▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at ____.

AUSTRALIAN PRODUCT INFORMATION – UPLIZNA® (INEBILIZUMAB)

1. NAME OF THE MEDICINE

Inebilizumab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Uplizna is supplied in three (3) single-dose vials per dose. Each vial contains 100 mg of inebilizumab in 10 mL at a concentration of 10 mg/mL. The final concentration after dilution is 1.07 mg/mL.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Concentrated injection for infusion.

Uplizna is a sterile, clear to slightly opalescent, colourless to slightly yellow, preservative-free solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Uplizna 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.

4.2 Dose and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of NMOSD, and administered under the supervision of a healthcare professional and with access to appropriate medical support to manage potential severe reactions such as serious infusion-related reactions.

The patient should be monitored for infusion reactions during and for at least one hour after the completion of the infusion (see Section 4.4 Special warnings and precautions for use).

Assessments prior to first dose of Uplizna

Prior to initiating treatment, testing should be performed for:

- Quantitative serum immunoglobulins, B-cell count, and complete blood count (CBC), including differentials (see Sections 4.3 Contraindications and 4.4 Special warnings and precautions for use)
- Hepatitis B virus (HBV) screening (see Sections 4.3 Contraindications and 4.4 Special warnings and precautions for use)
- Hepatitis C virus (HCV) screening and treatment started prior to initiating Uplizna treatment (see Sections 4.3 Contraindications and 4.4 Special warnings and precautions for use)
- Evaluate for active tuberculosis and test for latent infection (see Sections 4.3 Contraindications and 4.4 Special warnings and precautions for use)

All immunisations should be administered according to immunisation guidelines at least 4 weeks prior to initiation of Uplizna for live or live attenuated vaccines (see Section 4.4 Special warnings and precautions for use).

If loss of efficacy is thought to be caused by immunogenicity, the physician should follow CD20+ B-cell counts as a direct measure of clinical impact (see Section 5.1 Pharmacodynamic properties).

Assessment and premedication before every infusion

Infection assessment

Prior to every infusion of Uplizna, it should be determined whether there is an active infection. In case of active infection, infusion of Uplizna should be delayed until the infection resolves (see Section 4.4 Special warnings and precautions for use, Infections).

Required premedication

Specific premedication should be administered prior to each infusion of Uplizna to reduce the frequency and severity of infusion reactions (see Section 4.4 Special warnings and precautions for use, Infusion-related reactions and hypersensitivity). Table 1 shows premedication to administer prior to each infusion of Uplizna.

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

Dosage (dose and interval)

The recommended dosage is:

- Initial dose: 300 mg (3 vials of 100 mg) intravenous infusion followed 2 weeks later by a second 300 mg intravenous infusion.
- Maintenance doses (starting 6 months from the first infusion): single 300 mg intravenous infusion every 6 months.

Method of administration

Administration

Uplizna is administered as an intravenous infusion (see Table 2). Uplizna must be diluted prior to administration (See Section 4.2 Dose and method of administration).

Prior to the start of the intravenous infusion, the prepared infusion solution should be at room temperature.

Administer Uplizna under the supervision of an experienced healthcare professional with access to appropriate medical support to manage potential severe reactions such as serious infusion reactions (see Section 4.4 Special warning and precautions for use, Infusion-related reactions and hypersensitivity).

Administer the diluted solution intravenously via an infusion pump at an increasing rate to completion, approximately 90 minutes, according to the schedule in Table 2. Administer through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.

Table 2. Recommended infusion rate for administration when diluted in a 250 mL 9 mg/mL (0.9%) Sodium chloride intravenous bag

Elapsed time (minutes)	Infusion rate (mL/hour)
0 - 30	42
31 - 60	125
61 - completion	333

Preparation

Visually inspect Uplizna solution for particulate matter and discolouration. The vial should be discarded if the solution is cloudy, discoloured, or it contains discrete particulate matter. Do not shake the vial.

- Obtain an intravenous bag containing 250 mL of 9 mg/mL (0.9%) Sodium chloride solution for injection. 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.

Monitoring

Monitor the patient closely for infusion reactions during and for at least one hour after the completion of the infusion. (See Section 4.4 Special warning and precautions for use, Infusion-related reactions and hypersensitivity for actions to be taken in case of infusion-related reactions.)

