

1. NAME OF THE MEDICINAL PRODUCT

UPLIZNA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of inebilizumab in 10 mL at a concentration of 10 mg/mL. The final concentration after dilution is 1.0 mg/mL (see section 6.6).

Inebilizumab is a humanised monoclonal antibody produced in Chinese hamster ovary cell line by recombinant DNA technology.

Excipient with known effect

This medicinal product contains 16.1 mg of sodium per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear to slightly opalescent, colourless to slightly yellow solution. The solution has a pH of approximately 6.0 and an osmolality of approximately 280 mOsm/kg.

Patient card

The marketing of Uplizna is subject to a risk management plan (RMP) including a 'Patient card'. The 'Patient card' emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment and the implications of this treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuromyelitis optica spectrum disorders (NMOSD)

Uplizna is indicated as monotherapy for the treatment of adult patients with NMOSD who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive.

Immunoglobulin G4-related disease (IgG4-RD)

Uplizna is indicated for the treatment of adult patients with active IgG4-RD.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of NMOSD or IgG4-RD 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).

Assessments prior to first dose of inebilizumab

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 and 4.4)
- Hepatitis B virus (HBV) screening (see sections 4.3 and 4.4)
- Hepatitis C virus (HCV) screening and treatment started prior to initiating inebilizumab treatment (see section 4.4)
- Evaluate for active tuberculosis and test for latent infection (see sections 4.3 and 4.4)

All immunisations should be administered according to immunisation guidelines at least 4 weeks prior to initiation of inebilizumab for live or live-attenuated vaccines (see section 4.4).

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

Posology

Initial doses

The recommended loading dose is 300 mg (3 vials of 100 mg) intravenous infusion followed 2 weeks later by a second 300 mg intravenous infusion.

Maintenance doses

The recommended maintenance dose is 300 mg intravenous infusion every 6 months. Inebilizumab is for chronic treatment.

Based upon the chronic nature of IgG4-RD, treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

Delayed or missed doses

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

Premedication for infusion-related reactions

Infection assessment

Prior to every infusion of inebilizumab, it should be determined whether there is a clinically significant infection. In case of infection, infusion of inebilizumab should be delayed until the infection resolves.

Required premedication

Premedication with a corticosteroid (e.g., methylprednisolone 80-125 mg intravenous or equivalent) should be administered approximately 30 minutes prior to each inebilizumab infusion; and an antihistamine (e.g., diphenhydramine 25-50 mg orally or equivalent) and an anti-pyretic (e.g., paracetamol 500-650 mg orally or equivalent) approximately 30-60 minutes prior to each inebilizumab infusion (see section 4.4).

Special populations

Elderly

Inebilizumab has been administered to 42 elderly patients (≥ 65 years of age) in clinical studies. Based on the data available, no dose adjustment is considered necessary in patients over 65 years old (see section 5.2).

Renal and hepatic impairment

Inebilizumab 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).

Paediatric population

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

Method of administration

For intravenous use.

Vials should not be shaken.

Vials should be stored upright.

The prepared solution should be administered intravenously via an infusion pump at an increasing rate to completion (approximately 90 minutes) through an intravenous line containing a sterile, low protein-binding 0.2 or 0.22 micron in-line filter according to the schedule in table 1.

Table 1. Recommended infusion rate for administration when diluted in a 250 mL intravenous bag

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

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Severe active infection, including active chronic infection such as hepatitis B
- Active or untreated latent tuberculosis
- History of progressive multifocal leukoencephalopathy (PML)
- Severely immunocompromised state
- Active malignancies

4.4 Special warnings and precautions for use

Instructions for patients at the time of prescribing

Patients treated with Uplizna should be given a patient card which includes information that inebilizumab treatment may increase the risk of infections, including serious infections, viral reactivation, opportunistic infections, and progressive multifocal leukoencephalopathy (PML), and how to seek early medical care in case of signs and symptoms of infection and PML.

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

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

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).

During the infusion

The patient should be monitored for infusion-related reactions. Management recommendations for infusion reactions depend on the type and severity of the reaction. For life-threatening infusion reactions, treatment should be stopped immediately and permanently, and appropriate supportive treatment should be administered. For less severe infusion reactions, management may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.

After the infusion

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

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 (see section 4.8).

