PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**UPLIZNA®**

Inebilizumab for injection

100 mg / 10 mL (10 mg / mL) solution for intravenous infusion

Professed Standard

CD19-directed cytolytic antibody

Manufactured by:
Horizon Therapeutics Ireland DAC
70 St. Stephen's Green
Dublin 2
Ireland, DO2E2X4

Imported and Distributed by:
Horizon Therapeutics Canada
9131 Keele St., Unit 4A
Vaughan, Ontario L4K 0G7
Canada

Date of Initial Authorization:
DEC 15, 2023

Submission Control Number: 271065

RECENT MAJOR LABEL CHANGES

NOT APPLICABLE

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

UPLIZNA (inebilizumab for injection) is indicated as monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive.

Treatment should be administered under the supervision of a qualified healthcare professional.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): The safety and efficacy of Uplizna have been studied in a limited number of geriatric patients up to 74 years of age (n=6 aged 65-74). Clinical studies of Uplizna did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger patients. See 4.2 Recommended Dose and Dosage Adjustment and 7.1.4 Geriatrics.

2 CONTRAINDICATIONS

Uplizna is contraindicated in patients who:

- Are hypersensitive to this drug or to any ingredient in the formulation, including any nonmedicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Have a history of a life-threatening infusion reaction to Uplizna. See 7 WARNINGS AND PRECAUTIONS.
- Have severe active infection including active chronic infection such as hepatitis B infection. See 7 WARNINGS AND PRECAUTIONS.
- Have active or untreated latent tuberculosis. See 7 WARNINGS AND PRECAUTIONS.
- Have a history of progressive multifocal leukoencephalopathy (PML). See 7 WARNINGS AND PRECAUTIONS.
- Are in a severely immunocompromised state. See 7 WARNINGS AND PRECAUTIONS.
- Have active malignancy. See 7 WARNINGS AND PRECAUTIONS.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Treatment should be administered under the supervision of a qualified healthcare professional and with access to appropriate medical support to manage potential severe reactions such as serious infusion-related reactions. See 7 WARNINGS AND PRECAUTIONS.

Assessments Prior to First Dose of Uplizna

Prior to initiating Uplizna, perform testing for quantitative serum immunoglobulins, B-cell count, and complete blood count (CBC), including differentials. For patients with low serum immunoglobulins, consult immunology experts before initiating treatment with Uplizna. See 7 WARNINGS AND PRECAUTIONS.

Hepatitis B Virus Screening

Prior to initiating Uplizna, perform Hepatitis B virus (HBV) screening. Uplizna is contraindicated in patients with active HBV confirmed by positive results for surface antigen [HBsAg] and anti-HBV tests. For patients who are negative for HBsAg and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment with Uplizna. See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS.

Hepatitis C Virus Screening

Patients positive for Hepatitis C virus (HCV) were excluded from clinical trials with inebilizumab. Baseline screening for HCV is required to detect and start treatment prior to initiating inebilizumab treatment.

Tuberculosis Screening

Prior to initiating Uplizna, evaluate for active tuberculosis and test for latent infection. For patients with active tuberculosis or positive tuberculosis screening without a history of appropriate treatment, consult infectious disease experts before initiating treatment with Uplizna. See 2 CONTRAINDICATIONS and 7 WARNINGS and PRECAUTIONS.

Vaccinations

Because vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation until B-cell repletion, administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of Uplizna for live or live-attenuated vaccines. See 7 WARNINGS and PRECAUTIONS and 10 CLINICAL PHARMACOLOGY.

Oral Corticosteroids

A 2-week course of oral corticosteroids (plus a 1-week taper) was administered at the start of inebilizumab treatment (prior to the first infusion only) in the pivotal study.

Assessment and Premedication Before Every Infusion

Infection Assessment

Prior to every infusion of Uplizna, determine whether there is a clinically significant infection. In case of infection, delay infusion of Uplizna until the infection resolves. See 7 WARNINGS and PRECAUTIONS.

Premedication

Specific pre-medication should be administered prior to each infusion of UPLIZNA.

Table 1 shows premedication to administer prior to each infusion of Uplizna to reduce the frequency and severity of infusion reactions.

Table 1 - Premedication Prior to Each UPLIZNA Infusion

Type of Premedication	Route of Administration	Examples (or Equivalent)	Administration Time Prior to UPLIZNA Infusion
corticosteroid	intravenous	methylprednisolone 80 mg to 125 mg	30 minutes
antihistamine	Oral	diphenhydramine 25 mg to 50 mg	30 to 60 minutes
antipyretic	Oral	acetaminophen 500 mg to 650 mg	30 to 60 minutes

4.2 Recommended Dose and Dosage Adjustment

Uplizna is administered as an intravenous infusion (see Table 3) to adults. Health Canada has not authorized an indication for pediatric use.

The recommended dosage is:

- Initial dose: 300 mg intravenous infusion followed 2 weeks later by a second 300 mg intravenous infusion.
- Subsequent doses (starting 6 months from the first infusion): single 300 mg intravenous infusion every 6 months.