Delayed or missed doses

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

Dosage adjustment

Patients with hepatic and/or renal impairment

Uplizna has not been studied in patients with severe renal or hepatic impairment. However, dose adjustment based on renal or hepatic function is not warranted because immunoglobulin (Ig) G monoclonal antibodies are not primarily cleared via renal or hepatic pathways (see Section 5.2 Pharmacokinetic properties, Special populations).

4.3 Contraindications

- Known hypersensitivity to inebilizumab or to any of the excipients listed in Section 6.1 List of excipients
- Severe active infection, including active chronic infection such as hepatitis B (see Section 4.4 Special warnings and precautions for use, Infections)
- Active or untreated latent tuberculosis (see Section 4.4 Special warnings and precautions for use, Infections)
- History of progressive multifocal leukoencephalopathy (PML) (see Section 4.4 Special warnings and precautions for use, Infections)
- Severely immunocompromised state (see Section 4.4 Special warnings and precautions for use, Treatment of severely immunocompromised patients)
- Active malignancies (see Section 4.4 Special warnings and precautions for use, Malignancy)

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infusion-related reactions and hypersensitivity

Uplizna can cause infusion-related reactions and hypersensitivity reactions, which can include headache, nausea, somnolence, dyspnoea, fever, myalgia, rash, or other symptoms. Infusion-related reactions were most common with the first infusion, but were observed during subsequent infusions. Although rare, serious infusion reactions did occur in clinical trials of Uplizna (see Section 4.8 Adverse effects (Undesirable effects)).

Before the infusion

Premedication with a corticosteroid (e.g., methylprednisolone 80-125 mg intravenous or equivalent), an antihistamine (e.g., diphenhydramine 25-50 mg orally or equivalent), and an anti-pyretic (e.g., paracetamol 500-650 mg orally or equivalent) should be administered (see Section 4.2 Dose and method of administration). A 2-week course of oral corticosteroids (plus a 1-week taper) was administered at the start of Uplizna treatment in the pivotal study (see Section 5.1 Pharmacodynamic properties).

During the infusion

After the infusion

Patients should be monitored for infusion reactions for at least one hour after the completion of infusion.

Infections

Uplizna can cause infections. Uplizna 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, Uplizna may increase the susceptibility to infections (see Section 4.8 Adverse effects (Undesirable effects)).
A recent (i.e. within 6 months) complete blood cell count (CBC) including differentials and immunoglobulins should be obtained before initiation of Uplizna. 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 Uplizna, it should be determined whether there is a clinically significant infection. In case of infection, infusion of Uplizna should be delayed until the infection resolves. 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.

The most common infections reported by Uplizna-treated NMOSD patients in the randomised and open-label clinical trial periods included urinary tract infection (26.2%), nasopharyngitis (20.9%), upper respiratory tract infection (15.6%), influenza (8.9%) and bronchitis (6.7%).

Hepatitis B virus 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. HBV screening should be performed 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. Patients with chronic HBV were excluded from clinical trials with Uplizna (see Section 4.3 Contraindications).

Hepatitis C virus

Patients positive for HCV were excluded from clinical trials with Uplizna. Baseline screening for HCV is required to detect and start treatment prior to initiating Uplizna treatment.

Progressive multifocal leukoencephalopathy

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 and other therapies that affect immune competence. In Uplizna clinical trials, one subject died following the development of new brain lesions for which a definitive diagnosis could not be established, though the differential diagnosis included an atypical NMOSD relapse, PML, or acute disseminated encephalomyelitis.

Physicians should be vigilant for clinical symptoms or Magnetic Resonance Imaging (MRI) findings that may be suggestive of PML. 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.

At the first sign or symptom suggestive of PML, treatment with Uplizna should be suspended until PML has been excluded. Further evaluation, including consultation with a neurologist, MRI scan preferably with contrast, cerebrospinal fluid testing for JC viral DNA, and repeat neurological assessments, should be considered. If confirmed, treatment with Uplizna should be discontinued

Tuberculosis

Prior to initiating Uplizna, patients should be evaluated for active tuberculosis and tested for latent infection. For patients with active tuberculosis or positive tuberculosis screening without a history of appropriate treatment, infectious disease experts should be consulted before starting treatment with Uplizna.

Late neutropenia

Cases of late onset of neutropenia have been reported (see Section 4.8 Adverse effects (Undesirable effects)). 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 Uplizna. In patients with signs and symptoms of infection, measurement of blood neutrophils is recommended.

Treatment of severely immunocompromised patients

Patients in a severely immunocompromised state must not be treated until the condition resolves (see Section 4.3 Contraindications).