A recent (i.e. within 6 months) complete blood cell count (CBC) 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. In case of infection, infusion of inebilizumab 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 inebilizumab-treated NMOSD patients across the randomised controlled period (RCP) and the open-label period (OLP) included urinary tract infection (26.2%), nasopharyngitis (20.9%), upper respiratory tract infection (15.6%), influenza (8.9%), and bronchitis (6.7%). In the IgG4-RD RCP and OLP, the most common infections reported by inebilizumab-treated patients were upper respiratory tract infection (10.7%), nasopharyngitis (9.8%), urinary tract infection (8.9%), and influenza (6.3%).

Hepatitis B virus reactivation

Risk of HBV reactivation has been observed with other B-cell-depleting antibodies. Patients with chronic HBV were excluded from clinical trials with inebilizumab. HBV screening should be performed in all patients before initiation of treatment with inebilizumab. Inebilizumab should not be administered to patients with active hepatitis due to HBV who are positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients who are chronic carriers of HBV [HBsAg+] should consult a liver disease expert before starting and during treatment (see section 4.3).

Hepatitis C virus

Patients positive for 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

Prior to initiating inebilizumab, 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 inebilizumab.

Progressive multifocal leukoencephalopathy (PML)

PML is an opportunistic viral infection of the brain caused by the John Cunningham virus (JCV) that typically occurs in patients who are immunocompromised, and that may lead to death or severe disability. JCV infection resulting in PML has been observed in patients treated with other B-cell-depleting antibodies.

No confirmed cases of PML were identified in inebilizumab clinical trials. In inebilizumab clinical trials, one subject (NMOSD trial) died following the development of new brain lesions for which a definitive diagnosis could not be established. However, the differential diagnosis included atypical NMOSD attack, 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 inebilizumab 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 inebilizumab should be discontinued.

Late neutropenia

Cases of late onset of neutropenia have been reported (see section 4.8). 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.

Treatment of severely immunocompromised patients

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

Inebilizumab 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 inebilizumab. The efficacy and safety of immunisation with live or live-attenuated vaccines following inebilizumab therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion.

Infants of mothers exposed to inebilizumab during pregnancy should not be administered 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 inebilizumab is not known (see section 5.1).

Pregnancy

As a precautionary measure, it is preferable to avoid the use of inebilizumab during pregnancy and in women of childbearing potential not using contraception (see section 4.6). Patients should be instructed that if they are pregnant or plan to become pregnant while taking inebilizumab, they should inform their healthcare provider. Women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) while receiving Uplizna and for 6 months after the last administration of Uplizna.

Malignancy

Immunomodulatory medicinal products may increase the risk of malignancy. On the basis of limited experience with inebilizumab in NMOSD and IgG4-RD (see section 4.8), 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.

Sodium content

This medicinal product contains 48.3 mg sodium per dose, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The primary elimination pathway for therapeutic antibodies is clearance by the reticuloendothelial system. Cytochrome P450 enzymes, efflux pumps, and protein-binding mechanisms are not involved in the clearance of therapeutic antibodies. Therefore, the potential risk of pharmacokinetic interactions between inebilizumab and other medicinal products is low.

Vaccinations

The efficacy and safety of immunisation with live or live-attenuated vaccines following inebilizumab therapy has 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 inebilizumab therapy (see section 4.4).

Immunosuppressants

No data are available on the safety or efficacy of combining inebilizumab with other immunosuppressants. In the pivotal NMOSD study, during the RCP, a 2-week course of oral corticosteroids (plus a 1-week taper) was given to all subjects following the first administration of inebilizumab. In the pivotal IgG4-RD study, during the RCP, subjects were at a uniform dose of glucocorticoids (GCs) at the time of initiation of inebilizumab and then began a prespecified taper to discontinuation at the end of 8 weeks (see section 5.1).

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

When initiating inebilizumab after other immunosuppressive therapies with prolonged immune effects or initiating other immunosuppressive therapies with prolonged immune effects after inebilizumab, 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).

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) while receiving Uplizna and for 6 months after the last administration of Uplizna.

Pregnancy

There are limited amount of data from the use of inebilizumab 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.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity; however, they have shown a B-cell depletion in the foetal livers of progeny (see section 5.3).

Treatment with inebilizumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.

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 (see section 5.3). B-cell levels in infants following maternal exposure to inebilizumab have not been studied in clinical trials. The potential duration of B-cell depletion in infants exposed to inebilizumab *in utero*, and the impact of B-cell depletion on the safety and effectiveness of vaccines, are unknown (see sections 4.4 and 5.1). 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).

Breast-feeding

The use of inebilizumab in women during lactation has not been studied. It is unknown whether inebilizumab is excreted in human milk. In humans, excretion of IgG antibodies in milk occurs during the first few days after birth, which is decreasing to low concentrations soon afterwards.