4.3 Reconstitution

Visually inspect Uplizna solution for particulate matter and discoloration. See 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

If the solution is cloudy, discolored, or it contains discrete particulate matter, do not use and contact the manufacturer. Do not shake the vial.

- 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 3 vials contained in the carton and transfer a total of 30 mL into the 250 mL intravenous bag. Mix diluted solution by gentle inversion. Do not shake the solution.
- Discard the unused portion remaining in the vials. See 12 SPECIAL HANDLING INSTRUCTIONS.

Uplizna does not contain a preservative. Administer the prepared infusion solution immediately. If not administered immediately, store the infusion solution for a maximum of 24 hours in the refrigerator between 2°C to 8°C or 4 hours at room temperature between 20°C to 25°C prior to the start of the infusion. See 11 STORAGE, STABILITY AND DISPOSAL.

Table 2 - Reconstitution

Approximate Volume of Intravenous Bag	Volume of UPLIZNA to be Added to Intravenous Bag	Approximate Available Volume	Approximate Concentration per mL
250 mL of 0.9% Sodium Chloride Injection USP	30 mL (10 mL from each of the 3 10 mg/mL vials contained in the carton)	280 mL	1.07 mg/mL

4.4 Administration

Uplizna must be diluted prior to administration. See 4.3 Reconstitution.

Prior to the start of the intravenous infusion, the prepared infusion solution should be at room temperature. 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. See 7 WARNINGS AND PRECAUTIONS.

Administer the prepared solution intravenously via an infusion pump at an increasing rate to completion, approximately 90 minutes, according to the schedule in Table 3. Administer through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.

Table 3 - Recommended Infusion Rate for UPLIZNA Administration When Diluted in a 250 mL Intravenous Bag

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

Monitor the patient closely for infusion reactions during and for at least one hour after the completion of the infusion.

4.5 Missed Dose

If a dose of Uplizna is missed, it should be administered as soon as possible and not delayed until the next planned dose.

5 OVERDOSAGE

There is no specific antidote in the event of an overdose; the infusion should be interrupted immediately and the patient should be observed for infusion-related reactions. See 7 WARNINGS AND PRECAUTIONS.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	10 mg/mL inebilizumab solution	L-Histidine, L-Histidine hydrochloride monohydrate, Polysorbate 80, Sodium chloride, Trehalose dihydrate, Water for Injection

Uplizna is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous infusion supplied in single-dose vials containing 100 mg inebilizumab in 10 mL solution.

Each carton contains three single-use vials.

7 WARNINGS AND PRECAUTIONS

General

Infusion Reactions

Uplizna can cause infusion reactions, which can include headache, nausea, somnolence, dyspnea, fever, myalgia, rash, or other signs or symptoms. Infusion reactions were most common with the first infusion but were also observed during subsequent infusions. Although rare, serious infusion reactions can occur. (see 8 ADVERSE REACTIONS).

To reduce the risk of infusion reactions, administer pre-medication with a corticosteroid, an antihistamine, and an anti-pyretic (see 4.1 Dosing Considerations) . Patients should be monitored for infusion reactions for at least one hour after the completion of infusion. Management recommendations for infusion reactions depend on the type and severity of the reaction.

For life-threatening infusion reactions, immediately and permanently stop Uplizna and administer appropriate supportive treatment.

For less severe infusion reactions, management may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.

Immune

Infections

Inebilizumab causes reduction in peripheral blood lymphocyte count and Ig levels consistent with the mechanism of action of B-cell depletion. Reduction of neutrophil counts were also reported. Therefore, inebilizumab may increase the susceptibility to infections. A recent (i.e. within 6 months) complete blood cell count including differentials and immunoglobulins should be obtained before initiation of inebilizumab. Assessments of CBC including differentials and immunoglobulins are also recommended periodically during treatment and after discontinuation of treatment until B-cell repletion. Prior to every infusion of inebilizumab, it should be determined whether there is a clinically significant infection. Delay Uplizna administration in patients with clinically significant infection until the infection is resolved. Patients should be instructed to promptly report symptoms of infection to their physician. Treatment discontinuation should be considered if a patient develops a serious opportunistic infection or recurrent infections if Ig levels indicate immune compromise. (see 4.1 Dosing Considerations and 8 ADVERSE REACTIONS)

Treatment of severely immunocompromised patients

Patients in severely immunocompromised state must not be treated until the condition resolves. Patients with a known congenital or acquired immunodeficiency, including HIV infection or splenectomy, have not been studied (See 2 CONTRAINDICATIONS).

Uplizna has not been studied in combination with other immunosuppressants. If combining Uplizna with another immunosuppressive therapy, consider the potential for increased immunosuppressive effects.

Hepatitis B Virus (HBV) Reactivation

Risk of HBV reactivation has been observed with other B-cell-depleting antibodies. There have been no cases of HBV reactivation in patients treated with Uplizna, but patients with chronic HBV infection were

excluded from clinical trials. Perform HBV screening in all patients before initiation of treatment with Uplizna. Do not administer Uplizna to patients with active hepatitis. For patients who are chronic carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment. See 2 CONTRAINDICATIONS.