Uplizna has not been tested together with other immunosuppressants. If combining it with another immunosuppressive therapy, consider the potential for increased immunosuppressive effects.

Patients with a known congenital or acquired immunodeficiency, including HIV infection or splenectomy, have not been studied.

Vaccinations

All immunisations should be administered according to immunisation guidelines at least 4 weeks prior to initiation of Uplizna. The efficacy and safety of immunisation 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 Ig-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 Uplizna 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. For more information, refer to Section 4.5 Interactions with other medicines and other forms of interaction.

Reduction in immunoglobulins

Uplizna may cause hypogammaglobulinaemia or decline in the levels of total and individual immunoglobulins (see Section 4.8 Adverse effects (Undesirable effects)). Monitor the levels of quantitative serum immunoglobulins during treatment, 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.

Malignancy

Immunomodulatory medicinal products may increase the risk of malignancy. On the basis of limited experience with Uplizna in NMOSD (see Section 4.8 Adverse effects (Undesirable effects)), the current data do not seem to suggest any increased risk of malignancy. However, the possible risk for the development of solid tumours cannot be excluded at this time.

Use in elderly

Uplizna has been administered to 10 elderly patients (≥ 65 years of age) in clinical studies. Based on the limited data available, no dose adjustment is considered necessary in patients over 65 years old (see Section 5.2 Pharmacokinetic properties, Special populations).

Paediatric use

The safety and efficacy of Uplizna in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

Effect on laboratory tests

Refer to Section 4.8 Adverse effects (Undesirable effects) and Section 5.1 Pharmacodynamic properties.

4.5 Interactions with other medicines and other forms of interaction

No interaction studies have been performed.

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.

Vaccinations

The efficacy and safety of immunisation with live or live-attenuated vaccines following Uplizna therapy have not been studied. The response to vaccination could be impaired when B-cells are depleted. It is recommended that patients complete immunisations prior to the start of Uplizna therapy (see Section 4.4 Special warnings and precautions for use, Treatment of severely immunocompromised patients).

Immunosuppressive or immune-modulating therapies

Uplizna 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 Uplizna with other

immunosuppressants. In the pivotal study, a 2-week course of oral corticosteroids (plus a 1-week taper) was given to all subjects following the first administration of Uplizna.

Concomitant usage of Uplizna with immunosuppressants, including systemic corticosteroids, may increase the risk of infection. The effects of Uplizna on B-cells and immunoglobulins may persist for 6 months or longer following its administration.

When initiating Uplizna, after other immunosuppressive therapies with prolonged immune effects or initiating other immunosuppressive therapies with prolonged immune effects after Uplizna, the duration and mode of action of these medicinal products should be taken into account because of potential additive immunosuppressive effects (see Section 5.1 Pharmacodynamic properties).

4.6 Fertility, pregnancy and lactation

Effects on fertility

There are limited data on the effect of Uplizna on human fertility; however, studies in animals have shown reduced fertility. Intravenous administration of inebilizumab by weekly doses of 3 or 30 mg/kg to human CD19 transgenic (hu9CD19 Tg) male and female mice prior to and during mating and continuing in females through gestation day 15 resulted in reduced fertility at both doses tested at subclinical doses. A dose level that does not cause adverse effect on fertility was not identified.

Use in pregnancy

Category C

There are limited data from the use of Uplizna in pregnant women. Inebilizumab is a humanised IgG1 monoclonal antibody and immunoglobulins are known to cross the placental barrier. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other B-cell depleting antibodies during pregnancy.

Intravenous administration of inebilizumab by weekly doses of 3 or 30 mg/kg 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 subclinical doses.

These results demonstrate that inebilizumab crosses the placenta and depletes B cells in the fetus.

In case of exposure during pregnancy, depletion of B-cells may be expected in newborns due to the pharmacological properties of the product and findings from animal studies.

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 Section 4.4, Special warnings and precautions for use, Treatment of severely immunocompromised patients, and Section 5.1 Pharmacodynamic properties). Consequently, newborns should be monitored for B-cell depletion and vaccinations with live virus vaccines, such as Bacillus Calmette-Guérin (BCG) vaccine, should be postponed until the infant's B-cell count has recovered (see Section 4.4 Special warnings and precautions for use, Treatment of severely immunocompromised patients).

Advise women of reproductive potential to use effective contraception (methods that result in less than 1% pregnancy rates) while receiving Uplizna and for at least 6 months after the last dose.