Consequently, a risk to the breast-fed child cannot be excluded during this short period. Afterwards, Uplizna could be used during breast-feeding if clinically needed. However, if the patient was treated with Uplizna up to the last few months of pregnancy, breast-feeding can be started immediately after birth.

Fertility

There are limited data on the effect of inebilizumab on human fertility; however, studies in animals have shown reduced fertility. The clinical significance of these nonclinical findings is not known (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions by inebilizumab-treated patients were urinary tract infection (26.2%), nasopharyngitis (20.9%), upper respiratory tract infection (15.6%), arthralgia (17.3%), back pain (13.8%), and lymphopenia (10.7%) across both the randomised controlled period (RCP) and open-label period (OLP).

The most frequently reported serious adverse reactions by inebilizumab-treated patients across the RCP and OLP were infections (11.1%) (including urinary tract infections (4.0%), pneumonia (1.8%)) and NMOSD (1.8%).

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials and post-marketing experience following treatment with inebilizumab are listed in table 2 according to the following frequency categories: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Table 2. Adverse reactions reported in inebilizumab clinical trials, including patients with NMOSD and IgG4-RD as well as from post-marketing experience

MedDRA organ class	system	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)
Infections and infestations		Urinary tract infection, respiratory tract infection, nasopharyngitis, influenza	Pneumonia, cellulitis, herpes zoster, sinusitis	Sepsis, subcutaneous abscess, bronchiolitis
Blood and lymphatic system disorders		Lymphopenia*	Neutropenia, late-on-set neutropenia	

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Musculoskeletal and connective tissue disorders	Arthralgia, back pain	Myalgia	
General disorders and administration site conditions		Pyrexia	
Investigations	Immunoglobulins decreased		
Injury, poisoning and procedural complications	Infusion-related reaction		

* Lymphopenia includes lymphocyte count decreased

Description of selected adverse reactions

Infusion-related reactions

Inebilizumab can cause infusion-related reactions, which can include headache, nausea, somnolence, dyspnoea, fever, myalgia, rash, palpitations or other symptoms. All patients were given premedication. Infusion reactions were observed in 9.2% of NMOSD patients during the first course of inebilizumab compared to 10.7% of placebo-treated patients. Infusion reactions to inebilizumab were observed in 7.4% of IgG4-RD patients compared to 14.9% of placebo-treated patients during the RCP. Infusion-related reactions were most common with the first infusion but were observed during subsequent infusions. The majority of infusion-related reactions reported in inebilizumab-treated patients were either mild or moderate in severity.

Infections

In clinical trials, an infection was reported by 74.7% of NMOSD patients and 70.5% of IgG4-RD patients treated with inebilizumab across the RCP and OLP. The most common infections in NMOSD patients 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 inebilizumab-treated NMOSD patient were urinary tract infection (4.0%) and pneumonia (1.8%). The most common infections in IgG4-RD patients included upper respiratory tract infection (10.7%), nasopharyngitis (9.8%), urinary tract infection (8.9%), and influenza (6.3%). Serious infections reported by more than one inebilizumab-treated IgG4-RD patient was pneumonia (1.8%). See section 4.4 for action to be taken in case of infection.

Opportunistic and serious infections

In NMOSD study during the RCP, no opportunistic infections occurred in either treatment group, and a single grade 4 infectious adverse reaction (atypical pneumonia) occurred in a patient treated with inebilizumab. During the OLP, 2 inebilizumab-treated patients (0.9%) experienced an opportunistic infection (one of which was not confirmed) and 3 inebilizumab-treated patients (1.4%) experienced a grade 4 infectious adverse reaction. See section 4.4 for action to be taken in case of infection. In IgG4-RD study, 3 inebilizumab-treated patients (2.7%) experienced an opportunistic infection (all non-serious herpes zoster) across the RCP and OLP.

Laboratory abnormalities

Decreased immunoglobulins

Consistent with its mechanism of action, average immunoglobulin levels decreased with inebilizumab use. In NMOSD study, 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 9.8% inebilizumab and 3.1% placebo, IgE 10.6% inebilizumab and 12.5% placebo, IgG 3.8% inebilizumab and 9.4% placebo, and IgM 29.3% inebilizumab and 15.6% placebo. A single adverse reaction of IgG decreased was reported (grade 2, during the OLP). The proportion of inebilizumab-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%. In IgG4-RD study at the end of the 12-month RCP, the total immunoglobulin level was reduced by approximately 12% from baseline for patients treated with inebilizumab as compared to an increase of 21% in patients treated with placebo. The mean decreases from baseline in immunoglobulin G (IgG) and immunoglobulin M (IgM) were approximately 9% and 32%, respectively, in patients treated with inebilizumab, whereas IgG was increased by 26% and IgM was increased by approximately 3% in placebo-treated patients.