Progressive Multifocal Leukoencephalopathy (PML)

PML is an opportunistic viral infection of the brain caused by the John Cunningham (JC) virus that typically occurs in patients who are immunocompromised, and that may lead to death or severe disability. Although no confirmed cases of 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.

In Uplizna clinical trials one subject died following the development of new brain lesions for which a definitive diagnosis could not be established. However, the differential diagnosis included an atypical NMOSD relapse, PML, or acute disseminated encephalomyelitis. At the first sign or symptom suggestive of PML, withhold Uplizna and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. See 2 CONTRAINDICATIONS.

Late neutropenia

Cases of late onset of neutropenia have been reported. Although some cases were Grade 3, the majority of cases were Grade 1 or 2. Cases of late onset of neutropenia have been reported at least 4 weeks after the latest infusion of inebilizumab. In patients with signs and symptoms of infection, measurement of blood neutrophils is recommended. See 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data.

Tuberculosis

Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating Uplizna. Consider anti-tuberculosis therapy prior to initiation of Uplizna in patients with a history of latent tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consult infectious disease experts regarding whether initiating anti-tuberculosis therapy is appropriate before starting treatment. See 2 CONTRAINDICATIONS.

Vaccinations

Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of Uplizna. The safety of immunization with live or live-attenuated vaccines following Uplizna therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion.

In infants of mothers exposed to Uplizna during pregnancy, do not administer live or live-attenuated vaccines before confirming recovery of B-cell counts in the infant. Depletion of B-cells in these exposed infants may increase the risks from live or live-attenuated vaccines. Non-live vaccines, as indicated, may be administered prior to recovery from B-cell and immunoglobulin level depletion, but consultation with a qualified specialist should be considered to assess whether a protective immune response was mounted.

B-cell repletion time

The time to B-cell repletion following administration of inebilizumab is not known. B-cell depletion below the lower limit of normal was maintained in 94% of patients for at least 6 months following treatment.

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. See 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data.

Monitor the levels of quantitative serum immunoglobulins during treatment with Uplizna, especially in patients with opportunistic or recurrent infections, and until B-cell repletion after discontinuation of therapy. Consider discontinuing Uplizna therapy if a patient with low immunoglobulin G or M develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

Malignancy

Immunomodulatory medicinal products may increase the risk of malignancy. On the basis of limited experience with inebilizumab in NMOSD, the current data do not suggest any increased risk of malignancy. However, the possible risk for the development of solid tumours cannot be excluded at this time. See 2 CONTRAINDICATIONS.

Reproductive Health: Female and Male Potential

Women of childbearing potential should use effective contraception while receiving Uplizna and for 6 months after the last infusion of Uplizna. See 7.1.1 Pregnant Women.

- **Fertility**

  There are limited data on the effect of inebilizumab on human fertility; however, a study in animals has shown reduced fertility. The clinical significance of these nonclinical findings is not known. See 16 NON-CLINICAL TOXICOLOGY.

7.1 Special Populations

7.1.1 Pregnant Women

Uplizna is a humanized IgG1 monoclonal antibody and immunoglobulins are known to cross the placental barrier. Animal data has shown the presence of inebilizumab in fetal and offspring serum following maternal exposure, indicating that inebilizumab crosses the placental barrier and/or is excreted in milk (see 16 NON-CLINICAL TOXICOLOGY).

There are no adequate data on the developmental risk associated with the use of Uplizna in pregnant women. However, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other B-cell depleting antibodies during pregnancy. B-cell levels in infants following maternal exposure to Uplizna have not been studied in clinical trials. The potential duration of B-cell depletion in such infants, and the impact of B-cell depletion on vaccine safety and effectiveness, is unknown (see 7 WARNINGS AND PRECAUTIONS, Immune, Vaccination).

Based on animal data, Uplizna may cause fetal harm due to B-cell lymphocytopenia and reduce antibody response in offspring exposed to Uplizna even after B-cell depletion (see 16 NON-CLINICAL

TOXICOLOGY).

Advise women of reproductive potential to use effective contraception while receiving Uplizna and for at least 6 months after the last dose.

7.1.2 Breast-feeding

The use of inebilizumab in women during lactation has not been studied. It is unknown if Uplizna is excreted in human milk. Human IgG is excreted in human milk, and the potential for absorption of Uplizna leading to B-cell depletion in the breastfed infant cannot be excluded. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Uplizna and the potential adverse effects on the breastfed infant from Uplizna.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

- **Geriatrics (≥ 65 years of age)**: The safety and efficacy of Uplizna have been studied in a limited number of geriatric patients up to 74 years of age (n=6 aged 65-74). Clinical studies of Uplizna did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Across both the randomized and open-label treatment in Study 1155, the most common adverse reactions (≥ 10 %) seen in patients with NMOSD anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive were urinary tract infection (27%), nasopharyngitis (21%), arthralgia (17%), upper respiratory tract infection (17%), headache (16%), back pain (13%), and infusion related reaction (13%).

