June 19–22, 2021

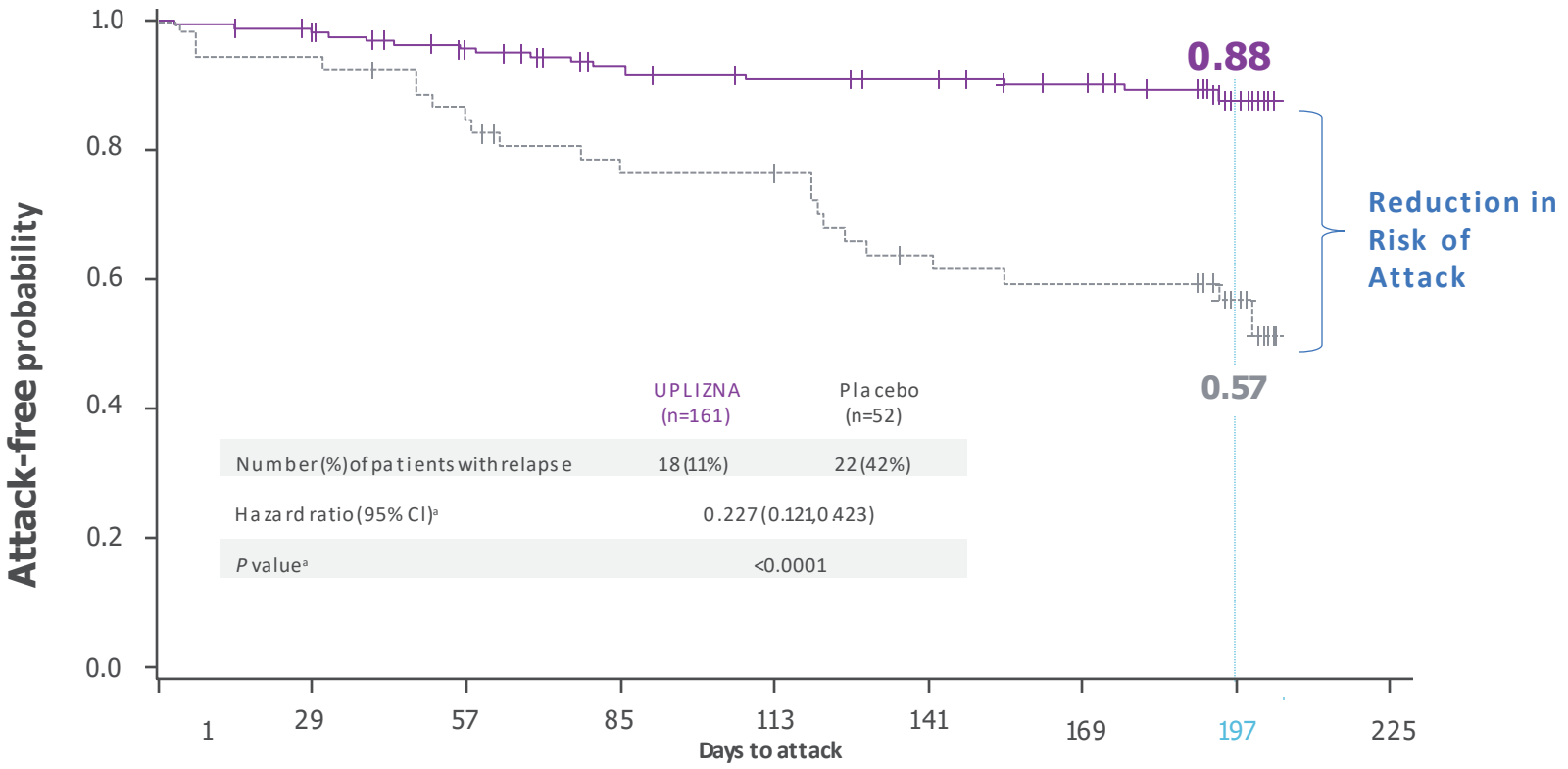
UPLIZNA Showed Significant Reduction In Healthcare Resource Utilization in the N-MOmentum Clinical Study

Reduced the annualized rate of hospitalization[1]	Shorter duration of hospitalizations vs. placebo[1]	Fewer emergency department visits vs. placebo[2]
78% relative reduction in the annualized rate of hospitalization for UPLIZNA vs. placebo (0.11 vs. 0.5)[3]	**6.6** days/event for UPLIZNA	**6.2%** for UPLIZNA
and	vs.	vs.
11% chance of hospitalization over one year with UPLIZNA vs. 50% with placebo	**8.9** days/event for placebo	**17.3%** for placebo

1. UPLIZNA® (inebilizumab-cdon) [prescribing information] Horizon.
2. Data on File. Horizon, June 2021.

UPLIZNA Monotherapy Significantly Reduced Risk of NMOSD Attacks In the Randomized Controlled Period[1]