Decreased neutrophil counts

In NMOSD study, after 6.5 months of treatment, neutrophil counts between $1.0\text{--}1.5 \times 10^9/\text{L}$ (grade 2) were observed in 7.5% of inebilizumab-treated patients versus 1.8% of placebo-treated patients. Neutrophil counts between $0.5\text{--}1.0 \times 10^9/\text{L}$ (grade 3) were observed in 1.7% of inebilizumab-treated patients versus 0% of placebo-treated patients. In IgG4-RD study during the 12-month RCP, neutrophil counts between $1.0\text{--}1.5 \times 10^9/\text{L}$ were observed in 7.5% of inebilizumab-treated patients versus 3% of placebo-treated patients. Neutrophil counts between $0.5\text{--}1.0 \times 10^9/\text{L}$ were observed in 0% of inebilizumab-treated patients versus 1.5% of placebo-treated patients. Neutropenia was generally transient and was not associated with serious infections.

Decreased lymphocyte counts

In NMOSD study, during 6.5 months of treatment, a reduction in lymphocyte counts was observed more commonly in patients treated with inebilizumab than placebo: lymphocyte counts between $500\text{--}< 800/\text{mm}^3$ (grade 2) were observed in 21.4% of inebilizumab-treated patients versus 12.5% of placebo-treated patients. Lymphocyte counts between $200\text{--}< 500/\text{mm}^3$ (grade 3) were observed in 2.9% of inebilizumab-treated patients versus 1.8% of placebo-treated patients. In IgG4-RD study, during 12 months of treatment in RCP, a reduction in lymphocyte counts was observed more commonly in patients treated with inebilizumab than placebo: lymphocyte counts between $500\text{--}< 800/\text{mm}^3$ (grade 2) were observed in 26.9% of both inebilizumab-treated and placebo-treated patients. Lymphocyte counts between $200\text{--}< 500/\text{mm}^3$ (grade 3) were observed in 10.4% of inebilizumab-treated patients versus 3.0% 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il>

4.9 Overdose

The highest dose of inebilizumab tested in autoimmune patients was 1,200 mg, administered as two 600 mg intravenous infusions separated by 2 weeks. The adverse reactions were similar to what was observed in the inebilizumab 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). The patient should be closely monitored for signs or symptoms of adverse reactions and supportive care instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, selective immunosuppressants, ATC code: L04AA47

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 cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). B cells are believed to play a central role in the pathogenesis of NMOSD and IgG4-RD. The mechanism by which inebilizumab exerts its therapeutic effects in these diseases 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 inebilizumab were assessed with an assay for CD20+ B cells, since inebilizumab can interfere with the CD19+ B-cell assay. Treatment with inebilizumab reduces CD20+ B-cell counts in blood by 8 days after infusion. In the clinical study of 174-NMOSD patients, CD20+ B-cell counts were reduced below the lower limit of normal by 4 weeks in 100% of patients treated with inebilizumab and remained below the lower limit of normal in 94% of patients for 28 weeks after initiation of treatment. In the clinical study of 68-IgG4-RD patients, CD20+ B-cell counts were reduced below the lower limit of normal by week 2 in 100% of patients treated with inebilizumab and remained below the lower limit of normal in 82% and 79% of patients at week 26 and 52, respectively, with 6-month treatment interval. The time to B-cell repletion following administration of inebilizumab is not known.

During the RCP of clinical studies of inebilizumab in NMOSD and IgG4-RD, treatment-emergent anti-drug antibodies (ADAs) were observed in 2.9% and 8.8% of patients, respectively. ADA-positive status appeared to have no clinically relevant impact on PK and PD (B-cell) parameters and did not impact the long-term safety profile. There was no apparent effect of ADA status on the efficacy outcome; however, the impact cannot be fully assessed given the low incidence of ADA associated with inebilizumab treatment.

Clinical efficacy and safety

Neuromyelitis optica spectrum disorders (NMOSD)

The efficacy of inebilizumab for the treatment of NMOSD was studied in 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 inebilizumab treatment in the pivotal study.