Use in lactation

The use of Uplizna in women during lactation has not been studied. It is unknown if Uplizna is excreted in human milk. There is no data on the presence of inebilizumab in human milk, the effects on the breastfed infant, or the effects on milk production.

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 mother's clinical need for Uplizna and the potential adverse effect on the breastfed infant should be considered along with the developmental benefits of breastfeeding.

Intravenous administration of inebilizumab at doses of 3 or 30 mg/kg to huCD19 Tg mice every three days throughout organogenesis and lactation resulted in depletion of B-cells and persistent reductions in immune function (even following repletion of B-cells and lasting into adulthood) in offspring at subclinical doses. At the end of the lactation period, plasma inebilizumab levels in offspring were only slightly lower those in maternal plasma, indicative of milk secretion.

4.7 Effects on ability to drive and use machines

The pharmacological activity and adverse reactions reported to date suggest that Uplizna has no or negligible influence on the ability to drive and use machines.

4.8 Adverse effects (Undesirable effects)

Summary of the safety profile

The safety of Uplizna was evaluated in the pivotal study, Study 1 (see Section 5.1 Pharmacodynamic properties), in which 161 patients with AQP4-IgG seropositive NMOSD were exposed to Uplizna at the recommended dosage regimen and 52 patients with AQP4-IgG seropositive NMOSD received placebo during the randomised, controlled

treatment period. Subsequently, 201 patients with AQP4-IgG seropositive NMOSD were exposed to Uplizna during an open-label treatment period.

Two-hundred and eight patients with AQP4-IgG seropositive NMOSD in the randomised and open-labelled treatment periods had a total of 667.51 person-years of exposure to Uplizna.

Table 3 lists treatment emergent adverse events (TEAEs) that occurred in ≥ 5% of patients with AQP4-IgG seropositive NMOSD treated with Uplizna during the randomised, controlled treatment period in Study 1.

Table 3. Treatment Emergent Adverse Events in ≥ 5% in Uplizna-Treated Patients with AQP4-IgG Seropositive NMOSD

System Organ Class	Adverse Events Preferred Term	Overall Subject Incidence during RCP	
		Uplizna (N = 161) n (%)	Placebo (N = 52) n (%)
Infections and infestations	Urinary tract infection	18 (11.2%)	5 (9.6%)
	Nasopharyngitis	12 (7.5%)	6 (11.5%)
Musculoskeletal and connective tissue disorders	Arthralgia	17 (10.6%)	3 (5.8%)
	Back pain	11 (6.8%)	2 (3.8%)
Nervous system disorders	Headache	14 (8.7%)	4 (7.7%)
Injury, poisoning and procedural complications	Infusion-related reaction	15 (9.3%)	5 (9.6%)

RCP = randomised, controlled treatment period

Tabulated list of adverse reactions

Adverse reactions reported across the randomised and open-label treatment period in the clinical trial of Uplizna in NMOSD (including AQP4-IgG seropositive and seronegative patients) are listed in Table 4 according to the following frequency categories: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

The most frequently reported adverse reactions by Uplizna-treated patients were urinary tract infection (26.2%), nasopharyngitis (20.9%), arthralgia (17.3%), upper respiratory tract infection (15.6%), and back pain (13.8%) across both the randomised and open-label treatment period in Study 1.

The most frequently reported serious adverse reactions by Uplizna-treated patients across the randomised and open-label treatment period were infections (11.1%) (including urinary tract infections (4.0%), pneumonia (1.8%)) and NMOSD (1.8%).

Table 4. Adverse reactions in Patients with NMOSD from Study 1

MedDRA System Organ Class	Adverse reaction	Frequency
Infections and infestations	Urinary tract infection, respiratory tract infection, nasopharyngitis, influenza	Very Common
	Pneumonia, cellulitis, herpes zoster, sinusitis,	Common
	Sepsis, subcutaneous abscess, bronchiolitis	Uncommon
Blood and lymphatic system disorders	Lymphopenia, Neutropenia, Late-onset neutropenia	Common
Musculoskeletal and connective tissue disorders	Arthralgia, back pain	Very Common
Nervous System Disorders	Headache	Very Common
Investigations	Immunoglobulins decreased	Very Common
Injury, poisoning and procedural complications	Infusion-related reaction	Very Common

Description of selected adverse reactions

Infusion-related reactions

Uplizna can cause infusion-related reactions, which can include headache, nausea, somnolence, dyspnoea, fever, myalgia, rash, or other symptoms. All patients were given premedication in Study 1. Infusion reactions were observed in 9.2% of NMOSD patients during the first course of Uplizna compared to 10.7% 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 Section 4.4 Special warnings and precautions for use, Infusion-related reactions and hypersensitivity for actions to be taken in case of infusion-related reactions.