Across both the randomized and open-label treatment in Study 1155, the most common serious adverse reactions (≥ 2 %) seen in patients with NMOSD anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive were infections (11%) (including urinary tract infections (4%), pneumonia (2%)).

Across both the randomized and open-label treatment in Study 1155, 6 patients with NMOSD anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive had adverse events leading to permanent discontinuation. The adverse events leading to permanent discontinuation were neutropenia, steroid withdrawal syndrome, hepatic steatosis, atypical pneumonia, pneumonia, liver function test increased, and myasthenia gravis.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of Uplizna was evaluated in Study 1155, a randomized, double-blind, placebo-controlled

study with an open-label treatment period.

In Study 1155, 161 patients with anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive NMOSD were exposed to Uplizna at the recommended dosage regimen during the randomized, controlled treatment period; during which 52 patients received placebo. Overall, across both the randomized and open-label treatment in Study 1155, 208 anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive NMOSD patients received one or more doses of Uplizna. Among these, 197 patients were exposed to Uplizna for at least 6 months and 189 patients were exposed to Uplizna for at least 1 year. See 4 DOSAGE AND ADMINISTRATION and 14 CLINICAL TRIALS.

The treatment-emergent adverse events reported in ≥5% Uplizna-treated patients and at a higher frequency than in placebo-treated patients with NMOSD AQP4-IgG seropositive in the randomized, controlled treatment period of Study 1155 are presented in Table 5.

Table 5 - Treatment-emergent adverse events reported in ≥5% of Uplizna-treated patients and at a higher frequency than placebo of patients with anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive NMOSD in the Randomized, Controlled Treatment Period of Study 1155

	UPLIZNA N = 161 (%)	**Placebo N = 52 (%)**
Infections and Infestations		
Urinary Tract Infection	11%	10%
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	11%	6%
Back Pain	7%	4%
Nervous System Disorders		
Headache	9%	8%

Description of Selected Adverse Reactions

Infusion-related reactions

Uplizna can cause infusion-related reactions, which can include headache, nausea, somnolence, dyspnea, fever, myalgia, rash, or other symptoms. All patients were given premedication. Infusion reactions were observed in 9.3% of NMOSD anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive patients during the first course of Uplizna compared to 9.6% of placebo-treated patients. Infusion-related reactions were most common with the first infusion but were observed during subsequent infusions. The majority of infusion-related reactions reported in Uplizna-treated patients were either mild or moderate in severity. See 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS.

Infections

Across both the randomized and open-label treatment in Study 1155, an infection was reported in 158/208 (76%) of NMOSD anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive patients treated with Uplizna. The most common infections included urinary tract infection (27%), nasopharyngitis

(21%), and upper respiratory tract infection (17%), and influenza (10%). See 7 WARNINGS AND PRECAUTIONS.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Not applicable

8.3 Less Common Clinical Trial Adverse Reactions

Treatment-Emergent Adverse Events Reported with a frequency of ≥1% and <5% of NMOSD anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive patients within the randomized, controlled treatment period of Study 1155 were:

Blood and Lymphatic System Disorders: neutropenia
Infections and Infestations: cystitis
Injury, poisoning and procedural complications: fall
Nervous System Disorders: paraesthesia
Skin and Subcutaneous Tissue Disorders: rash

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Not applicable

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

Decreased immunoglobulins

At the end of the 6.5-month RCP, the proportion of patients with levels below the lower limit of normal was as follows: IgA 8.1% inebilizumab and 0% placebo, IgG 2.5% inebilizumab and 3.8% placebo, and IgM 24.8% inebilizumab and 9.6% placebo. The proportion of inebilizumab-treated patients with IgG levels below the lower limit of normal at year 1 was 6.3% and at year 2 was 9.6%. The proportion of patients treated with UPLIZNA who had IgM levels below the lower limit of normal at year 1 was 30.5% and at year 2 was 40.1%. With a median exposure of 3.2 years, the frequency of moderate IgG reduction (300 to <500 mg/dL) was 13.0% and the frequency of severe IgG reduction (<300 mg/dL) was 3.4%. See 7 WARNINGS AND PRECAUTIONS.

Decreased neutrophil counts

After 6.5 months of treatment, neutrophil counts between 1.0-1.5 $x10^9$/L (Grade 2) were observed in 7.5% of inebilizumab-treated patients versus 1.9% of placebo-treated patients. Neutrophil counts between 0.5-1.0 $x10^9$/L (Grade 3) were observed in 1.9% of inebilizumab-treated patients versus 0% of placebo-treated patients.

Decreased lymphocyte counts

After 6.5 months of treatment, a reduction in lymphocyte counts was observed more commonly in patients treated with inebilizumab than placebo: lymphocyte counts between 500-< 800/mm3 (Grade 2) were observed in 22.5% of inebilizumab-treated patients versus 13.5% of placebo-treated patients. Lymphocyte counts between 200-< 500/mm3 (Grade 3) were observed in 3.1% of inebilizumab-treated patients versus 1.9% of placebo-treated patients.