Patients were treated with intravenous infusions of inebilizumab 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 (RCP). All potential attacks were evaluated by a blinded, independent, Adjudication Committee (AC), 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 3).

Table 3. 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
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 AC-determined attack in the RCP, or who completed the day 197 visit without an attack, exited the RCP and had the option to enrol into an OLP and initiate or continue treatment with inebilizumab.

A total of 230 patients were enrolled: 213 patients were AQP4-IgG seropositive patients and 17 were seronegative patients were enrolled; 174 patients were treated with inebilizumab and 56 patients were treated with placebo in the RCP of the study. Of the 213 AQP4-IgG seropositive patients, 161 were treated with inebilizumab and 52 were treated with placebo in the RCP of the study. Baseline and efficacy results are presented for the AQP4-IgG seropositive patients.

Baseline demographics and disease characteristics were balanced across the 2-treatment groups (see table 4).

Table 4. Demographics and baseline characteristics of the AQP4-IgG seropositive NMOSD patients

Characteristic	Placebo N = 52	Inebilizumab 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)

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 AC-determined NMOSD attack on or before day 197. Additional key secondary endpoint measures included worsening from baseline in EDSS at last visit during the RCP, change from baseline in low-contrast visual acuity binocular score measured by low-contrast Landolt C Broken Rings Chart at last visit during the RCP, cumulative total active MRI lesions (new gadolinium-enhancing or new/enlarging T2 lesions) during the RCP, 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 OLP, the annualised attack rate across both randomised and open-label treatment was determined.

Results in AQP4-IgG seropositive patients are presented in table 5 and figure 1. In this study, treatment with inebilizumab statistically significantly reduced the risk of an AC-determined NMOSD attack as compared to treatment with placebo (hazard ratio: 0.227, $p < 0.0001$; 77.3% reduction in risk of AC-determined NMOSD attack) in AQP4-IgG seropositive patients. There was no treatment benefit observed in AQP4-IgG seronegative patients.

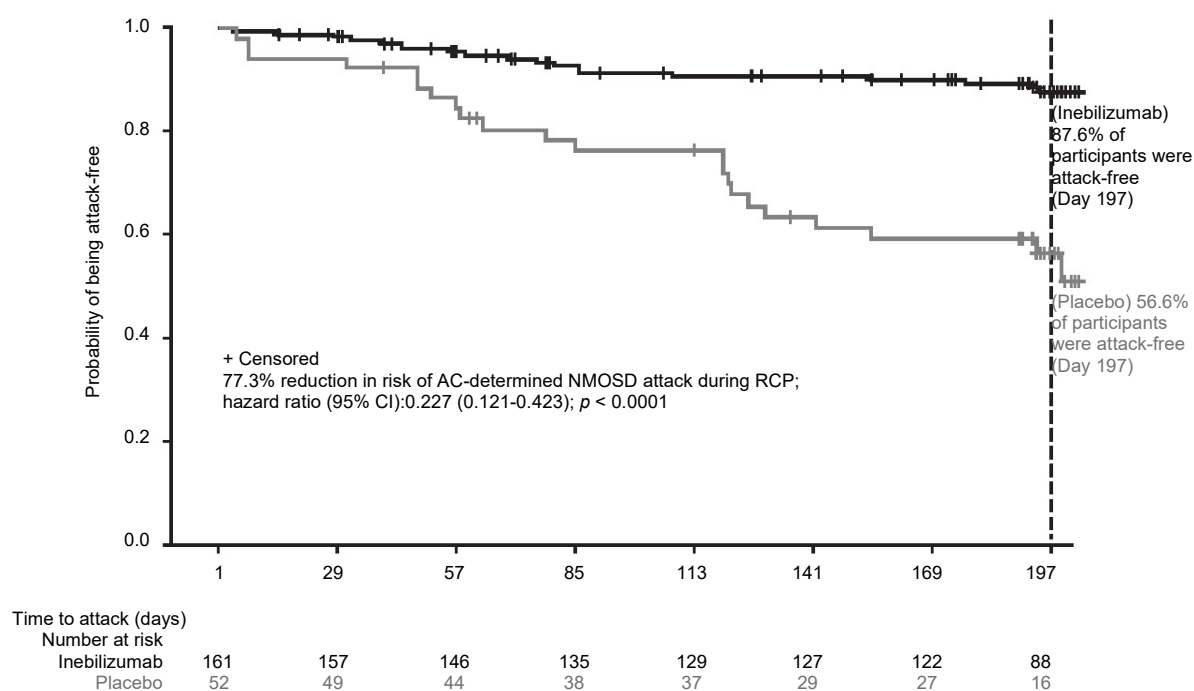
In the inebilizumab group EDSS worsening was significantly less than placebo group (14.9% versus 34.6% of the subjects). There were no differences in the low-contrast visual acuity binocular score between the study arms. The mean cumulative number of total active MRI lesions (1.7 versus 2.3) and mean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