Infections

An infection was reported by 74.7% of NMOSD patients treated with Uplizna across the randomised, controlled treatment period and open-label treatment period. The most common infections included urinary tract infection (26.2%), nasopharyngitis (20.9%), and upper respiratory tract infection (15.6%), influenza (8.9%), and bronchitis (6.7%). Serious infections reported by more than one Uplizna-treated patient were urinary tract infection (4.0%) and pneumonia (1.8%). See Section 4.4 Special warnings and precautions for use, Infections for use for action to be taken in case of infection.

Opportunistic and serious infections

During the randomised, controlled treatment period, no opportunistic infections occurred in either treatment group, and a single Grade 4 infectious adverse reaction (atypical pneumonia) occurred in a patient treated with Uplizna. During the open-label treatment period, two Uplizna-treated patients (0.9%) experienced an opportunistic infection (one of which was not confirmed) and three Uplizna-treated patients (1.4%) experienced a Grade 4 infectious adverse reaction. See Section 4.4 Special warnings and precautions for use, Infections for use for action to be taken in case of infection.

Laboratory abnormalities

Decreased immunoglobulins

Consistent with its mechanism of action, average immunoglobulin levels decreased with Uplizna use. At the end of the 6.5-month randomised, controlled period, the proportion of patients with levels below the lower limit of normal was as follows: IgA 9.8% Uplizna and 3.1% placebo, IgE 10.6% Uplizna and 12.5% placebo, IgG 3.8% Uplizna and 9.4%

placebo, and IgM 29.3% Uplizna and 15.6% placebo. A single adverse reaction of IgG decreased was reported (Grade 2, during the open-label treatment period). The proportion of Uplizna-treated patients with IgG levels below the lower limit of normal at year 1 was 7.4% and at year 2 was 9.9%. With a median exposure of 3.2 years, the frequency of moderate IgG reduction (300 to <500 mg/dL) was 14.2% and the frequency of severe IgG reduction (<300 mg/dL) was 3.6%.

Decreased neutrophil counts

After 6.5 months of treatment, neutrophil counts between 1.0-1.5 x109/L (Grade 2) were observed in 7.5% of Uplizna-treated patients versus 1.8% of placebo-treated patients. Neutrophil counts between 0.5-1.0 $x10^9$/L (Grade 3) were observed in 1.7% of Uplizna-treated patients versus 0% of placebo-treated patients. Neutropenia was generally transient and was not associated with serious infections.

Decreased lymphocyte counts

After 6.5 months of treatment, a reduction in lymphocyte counts was observed more commonly in patients treated with Uplizna than placebo: lymphocyte counts between 500-< 800/mm^3 (Grade 2) were observed in 21.4% of Uplizna-treated patients versus 12.5% of placebo-treated patients. Lymphocyte counts between 200-< 500/mm^3 (Grade 3) were observed in 2.9% of Uplizna-treated patients versus 1.8% of placebo-treated patients. This finding is consistent with the mechanism of action of B-cell depletion since B-cells are a subset of the lymphocyte population.

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 neutralising 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 1, 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.

Reporting of suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 Overdose

No information is available for patients who have received an overdosage in Uplizna in clinical studies.

The highest dose of Uplizna tested in autoimmune patients was 1200 mg, administered as two 600 mg intravenous infusions separated by 2 weeks. The adverse reactions were similar to what was observed in the Uplizna pivotal clinical study. 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 section 4.4 Special warning and precautions for use). The patient should be closely monitored for signs or symptoms of adverse reactions and supportive care instituted as required. For information on the management of overdose contact the Poisons Information Centre on 131126 Australia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Inebilizumab is a monoclonal antibody that specifically binds to CD19, a cell surface antigen present on pre-B and mature B-cell lymphocytes, including plasmablasts and some plasma cells. Following cell surface binding to B lymphocytes, inebilizumab supports antibody-dependent cellular cytolysis (ADCC) and antibody-dependent cellular phagocytosis (ADCP). B-cells are believed to play a central role in the pathogenesis of NMOSD. The precise mechanism by which inebilizumab exerts its therapeutic effects in NMOSD is unknown but is presumed to involve B-cell depletion and may include the suppression of antibody secretion, antigen presentation, B-cell–T-cell interaction, and the production of inflammatory mediators.