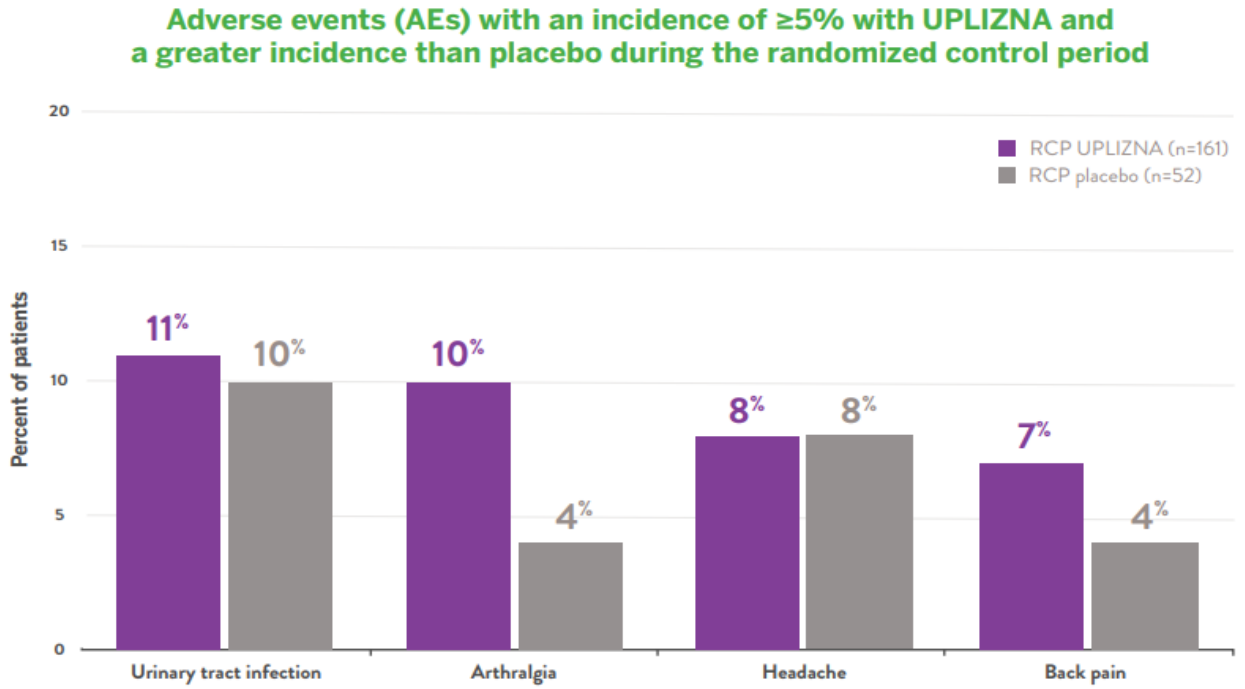
Time to onset of adjudicated attack in the AQP4-IgG+ population[2]



At risk								
UPLIZNA	161	157	146	135	129	127	122	88
Placebo	52	49	44	38	37	29	27	16

1. UPLIZNA (inebilizumab-cdon) [prescribing information] Horizon.

UPLIZNA Has a Favorable Safety Profile



- No new safety signals were identified after more than four years of treatment[2]
- UPLIZNA has not shown an increased risk of meningitis and may be used in patient populations who are unvaccinated and/or are not able to use prophylactic antibiotics[3]

1. UPLIZNA (inebilizumab-cdon) [prescribing information] Horizon.
2. Rensel M, Zabeti A, Mealy MA et al. Long-term efficacy and safety of inebilizumab in neuromyelitis optica spectrum disorder: Analysis of aquaporin-4-immunoglobulin G-seropositive participants taking inebilizumab for ≥4 years in the N-MOmentum trial. Multiple Sclerosis Journal. 2021 [Epub ahead of print]. Doi 10.1177/13524585211047223.
3. CDC. "Taking Complement Inhibitors Increases Your Risk for Meningococcal Disease". Link

Indication and Important Safety Information

INDICATION

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

IMPORTANT SAFETY INFORMATION

UPLIZNA is contraindicated in patients with:

- A history of life-threatening infusion reaction to UPLIZNA
- Active hepatitis B infection
- Active or untreated latent tuberculosis

WARNINGS AND PRECAUTIONS

Infusion Reactions: UPLIZNA can cause infusion reactions, which can include headache, nausea, somnolence, dyspnea, fever, myalgia, rash, or other symptoms. Infusion reactions were most common with the first infusion but were also observed during subsequent infusions. Administer pre-medication with a corticosteroid, an antihistamine, and an anti-pyretic.

Infections: The most common infections reported by UPLIZNA-treated patients in the randomized and open-label periods included urinary tract infection (20%), nasopharyngitis (13%), upper respiratory tract infection (8%), and influenza (7%). Delay UPLIZNA administration in patients with an active infection until the infection is resolved.

Increased immunosuppressive effects are possible if combining UPLIZNA with another immunosuppressive therapy.

The risk of Hepatitis B Virus (HBV) reactivation has been observed with other B-cell-depleting antibodies. Perform HBV screening in all patients before initiation of treatment with UPLIZNA. Do not administer to patients with active hepatitis.