Table 5. Efficacy results in pivotal trial in AQP4-IgG seropositive NMOSD

	Treatment group	
	Placebo N = 52	Inebilizumab 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	0.227 (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 AC-determined NMOSD attack during the RCP in AQP4-IgG seropositive patients



AC = adjudication committee; AQP4-IgG = anti-aquaporin-4 immunoglobulin G; CI = confidence interval; NMOSD = neuromyelitis optica spectrum disorders; RCP = randomised control period.

Across the RCP and OLP, the annualised AC-determined NMOSD attack rate was analysed as a secondary endpoint and in AQP4-IgG seropositive patients treated with inebilizumab the result was 0.09.

Immunoglobulin G4-related disease (IgG4-RD)

The efficacy of inebilizumab for the treatment of IgG4-RD was studied in one randomised (1:1), double-blind, multicentre, 52-week placebo-controlled clinical trial that enrolled 135 adult patients with active IgG4-RD. Patients had active disease, defined by clinical, imaging, laboratory or biopsy features, and required treatment in the judgement of the physician. Eligible patients had newly diagnosed or recurrent IgG4-RD that required glucocorticoid (GC) treatment at screening, had a confirmed history of organ involvement at any time in the course of the disease, and met the 2019 ACR/EULAR classification criteria.

All potential flares during the study were assessed by the investigator and subsequently reviewed by a blinded, independent, adjudication committee, who determined whether the flare met one or more of the protocol-defined, organ-specific flare diagnostic criteria. Disease flare was defined as new/worsening signs or symptoms that were positively adjudicated and warranted treatment by the investigator. Absence of alternative diagnoses was required.

Patients received 300 mg IV of inebilizumab or placebo at Days 1, 15 and 183 of the RCP. Patients were at a uniform dose of glucocorticoids (GCs) at the time of randomisation (equivalent to 20 mg prednisone per day) and then began a prespecified taper of 5 mg per day every 2 weeks to discontinuation at the end of 8 weeks. The use of GCs during the trial was permitted for treatment of IgG4-RD flares, and for other purposes including premedication for investigational treatment, oral GC treatment up to 2 weeks, or at a dose of up to 2.5 mg per day of prednisone or equivalent for treatment of adrenal insufficiency. The concomitant use of biologic and non-biologic immunosuppressive agents was prohibited during the trial. Patients who completed the RCP had the option to enrol in an OLP and initiate or continue treatment with inebilizumab.

227 patients were screened for eligibility. Of the 135 enrolled IgG4-RD patients, 68 patients were randomised to receive inebilizumab and 67 were randomised to receive placebo. Baseline demographics and disease characteristics for IgG4-RD patients during the RCP were balanced across the treatment groups (see table 6). Although no comparator was available during the OLP, treated and AC-determined flares in the open-label treatment period were determined.