8.5 Post-Market Adverse Reactions

Not applicable.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Formal drug interaction studies have not been conducted with Uplizna. Concomitant usage of Uplizna with immunosuppressant drugs, including systemic corticosteroids, may increase the risk of infection. Consider the risk of additive immune system effects when co-administering immunosuppressive therapies with Uplizna.

9.4 Drug-Drug Interactions

The primary elimination pathway for therapeutic antibodies is clearance by the reticuloendothelial system. Cytochrome P450 enzymes and transporters are not involved in the clearance of inebilizumab; therefore, the potential risk of interactions between Uplizna and concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes and transporters is low.

Inebilizumab has been tested, and is intended to be used, as monotherapy for this indication. No data are available on the safety or efficacy of combining inebilizumab with other immunosuppressants.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The precise mechanism by which Uplizna 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 cytotoxicity.

10.2 Pharmacodynamics

Pharmacodynamics of Uplizna were assessed with an assay for CD20+ B cells, since Uplizna can interfere with the CD19+ B cell assay. Treatment with Uplizna reduces CD20+ B cell counts in blood by 8 days after infusion. In Study 1155, CD20+ B-cell counts were reduced below the lower limit of normal by 4 weeks in 100% of patients treated with Uplizna and remained below the lower limit of normal in 94% of patients for 28 weeks after initiation of treatment. See 14 CLINICAL TRIALS.

10.3 Pharmacokinetics

Following intravenous administration of 300 mg inebilizumab in NMOSD patients on Day 1 and Day 15, the mean maximum concentration was 104 µg/mL and 116 µg/mL, respectively, and the cumulative AUC by week 26 was 3130 µg·d/mL.

Distribution

Based on population pharmacokinetic analysis, the estimated typical central and peripheral volume of distribution of inebilizumab was 2.95L and 2.57L, respectively.

Metabolism

Inebilizumab is a humanized IgG1 monoclonal antibody that is degraded by proteolytic enzymes widely distributed in the body.

Elimination

In adult patients with NMOSD, the terminal elimination half-life was approximately 18 days. From population pharmacokinetic analysis, the estimated inebilizumab systemic clearance of the first-order elimination pathway was 0.19 L/day. At low pharmacokinetic exposure levels, inebilizumab was likely subject to the receptor (CD19)-mediated clearance, which decreased with time presumably due to the depletion of B cells by inebilizumab treatment.

Special Populations and Conditions

- **Geriatrics, Gender, Race:** A population pharmacokinetic analysis indicated that there was no significant effect of age, gender, and race on inebilizumab clearance**.**
- **Hepatic/Renal Impairment:** No formal clinical studies have been conducted to investigate the effect of hepatic or renal impairment on inebilizumab pharmacokinetic parameters.

11 STORAGE, STABILITY AND DISPOSAL

Store Uplizna vials in a refrigerator at 2°C to 8°C in original carton. Protect from light. Do not freeze. Do not shake. Store vials upright.

12 SPECIAL HANDLING INSTRUCTIONS

Discard the vial containing unused portion of Uplizna in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Inebilizumab

Molecular formula and molecular mass: The average size of the oligosaccharide moiety is approximately 1,300 Da per heavy chain, with overall mass of approximmately149 kDa. The oligosaccharides are predominantly neutral complex type N glycans.

Structural formula: Inebilizumab is a humanized IgG1κ monoclonal antibody of approximately 149 kDa that is composed of two identical heavy chains of 49,362 Da each, and two identical light chains of

23,836 Da each. It is engineered to be an afucosylated monoclonal antibody and is expected to have increased antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) activities. Inebilizumab has an N-linked oligosaccharide attachment site in the Fc region at residue Asn-301.

Physicochemical properties: Inebilizumab has an experimentally-determined Extinction Coefficient of 1.35 $(mg/mL)^{-1}cm^{-1}$, a pI between 7.9 – 8.5 and density of 1.022 g/mL.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 6 - Summary of patient demographics for clinical trials in anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive patients in Study 1155

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
CD-IA-MEDI-551-1155 (Study 1155)	A multicenter, multinational, randomized, double-blind, placebo-controlled-study with an open label extension	RCP: 300 mg IV inebilizumab or placebo on Day 1 and Day 15 (3:1 ratio) OLP: 300 mg IV inebilizumab on OLP Day 1, blinded 300 mg IV inebilizumab (or placebo) on OLP Day 15, then 300 mg IV inebilizumab Q26W thereafter	Total 213 Inebilizumab: n = 161 Placebo: n = 52	43 years (18, 74)	200 females / 13 males

RCP = randomized-controlled period; IV = intravenous; OLP = open-label period; Q26W = once every 26 weeks; AQP4-IgG+ = anti-aquaporin-4 immunoglobulin G seropositive (AQP4-IgG seropositive)

The efficacy of Uplizna for the treatment of NMOSD was established in Study 1155, a randomized (3:1), double-blind, placebo-controlled trial that enrolled 213 anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive patients with NMOSD.