Pharmacodynamic effects

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 1 (see Section 5.1 Pharmacodynamic properties, Clinical trials), a clinical study of 174 patients, 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. The time to B-cell repletion following administration of inebilizumab is not known.

Clinical trials

Neuromyelitis optica spectrum disorders (NMOSD)

The efficacy of Uplizna for the treatment of NMOSD was established in Study 1, a randomised (3:1), double-blind, placebo-controlled clinical trial in adults with AQP4-IgG seropositive or seronegative NMOSD.

The study included patients who had experienced at least one acute NMOSD attack in the prior year or at least 2 attacks in the prior 2 years that required rescue therapy (e.g., steroids, plasma exchange, intravenous immunoglobulin), and had an Expanded Disability Severity Scale (EDSS) score ≤ 7.5 (patients with a score of 8.0 were eligible if the patient was reasonably able to participate). Patients were excluded if previously treated with immunosuppressant therapies within an interval specified for each such therapy.

Background immunosuppressant therapies for the prevention of NMOSD attacks were not permitted. A 2-week course of oral corticosteroids (plus a 1-week taper) was administered at the start of Uplizna treatment in the pivotal study.

Patients were treated with intravenous infusions of Uplizna 300 mg on Day 1 and on Day 15, or matching placebo, and then followed for a period of up to 197 days or an adjudicated attack, termed the randomised-controlled period.

A total of 230 patients were enrolled: 213 patients were AQP4-IgG seropositive patients and 17 were seronegative patients. Of the 213 AQP4-IgG seropositive patients, 161 were treated with Uplizna and 52 were treated with placebo in the randomised, controlled treatment period of the study. Baseline and efficacy results are presented for the AQP4-IgG seropositive patients.

The baseline demographics and disease characteristics were balanced between the treatment groups (see Table 5).

Table 5. Demographics and baseline characteristics of the AQP4-IgG seropositive NMOSD patients

Characteristic	Placebo N = 52	Uplizna N = 161	Overall N = 213
Age (years): mean (standard deviation [SD])	42.4 (14.3)	43.2 (11.6)	43.0 (12.3)
Age ≥ 65 years, n (%)	4 (7.7)	6 (3.7)	10 (4.7)
Sex: Male, n (%)	3 (5.8)	10 (6.2)	13 (6.1)
Sex: Female, n (%)	49 (94.2)	151 (93.8)	200 (93.9)
Expanded disability status scale (EDSS): mean (SD)	4.35 (1.63)	3.81 (1.77)	3.94 (1.75)
Disease duration (years): mean (SD)	2.92 (3.54)	2.49 (3.39)	2.59 (3.42)
Number of prior relapses: ≥ 2, n (%)	39 (75.0)	137 (85.1)	176 (82.6)
Annualised Relapse Rate: mean (SD)	1.456 (1.360)	1.682 (1.490)	1.627 (1.459)

All potential NMOSD attacks were evaluated by a blinded, independent, adjudication committee, who determined whether the attack met protocol-defined criteria. The attack criteria recognised attacks in all domains affected by NMOSD (optic neuritis, myelitis, brain, and brainstem) and included criteria based exclusively on substantial clinical manifestations, as well as criteria that augmented more modest clinical findings with the use of MRI (see Table 6).

Table 6. Overview of the protocol-defined criteria for an NMOSD attack

Domain	Representative symptoms	Clinical-only findings	Clinical PLUS radiological findings
Optic nerve	Blurred vision Loss of vision Eye pain	8 criteria based on changes in visual acuity or relative afferent pupillary defect (RAPD)	3 criteria based on changes in visual acuity or RAPD plus presence of corresponding optic nerve MRI findings
Spinal cord	Deep or radicular pain Extremity paraesthesia Weakness Sphincter dysfunction Lhermitte's sign (not in isolation)	2 criteria based on changes in pyramidal, bladder/bowel, or sensory functional scores	2 criteria based on changes in pyramidal, bladder/bowel, or sensory functional scores PLUS corresponding spinal cord MRI findings

Domain	Representative symptoms	Clinical-only findings	Clinical PLUS radiological findings
Brainstem	Nausea Intractable vomiting Intractable hiccups Other neurological signs (e.g., double vision, dysarthria, dysphagia, vertigo, oculomotor palsy, weakness, nystagmus, other cranial nerve abnormality)	None	2 criteria based on symptoms or changes in brainstem/cerebellar functional scores PLUS corresponding brainstem MRI findings
Brain	Encephalopathy Hypothalamic dysfunction	None	1 criterion based on changes in cerebral/sensory/pyramidal functional scores PLUS corresponding brain MRI findings

Patients who experienced an adjudication committee-determined attack in the randomised, controlled treatment period, or who completed the Day 197 visit without an attack, exited the randomised, controlled treatment period and had the option to enrol into an open-label treatment period and initiate or continue treatment with Uplizna.