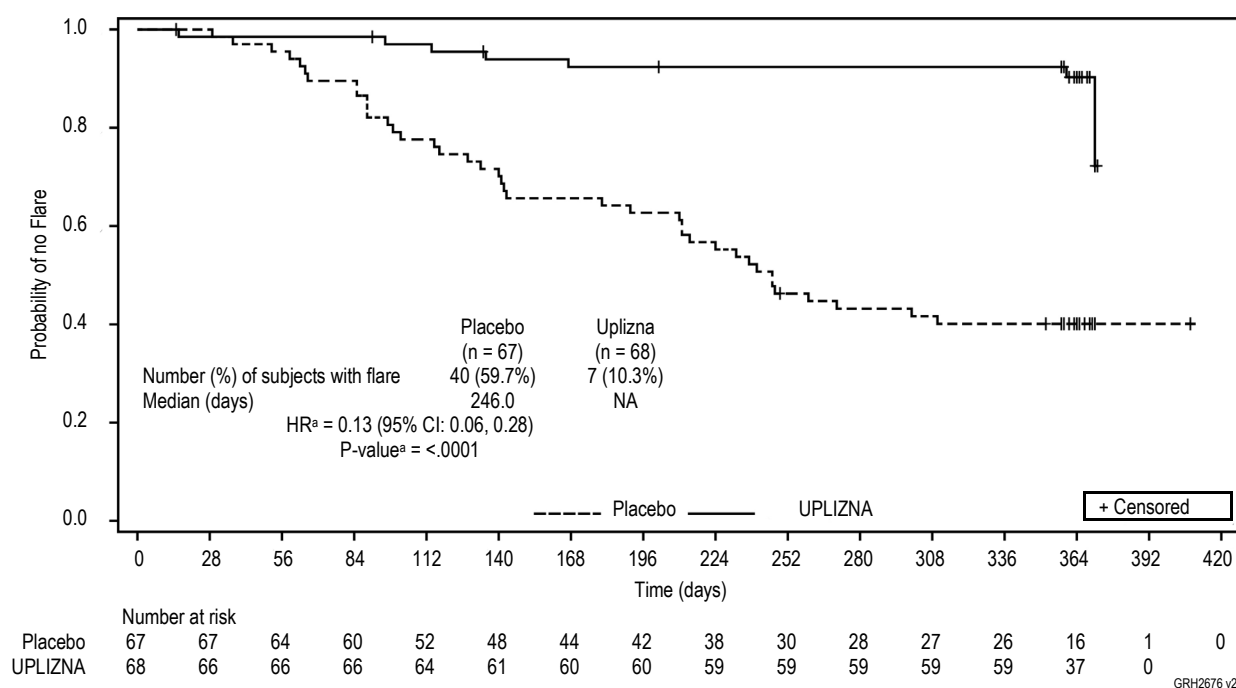
Table 6. Demographics and baseline characteristics of IgG4-RD patients

Characteristic	Placebo N = 67	Inebilizumab N = 68	Overall N = 135
Age (years): mean (standard deviation [SD])	58.2 (12.2)	58.2 (11.5)	58.2 (11.8)
Age ≥ 65 years, n (%)	21 (31.3%)	21 (30.9%)	42 (31.1%)
Sex: Male, n (%)	49 (73.1%)	39 (57.4%)	88 (65.2%)
Disease duration (years): mean (SD)	2.54 (3.06)	2.64 (3.73)	2.59 (3.40)
Ig-G4 manifestation Newly diagnosed	31 (46.3%)	31 (45.6%)	62 (45.9%)
ACR/EULAR Classification Criteria score Mean (SD)	38.3 (11.7)	40.1 (12.1)	39.2 (11.9)
Prior non-glucocorticoid therapy for IgG4-RD Yes	20 (29.9%)	17 (25.0%)	37 (27.4%)
Baseline IgG4-RD Responder Index score Mean (SD)	6.0 (4.0)	5.4 (4.0)	5.7 (4.0)

Results in IgG4-RD patients are presented in figure 2 and table 7.

The study met the primary efficacy endpoint, time to the first treated and AC-determined IgG4-RD flare, which was longer in the inebilizumab group, compared with the placebo group (hazard ratio: 0.13; $p < 0.0001$; see figure 2). The key secondary endpoints were also met with statistical significance (see table 7).

Figure 2. Primary endpoint - Kaplan-Meier plot of time to first treated and AC-determined IgG4-RD flare during the randomised-controlled period



^a Based on Cox regression method, with placebo as the reference group.

Patients who did not complete the RCP and who did not have a treated and AC-determined flare during the RCP were censored at the time of discontinuation.

Table 7. Key secondary efficacy results in IgG4-RD patients

	Treatment group	
	Uplizna N = 68	Placebo N = 67
Annualised flare rate for treated and AC-determined IgG4-RD flares	0.10	0.71
Rate ratio (95% CI) ^a	0.14 (0.06, 0.31)	
p-value ^a	< 0.0001	
Proportion of subjects achieving treatment-free, flare-free complete remission at week 52^b	39 (57.4%)	15 (22.4%)
Odds ratio (95% CI) ^c	4.68 (2.21, 9.91)	
p-value ^c	< 0.0001	
Proportion of subjects achieving corticosteroid-free, flare-free complete remission at week 52^d	40 (58.8%)	15 (22.4%)
Odds ratio (95% CI) ^c	4.96 (2.34, 10.52)	
p-value ^c	< 0.0001	

^a Estimated from the negative binomial regression, with placebo as the reference group.

^b Defined as the lack of evident disease activity (IgG4-RD RI = 0 or investigator's decision) at week 52, no AC-determined flare during the RCP, and no treatment for flare or disease control except the required 8-week GC taper.