Patients met the following eligibility criteria:

1. A history of one or more relapses that required rescue therapy within the year prior to screening, or 2 or more relapses that required rescue therapy in 2 years prior to screening.
2. Expanded Disability Status Scale (EDSS) score of 7.5 or less. Patients with an EDSS score of 8.0 were eligible if they were deemed capable of participating.
3. Patients were excluded if previously treated with immunosuppressant therapies within an interval specified for each such therapy.

The use of immunosuppressants during the blinded phase of the trial was prohibited. The use of oral or intravenous corticosteroids during the blinded phase of the trial was prohibited, with the exception of premedication for investigational treatment and treatment for a relapse.

Of the 213 enrolled patients, a total of 161 were randomized to receive treatment with Uplizna, and 52 were randomized to receive placebo.

The baseline demographic and disease characteristics were balanced between the treatment groups. Females accounted for 94% of the study population. 52% of patients were White, 21% Asian, and 9% Black or African American. The mean age was 43 years (range 18 to 74 years). The overall mean EDSS score was 3.94. The overall number of relapses in the two years prior to randomization was 2 or more in 83% of the patients.

Uplizna was administered according to the recommended dosage regimen. See 4.2 Recommended Dose and Dosage Adjustment.

All potential relapses were evaluated by a blinded, independent, adjudication committee, who determined whether the relapse met protocol-defined criteria. Patients who experienced an adjudicated relapse in the randomized-controlled period (RCP), or who completed the Day 197 visit without a relapse, exited the RCP.

14.2 Study Results

The primary efficacy endpoint was the time to the onset of the first adjudicated relapse on or before Day 197.

The time to the first adjudicated relapse was significantly longer in patients treated with Uplizna compared to patients who received placebo with a relative risk reduction of 77% ($p < 0.0001$) in the anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive population. Results are shown in Table 7 and Figure 1.

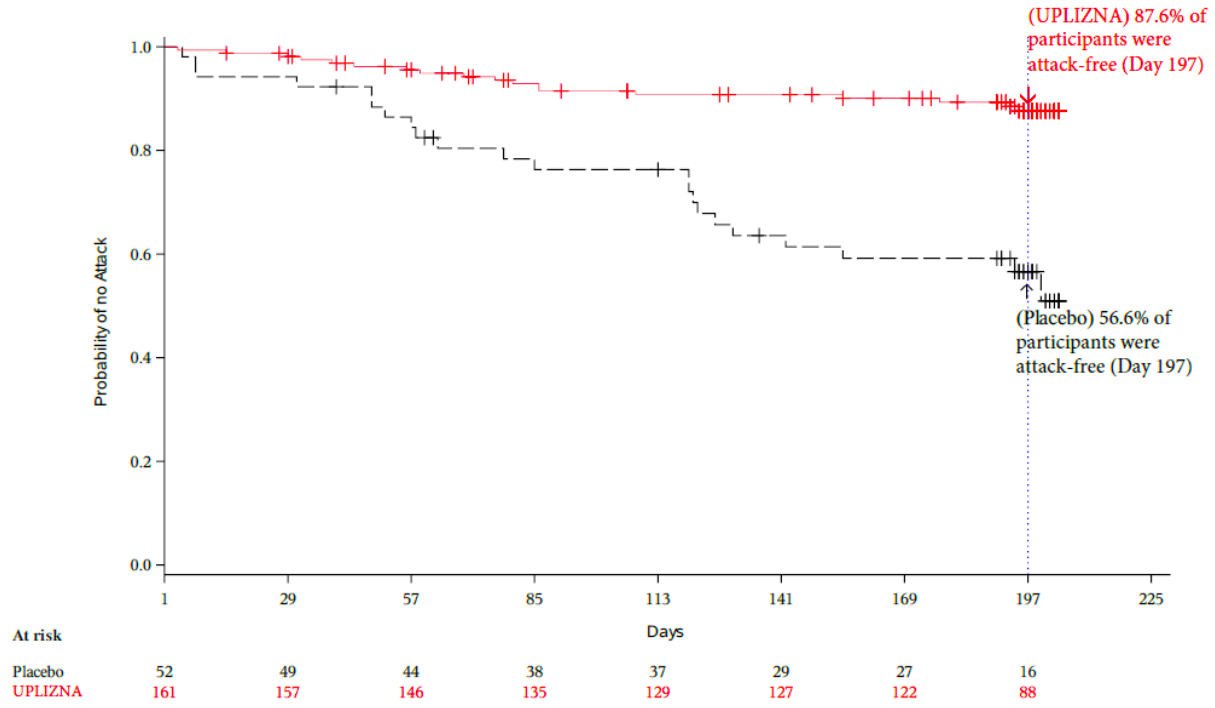
Table 7 – Efficacy results in Study 1155 in patients with NMOSD who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive

Primary Endpoint	UPLIZNA (N = 161)	Placebo (N = 52)
Time to Adjudication Committee-Determined Relapse		
Number (%) of patients with relapse	18 (11.2%)	22 (42.3%)
Hazard ratio [a] (95% CI)	0.227 (0.121, 0.423)	
p-value[a]	<0.0001	

CI = Confidence Interval

[a] Cox regression method, with placebo as the reference group

Figure 1- Kaplan-Meier Plot for Time to First Adjudication Committee-Determined NMOSD Relapse in the Randomized-Controlled Period of Study 1155 in anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive Patients



Note: Numbers of patients at risk are shown at each time point. AQP4 = aquaporin-4; CI = confidence interval; N = number of subjects; NA = not applicable.