Rescue therapy was initiated as needed for NMOSD attacks. All patients were pre-medicated prior to investigational product administration to reduce the risk of infusion-related reactions.

The primary efficacy endpoint was time (days) from Day 1 to onset of an adjudication committee-determined NMOSD attack on or before Day 197.

Additional key secondary endpoint measures included worsening from baseline in EDSS at last visit during the randomised, controlled treatment period, change from baseline in low-contrast visual acuity binocular score measured by low-contrast Landolt C Broken Rings Chart at last visit during the randomised, controlled treatment period, cumulative total active MRI lesions (new gadolinium-enhancing or new/enlarging T2 lesions) during the randomised, controlled treatment period, and the number of NMOSD-related in-patient hospitalisations. A patient was considered to have a worsening in EDSS score if one of the following criteria was met: (1) worsening of 2 or more points in EDSS score for patients with baseline score of 0; (2) worsening of 1 or more points in EDSS score for patients with baseline score of 1 to 5; (3) worsening of 0.5 points or more in EDSS score for patients with baseline score of 5.5 or more. Although no comparator was available

during the open-label period, the annualised attack rate across both randomised and open-label treatment was determined.

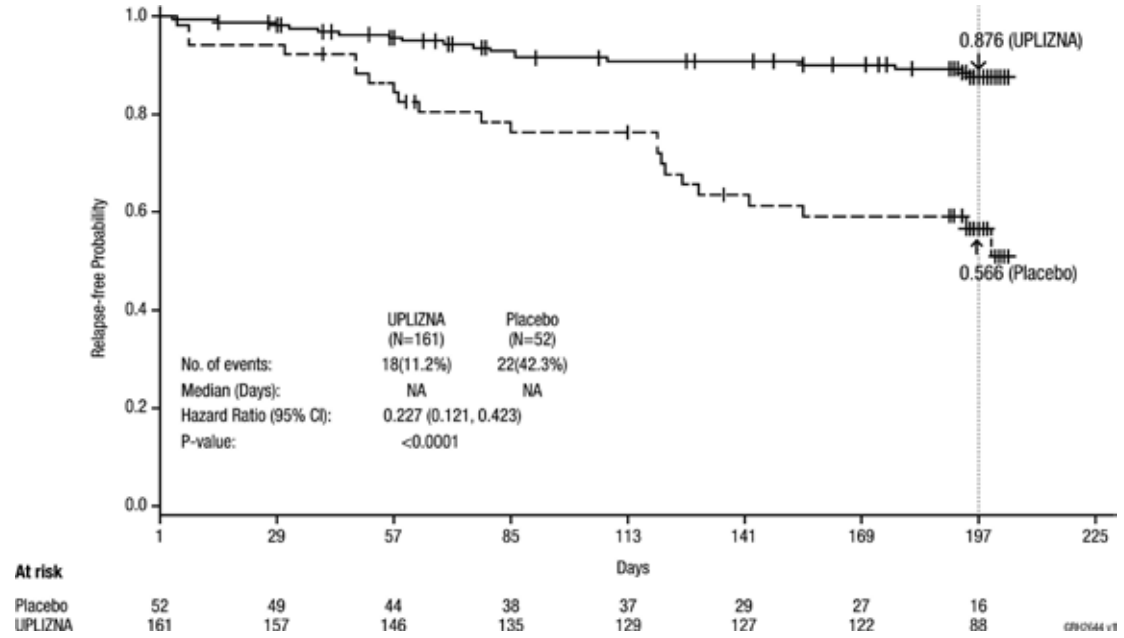
Treatment with Uplizna statistically significantly reduced the risk of an adjudication committee-determined NMOSD attack as compared to treatment with placebo (hazard ratio: 0.227, p < 0.0001; 77.3% reduction in risk of adjudication committee-determined NMOSD attack) in AQP4-IgG seropositive patients. Results in AQP4-IgG seropositive patients are presented in Table 7 and Figure 1. There was no treatment benefit observed in AQP4-IgG seronegative patients.