^c Based on logistic regression model, with placebo as the reference group.

^d Defined as the lack of evident disease activity (IgG4-RD RI = 0 or investigator's decision) at week 52, no AC-determined flare during the RCP, and no corticosteroid treatment for flare or disease control except the required 8-week GC taper.

The mean (SD) total GC use for IgG4-RD disease control per patient was lower in the inebilizumab group compared with the placebo group, with a mean (SD) of 118.25 (438.97) mg prednisone equivalent versus 1,384.53 (1,723.26) mg prednisone equivalent, respectively during the RCP. The mean (SD) daily GC use during the RCP per patient using GC was 3.34 (2.09) mg prednisone equivalent in the inebilizumab group versus 5.97 (4.20) mg prednisone equivalent in the placebo group. The mean (SD) total GC use during the RCP per patient using GC was 1,148.71 (877.92) mg prednisone equivalent in the inebilizumab group versus 2,208.65 (1,707.56) mg prednisone equivalent in the placebo group.

Available data from the OLP, in which patients continued to receive inebilizumab supports a sustained treatment effect of inebilizumab.

5.2 Pharmacokinetic properties

Absorption

Inebilizumab is administered as an intravenous infusion. In the NMOSD study, the mean maximum concentration was 108 µg/mL (300 mg, second dose on day 15), and the cumulative area under the curve (AUC) of the 26-week treatment period in which NMOSD patients received two intravenous administrations 2-week apart was 2,980 µg × d/mL. In the IgG4-RD study, the mean maximum concentration was 127 µg/mL (300 mg, second dose on day 15), and the cumulative AUC of the 52-week treatment period in which IgG4-RD patients received two intravenous administrations 2 weeks apart, followed by a third dose at week 26 was 4,290 µg × d/mL.

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.

Biotransformation

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

Elimination

In adult patients with NMOSD and IgG4-RD, 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

Paediatric population

Inebilizumab has not been studied in adolescents or children.

Elderly

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

Gender, 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.

Inebilizumab was evaluated in a combined fertility and embryo-foetal development study in female and male huCD19 Tg mice at intravenous doses of 3 and 30 mg/kg. There was no effect on

embryo-foetal development, however, there was a treatment-related reduction in fertility index at both tested doses. The relevance of this finding to humans is unknown. Additionally, there was a decrease in B-cell populations at the site of B-cell development in foetal mice born to inebilizumab-treated animals as compared to the offspring of control animals, suggesting that inebilizumab crosses the placenta and depletes B cells.

Only sparse toxicokinetic samples were collected in the combined fertility and embryo-foetal development study; based on first dose maximum concentration (C_{max}), the exposure multiples of 3 and 30 mg/kg in female huCD19 Tg mice were 0.4-fold and 4-fold, respectively for the 300 mg clinical therapeutic dose.

In a pre-/postnatal development study in transgenic mice, administration of inebilizumab to maternal animals from gestation day 6 to lactation day 20 resulted in depleted B-cell populations in offspring at postnatal day 50. B-cell populations in offspring recovered by postnatal day 357. The immune response to neoantigen in offspring of animals treated with inebilizumab was decreased relative to offspring of control animals, suggestive of impairment of normal B-cell function.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose dihydrate
Sodium chloride
L-Histidine hydrochloride monohydrate
L-Histidine
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after dilution

The prepared infusion solution should be administered immediately. If not administered immediately, store up to 24 hours in a refrigerator at 2°C to 8°C or 4 hours at room temperature prior to the start of the infusion.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Do not freeze. Do not shake.

Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL of concentrate in a Type 1 glass vial with an elastomeric stopper and a mist gray flip-off aluminium seal.

Pack size of 3 vials.

6.6 Special precautions for disposal

Preparation of infusion solution

Prior to the start of the intravenous infusion, the prepared infusion solution should be at room temperature between 20°C and 25°C.

The concentrate should be visually inspected for particulate matter and discolouration. The vial should be discarded if the solution is cloudy, discoloured, or it contains discrete foreign particulate matter.

- The vial should not be shaken.
- The vial should be stored upright.
- Obtain an intravenous bag containing 250 mL of sodium chloride 9 mg/mL (0.9%) solution for injection. Do not use other diluents to dilute inebilizumab as their use has not been tested.
- Use only a 21-gauge or smaller bore needle (e.g., 22 or 23-gauge) to puncture the vial stopper. Do not use vial spikes or closed system transfer devices, as these may damage the stopper and compromise vial integrity.
- 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.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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9. LICENSE NUMBER

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