Compared to placebo-treated patients, patients treated with Uplizna who were anti-AQP4 antibody positive had reduced incidence of EDSS worsening (15% for Uplizna vs. 35% for placebo), and annualized NMOSD-related hospitalization rates (0.12 for Uplizna vs. 0.50 for placebo).

14.4 Immunogenicity

As with all therapeutic proteins there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other inebilizumab products may be misleading.

In Study 1155, treatment-emergent antibodies (those that appeared or significantly increased from baseline after administration of Uplizna), were detected in 7.1% patients receiving Uplizna. Although these data do not demonstrate an impact of anti-inebilizumab antibody development on the efficacy or safety of Uplizna in these patients, the available data are too limited to make definitive conclusions.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Intravenous administration of inebilizumab to human CD19 transgenic (huCD19 Tg) mice for 13 weeks (0, 0.5, 3, or 30 mg/kg/week) or 6 months (0, 3, or 30 mg/kg/week) resulted in findings consistent with the pharmacological action of the drug. In the peripheral blood, spleen, lymph nodes, and bone marrow, B cell depletion was observed at all dose levels tested. These effects fully reversed during the 9-month treatment-free period. The NOAELs for both the 13-week and 6-month studies were 30.0 mg/kg/week, the highest dose tested. On an AUC basis, exposure at the NOAEL in the 6-month study was 13-fold the exposure in NMOSD patients following the recommended initial doses (300 mg on Days 1 and 15).

A subcutaneous, 13-week repeat dose study of inebilizumab in huCD19 Tg mice was conducted to compare findings observed after subcutaneous administration to those observed after intravenous administration. Subcutaneous administration of 0, 3, or 30 mg/kg/week inebilizumab also resulted in B cell depletion in the peripheral blood, spleen, lymph nodes, and bone marrow at both dose levels tested. Additional findings observed in both the subcutaneous and intravenous dose groups included alopecia (females only), as well as ulceration and bacterial infection of the skin, which were likely the result of immunosuppression. Increased red cell mass and other hematological changes in both the subcutaneous and intravenous dose groups were also observed. Due to the skin ulceration and infection, a NOAEL was not determined for the subcutaneous route of administration. On an AUC basis, exposure at the lowest dose tested (3 mg/kg/week) after subcutaneous administration was 6-fold the exposure in NMOSD patients following the recommended initial doses (300 mg on Days 1 and 15).

Carcinogenicity: No studies have been conducted to assess the carcinogenic potential of inebilizumab. During the 13-week subcutaneous repeat dose study of inebilizumab, an increase in bronchio-alveolar adenomas at 30 mg/kg/week was observed in males only at the end of the 6-month treatment-free period. However, similar increases were not observed in the 13-week or 6-month intravenous repeat-dose studies; therefore, the overall relationship of this finding to inebilizumab is uncertain.

Genotoxicity: No studies have been conducted to assess the genotoxic potential of inebilizumab.
Reproductive and Developmental Toxicology:

Intravenous administration of inebilizumab (0, 3, or 30 mg/kg/week) to huCD19 Tg male and female mice prior to and during mating and continuing in females through gestation day 15 resulted in no adverse effects on embryofetal development; however, there was a marked reduction in B cells in fetal blood and liver at both doses tested. Inebilizumab was also detected in fetal serum at both maternal doses. These results demonstrate that inebilizumab crosses the placenta and depletes B cells in the fetus. Reduced fertility was also seen at both doses tested. A NOAEL for adverse effects on fertility was not identified. At the lowest dose of 3 mg/kg/week, exposure after the last dose (averaged for males and females) was lower than the exposure in NMOSD patients following the recommended initial doses (0.67-fold), based on mean maximum serum concentration.

Intravenous administration of inebilizumab in a pre and postnatal development study (0, 3, or 30 mg/kg) to pregnant huCD19 Tg mice every three days throughout organogenesis and lactation resulted in depletion of B cells in peripheral blood, spleen, and bone marrow and persistent reductions in immune function (even following repletion of B cells and lasting into adulthood) in offspring at both doses tested. At the end of the lactation period, serum inebilizumab levels in offspring were only slightly lower than those in maternal serum. A NOAEL for immunotoxicity in the offspring was not

identified. At the lowest dose of 3 mg/kg, exposure in dams at the end of the lactation period was lower than the exposure in NMOSD patients following the recommended initial doses (0.40-fold), based on mean serum concentration.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]UPLIZNA®

Inebilizumab for injection

Read this carefully before you start taking **UPLIZNA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Uplizna.**

What is Uplizna used for?

- Uplizna is used to treat adults with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive.
- It is not known if Uplizna is safe or effective in children.