Table 7. Efficacy results in Study 1 in AQP4-IgG seropositive NMOSD

	Treatment group	
	Placebo N = 52	**Uplizna N = 161**
Time to adjudication committee-determined attack (primary efficacy endpoint)		
Number (%) of patients with attack	22 (42.3%)	18 (11.2%)
Hazard ratio (95% CI)[a]	0.22 (0.1214, 0.4232)	
p-value[a]	< 0.0001	

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

Figure 1. Kaplan-Meier plot of time to first adjudication committee-determined NMOSD attack during the RCP in AQP4-IgG seropositive patients



In the Uplizna group EDDS worsening was significantly less than placebo group (14.9% versus 34.6% of the subjects). There were no differences in the low-contrast visual acuity binocular score between the study arms. The mean cumulative number of total active MRI lesions (1.7 versus 2.3) and mean cumulative number of NMOSD related hospitalisations (1.0 vs 1.4) were reduced in the Uplizna study group.

Across the randomised, control treatment period and open-label period, the annualised adjudication committee-determined NMOSD attack rate was analysed as a secondary endpoint and in AQP4-IgG seropositive patients treated with Uplizna the result was 0.09.

5.2 Pharmacokinetic properties

The pharmacokinetics of inebilizumab in NMOSD patients following intravenous administration of Uplizna was biphasic with a mean terminal half-life of 18 days. The mean maximum concentration was 108 µg/mL (300 mg, second dose on Day 15), and the cumulative AUC of the 26-week treatment period in which NMOSD patients received two intravenous administrations 2 week apart was 2980 µg d/mL.

Absorption

Inebilizumab is administered as an intravenous infusion.

Distribution

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

Metabolism

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

Excretion

The results of population pharmacokinetic analysis indicated that 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 Uplizna treatment.

Special populations

Paediatric population

Inebilizumab has not been studied in children or adolescents.

Elderly

Based on population pharmacokinetic analysis, age did not affect inebilizumab clearance.

Gender and race

A population pharmacokinetic analysis indicated that there was no significant effect of gender and race on inebilizumab clearance.

Renal impairment

No formal clinical studies have been conducted to investigate the effect of renal impairment on inebilizumab. Due to the large molecular weight and hydrodynamic size of an IgG monoclonal antibody, inebilizumab is not expected to be filtered through the glomerulus. From population pharmacokinetic analysis, inebilizumab clearance in patients with varying degrees of renal impairment was comparable to patients with normal estimated glomerular filtration rate.

Hepatic impairment

No formal clinical studies have been conducted to investigate the effect of hepatic impairment on inebilizumab. In clinical studies, no subjects with severe hepatic impairment have been exposed to inebilizumab. IgG monoclonal antibodies are not primarily cleared via the hepatic pathway; change in hepatic function is, therefore, not expected to influence inebilizumab clearance. Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (AST, ALP, and bilirubin) had no clinically relevant effect on inebilizumab clearance.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Genotoxicity

No studies have been conducted on the mutagenic or clastogenic potential of inebilizumab. As inebilizumab is a monoclonal antibody, it is not expected to interact with DNA or chromosomes.

Carcinogenicity

No studies have been conducted on the carcinogenic potential of inebilizumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine

Histidine hydrochloride monohydrate

Sodium chloride

Trehalose dihydrate

Polysorbate 80

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, Uplizna must not be mixed with other medicinal products except those mentioned in Section 4.2 Dose and method of administration.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

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

Product is for single use in one patient only. Discard any residue.

After reconstitution and dilution

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.

6.5 Nature and contents of container

Uplizna is provided as 10 mL of sterile, clear to slightly opalescent, colourless to slightly yellow solution concentrate in a single-use vial. Each Uplizna carton contains three vials.

Uplizna is supplied in a single-use, Type 1 glass vial with an elastomeric stopper and a flip-off aluminium seal.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure

Inebilizumab is a CD19-directed cytolytic humanised afucosylated IgG1 monoclonal antibody targeting CD19+ B-cells produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture.

It is approximately 149 kDa that is composed of two identical heavy chains and two identical light chains.

CAS number

1299440-37-1

MEDICINE SCHEDULE (POISONS STANDARD)

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DATE OF FIRST APPROVAL

DD-MONTH-YYYY

DATE OF REVISION

Not Applicable

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information