Although no confirmed cases of Progressive Multifocal Leukoencephalopathy (PML) were identified in UPLIZNA clinical trials, JC virus infection resulting in PML has been observed in patients treated with other B-cell-depleting antibodies and other therapies that affect immune competence. At the first sign or symptom suggestive of PML, withhold UPLIZNA and perform an appropriate diagnostic evaluation.

Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating UPLIZNA.

Vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation, until B-cell repletion.

Reduction in Immunoglobulins: There may be a progressive and prolonged hypogammaglobulinemia or decline in the levels of total and individual immunoglobulins such as immunoglobulins G and M (IgG and IgM) with continued UPLIZNA treatment. Monitor the level of immunoglobulins at the beginning, during, and after discontinuation of treatment with UPLIZNA until B-cell repletion especially in patients with opportunistic or recurrent infections.

Fetal Risk: May cause fetal harm based on animal data. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment and for 6 months after stopping UPLIZNA.

Adverse Reactions: The most common adverse reactions (at least 10% of patients treated with UPLIZNA and greater than placebo) were urinary tract infection and arthralgia.

1. UPLIZNA (inebilizumab-cdon) [prescribing information] Horizon.

Preparation and Administration of UPLIZNA

Administer UPLIZNA under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage potential severe reactions such as serious infusion reactions. Monitor patients during and after the completion of infusion for at least one hour.

- Visually inspect UPLIZNA solution for particulate matter and discoloration. If the solution is cloudy, discolored or it contains discrete particulate matter, do not use and contact the manufacturer (1-866-479-6742). Do not shake the vial
- UPLIZNA must be diluted prior to administration. Obtain an intravenous bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. Do not use other diluents to dilute UPLIZNA
- Withdraw 10 mL of UPLIZNA from each of the three vials contained in the carton and transfer a total of 30 mL into the 250mL intravenous bag. Mix diluted solution by gentle inversion. Do not shake the solution. Discard the unused portion remaining in the vial
- Administer through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter

Recommended Infusion Rate for UPLIZNA Administration when Diluted in a 250 mL Intravenous Bag

Elapsed Time (Minutes)	Infusion Rate (mL/hr)
0-30	42
31-60	125
61 to completion	333

1. UPLIZNA (inebilizumab-cdon) [prescribing information] Horizon.

The First Dose of UPLIZNA May be Administered Inpatient for Patients hospitalized Due to an NMOSD Attack.

UPLIZNA is administered as an intravenous infusion via an infusion pump, titrated to completion, approximately 90 minutes[1]

- Subsequent doses are administered in the outpatient setting. Utilization of UPLIZNA is documented in the medication section of the patient's medical record
- Medicare Fee for Service beneficiaries accounted for 22.8% of UPLIZNA utilization in 2021[2]

Initial dose:

UPLIZNA is administered as a 300 mg intravenous infusion followed two weeks later by a second 300 mg intravenous infusion

Subsequent Doses:

Starting six months from the first infusion: UPLIZNA is administered as a single 300 mg intravenous infusion every six months

Timely administration of UPLIZNA upon receiving NMOSD diagnosis was associated with reduced disability progression over time.[3]

1. UPLIZNA (inebilizumab-cdon) [prescribing information] Horizon.
2. KFF. "Total Number of Medicare Beneficiaries." Link ; Horizon data on file.
3. Marignier R, Bennett JL, Kim HJ et al. Disability Outcomes in the N-MOmentum trial of inebilizumab in neuromyelitis optica spectrum disorder. Neurol Neuroimmunol Neuroinflamm. 2021;8:e978.

UPLIZNA is a Proven Therapy for NMOSD Patients that Reduces Risk of Relapse and Healthcare Resource Utilization

- **UPLIZNA is the only B-cell-depleting therapy FDA-approved to treat NMOSD**
- **UPLIZNA has a proven safety profile and did not show worsening disability over a 4-year study period[1,2,3]**
- **UPLIZNA demonstrated proven efficacy in clinical trials[1]**
  - 88% of AQP4-IgG+ patients were relapse-free at 28 weeks
  - 77% relative reduction in the risk of relapse for UPLIZNA vs. placebo in AQP4-IgG+ patients
  - 78% reduction in hospitalization rates when compared to placebo
- **UPLIZNA has the lowest dosing frequency of approved NMOSD treatments**
  - UPLIZNA requires only two yearly infusions after two initial doses[1]

1. UPLIZNA® (inebilizumab-cdon) [prescribing information] Horizon.
2. Marignier R, Bennett JL, Kim HJ et al. Disability Outcomes in the N-MOmentum trial of inebilizumab in neuromyelitis optica spectrum disorder. Neurol Neuroimmunol Neuroinflamm. 2021;8:e978.
3. Cree BAC, Bennett JL, Weinshenker BG et al. Safety and efficacy of inebilizumab in NMOSD over a mean treatment duration of 3.2 years: end of study data from the N-MOmentum trial. Poster presentation at the 37th Congress of ECTRIMS; October 13 – 15, 2021. Virtual Meeting.