How does Uplizna work?

Inebilizumab is a monoclonal antibody (a type of protein) that attaches to immune cells called B cells and destroys them. In most people with NMOSD, B cells produce antibodies that attack AQP4, a protein involved in nerve cell function. By reducing the numbers of B cells, the medicine is expected to prevent damage to nerve cells and reduce the symptoms of the condition.

What are the ingredients in Uplizna?

Medicinal ingredients: inebilizumab

Non-medicinal ingredients: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sodium chloride, trehalose dihydrate, and water for injection

Uplizna comes in the following dosage forms:

Injection: 3 vials of 100 mg/10 mL (10 mg/mL)

Do not use Uplizna if:

- you are hypersensitive to the drug or to any of the ingredients within the drug
- you have had a life-threatening infusion reaction to Uplizna
- you have a severe active infection or a chronic active infection such as hepatitis B virus infection
- you have active or untreated inactive (latent) tuberculosis
- you have a history of progressive multifocal leukoencephalopathy (PML)
- You are in a severely immunocompromised state
- You have active malignancy

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Uplizna. Talk about any health conditions or problems you may have, including if you:

- have or think you have an infection.
- Are severely immunocompromised, including HIV infection
- have ever taken, currently take, or plan to take medicines that affect your immune system, or other treatments for NMOSD. These medicines may increase your risk of getting an infection.
- have or have ever had hepatitis B or are a carrier of the hepatitis B virus.
- have or have ever had hepatitis C.

- have or have ever had tuberculosis.
- have had progressing multifocal leukoencephalopathy (PML)
- have active malignancy.
- have had a recent vaccination or are scheduled to receive any vaccinations. You should receive any required vaccines at least 4 weeks before you start treatment with Uplizna.
- have a baby and you were exposed to Uplizna during pregnancy. It is important to tell your baby's healthcare provider, so they can decide when your baby should receive any vaccinations.
- are pregnant or plan to become pregnant. It is not known if Uplizna will harm your unborn baby. Females should use effective birth control (contraception) during treatment with Uplizna and for 6 months after your last infusion of Uplizna.
- are breastfeeding or plan to breastfeed. It is not known if Uplizna passes into your breast milk. Talk to your healthcare professional about the best way to feed your baby if you receive Uplizna.

Other warnings you should know about:

Allergic Reactions:

Uplizna can cause infusion reactions. Tell your doctor or nurse immediately if you get any of these symptoms during your Uplizna infusion:

Headache, nausea, drowsiness, shortness of breath, fever, aches, or other signs or symptoms.

Decreased Immunoglobulins

Uplizna may cause a decrease in immunoglobulins (proteins in your blood that help your immune system fight infection). Your healthcare provider will do blood tests to check your blood immunoglobulin levels.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Uplizna:

No relevant drug-drug interactions are known however, use of Uplizna with drugs that suppress your immune system may increase the risk of infection. Inform healthcare professional of any other medications you are taking.

How to take Uplizna:

- Uplizna will be given to you by a qualified healthcare professional or in a healthcare setting.
- Uplizna is given through a needle placed in a vein (IV or intravenous infusion) in your arm.
- Before treatment with Uplizna, your healthcare professional will complete specific screening tests and will give you a corticosteroid medicine, an antihistamine, and a fever prevention medicine to help infusion reactions become less frequent or less severe.

Usual dose:

- Your first dose of Uplizna will be given as 2 separate infusions, 2 weeks apart.
- Your next doses of Uplizna will be given as one infusion every 6 months.
- Each infusion will last about 1 hour and 30 minutes. After each infusion, you will be monitored by a healthcare professional for at least 1 hour.

Overdose:

Uplizna is given by a healthcare professional only. This minimizes the chance of an overdose.

If you think you, or a person you are caring for, have taken too much Uplizna contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss an appointment for an infusion, contact your healthcare professional to make another one right away.

What are possible side effects from using Uplizna?

These are not all the possible side effects you may have when taking Uplizna. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Urinary tract infection
- Common cold
- Joint pain
- Upper respiratory tract infection
- Headache
- Back pain
- Infusion related reaction

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Infections: painful and frequent urination, nasal congestion, runny nose, sore throat, fever, chills, cough, body aches.		✓	
UNCOMMON			
Infusion reactions: headache, sleepiness, fever, rash, nausea, shortness of breath, muscle aches.		✓	
RARE			
Hepatitis B virus (HBV) reactivation: fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, clay-colored stool, joint pain, jaundice		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Progressive Multifocal Leukoencephalopathy (PML): weakness on one side of the body, changes in vision, confusion, loss of coordination arms and legs, changes in thinking or memory, changes in personality.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store Uplizna in a refrigerator at 2°C to 8°C in original carton.

Protect from light. Do not freeze. Do not shake.

Store vials upright.

Keep out of reach and sight of children.

If you want more information about Uplizna:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.horizontherapeutics.ca, or by calling 1-844-380-7850.

This leaflet was prepared by Horizon Therapeutics Ireland DAC.

Last Revised: