swissmedic

Date: 22 March 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Uplizna

International non-proprietary name: inebilizumab
Pharmaceutical form: concentrate for solution for infusion
Dosage strength(s): 100 mg/10mL
Route(s) of administration: intravenous use
Marketing authorisation holder: Horizon Therapeutics
Marketing authorisation no.: 69322
Decision and decision date: approved on 4 March 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for inebilizumab in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a[decies] no. 2 of the TPA.
Orphan drug status was granted on 10 May 2023.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

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 (see section "Warnings and Precautions").

2.2.2 Approved indication

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 (see section "Properties/effects").

2.2.3 Requested dosage

Summary of the requested standard dosage:
Initial doses
The recommended loading dose is a 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 a 300 mg intravenous infusion every 6 months. Inebilizumab is for chronic treatment.

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.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	2 June 2023
Formal control completed	29 June 2023
Preliminary decision	26 October 2023
Response to preliminary decision	3 December 2023
Final decision	4 March 2024
Decision	approval

Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority, the EMA. This SwissPAR relates to the publicly available assessment report Uplizna, Reference Number EMA/266309/2022, issued by the EMA.

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The SwissPAR relating to quality aspects refers to the publicly available assessment report Uplizna, Reference Number EMA/266309/2022, issued by the EMA.

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Uplizna, Reference Number EMA/266309/2022, issued by the EMA.

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The clinical aspects in this SwissPAR refer to the publicly available assessment report Uplizna, Reference Number EMA/266309/2022, issued by the EMA.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Uplizna was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See «Undesirable effects» for advice on the reporting of adverse reactions.

Uplizna®

Composition

Active substances

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

Excipients

Histidine, histidine hydrochloride monohydrate, sodium chloride, trehalose dihydrate, Polysorbate 80 (E433), water for injections.
This medicinal product contains 16.1 mg of sodium per vial.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion (sterile concentrate)
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.
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.

Indications/Uses

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 (see «Properties/Effects»).

Dosage/Administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of NMOSD 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 «Warnings and precautions»).

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 «Contraindications» and «Warnings and precautions»)

- Hepatitis B virus (HBV) screening (see «Contraindications» and «Warnings and precautions»)
- Hepatitis C virus (HCV) screening and treatment started prior to initiating inebilizumab treatment (see «Warnings and precautions»)
- Evaluate for active tuberculosis and test for latent infection (see «Contraindications» and «Warnings and precautions»)

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 «Warnings and precautions»).
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 «Properties/Effects»).

Usual dosage

Initiation of treatment

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 therapy

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

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 «Warnings and precautions»).

To ensure traceability of biotechnnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Special dosage instructions

Patients with hepatic and renal disorders

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 «Pharmacokinetics»).

Elderly patients

Inebilizumab has been administered to 6 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 «Pharmacokinetics»).

Children and adolescents

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

Delayed administration

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

Mode 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 «Instructions for handling».

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in «Composition»
- 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

Warnings and precautions

Infusion-related reactions and hypersensitivity

Inebilizumab 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 inebilizumab (see «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 «Dosage/Administration»). A 2-week course of oral corticosteroids (plus a 1-week taper) was administered at the start of inebilizumab treatment in the pivotal study (see «Properties/Effects»).

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 «Undesirable effects»).
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%).

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 «Contraindications»).

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.
In inebilizumab clinical trials, one subject died following the development of new brain lesions for which a definitive diagnosis could not be established. However, the differential diagnosis included 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 «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 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 «Contraindications»).
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 immunizations should be administered according to immunization guidelines at least 4 weeks prior to initiation of inebilizumab. The efficacy and safety of immunization 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. B-cell depletion below the lower limit of normal was maintained in 94% of patients for at least 6 months following treatment.

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 «Pregnancy, lactation»). 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 (see «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.

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.

Interactions

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 «Warnings and precautions»).

Immunosuppressants

Inebilizumab has been tested, and is intended to be used, as monotherapy for this indication. No data are available on the safety or efficacy of combining inebilizumab with other immunosuppressants. 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 inebilizumab.
Concomitant usage of inebilizumab with immunosuppressants, including systemic corticosteroids, may increase the risk of infection. The effects of inebilizumab on Bcells 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 «Properties/Effects»).

Pregnancy, 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 «Preclinical data»).
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 «Preclinical data»). 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 «Warnings and precautions» and «Properties/Effects»). 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 «Warnings and precautions»).

Lactation

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 «Preclinical data»).

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.

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%), and back pain (13.8%) across both the RCP and 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%).

List of adverse reactions

Adverse reactions reported in the clinical trial of inebilizumab in NMOSD are listed in Table 2 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).

Table 2. Adverse reactions

MedDRA System Organ Class	Adverse reaction	Frequency
Infections and infestations	Urinary tract infection (26.2%), respiratory tract infection (15.6%), nasopharyngitis (20.9%),	Very Common

MedDRA System Organ Class	Adverse reaction	Frequency
	Pneumonia, influenza, 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 (17.3%), back pain (13.8%)	Very Common
Investigations	Immunoglobulins decreased (3.8% - 29.3%)	Very Common
Injury, poisoning and procedural complications	Infusion-related reaction (12.9%)	Very Common

Description of specific adverse reactions and additional information

Infusion-related reactions

Inebilizumab can cause infusion-related reactions, which can include headache, nausea, somnolence, dyspnoea, fever, myalgia, rash, 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-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

An infection was reported by 74.7% of NMOSD patients treated with inebilizumab across the RCP and OLP. 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 inebilizumab-treated patient were urinary tract infection (4.0%) and pneumonia (1.8%). See «Warnings and precautions» for action to be taken in case of infection.

Opportunistic and serious infections

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 «Warnings and precautions» for action to be taken in case of infection.

Laboratory abnormalities

Decreased immunoglobulins

Consistent with its mechanism of action, average immunoglobulin levels decreased with inebilizumab use. 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%.

Decreased neutrophil counts

After 6.5 months of treatment, neutrophil counts between 1.0-1.5 x 10^9/l (Grade 2) were observed in 7.5% of inebilizumab-treated patients versus 1.8% of placebo-treated patients. Neutrophil counts between 0.5-1.0 x 10^9/l (Grade 3) were observed in 1.7% of inebilizumab-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 inebilizumab than placebo: lymphocyte counts between 500and < 800/mm^3 (Grade 2) were observed in 21.4% of inebilizumab-treated patients versus 12.5% of placebo-treated patients. Lymphocyte counts between 200 and < 500/mm^3 (Grade 3) were observed in 2.9% of inebilizumab-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.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

The highest dose of inebilizumab 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 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 «Warnings and precautions»). The patient should be closely monitored for signs or symptoms of adverse reactions and supportive care instituted as required.

Properties/Effects

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 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.

Pharmacodynamics

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 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 inebilizumab 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.
In the pivotal study of NMOSD patients the prevalence of anti-drug antibodies (ADA) was 14.7% at the end of the OLP; the overall incidence of treatment-emergent ADA was 7.1% (16 of 225) and the occurrence and titer of ADA positive timepoints decreased over time with inebilizumab treatment.

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

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	2 criteria based on changes in pyramidal, bladder/bowel, or	2 criteria based on changes in pyramidal, bladder/bowel, or sensory functional scores PLUS

Domain	Representative symptoms	Clinical-only findings	Clinical PLUS radiological findings
	Lhermitte's sign (not in isolation)	sensory functional scores	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; 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)

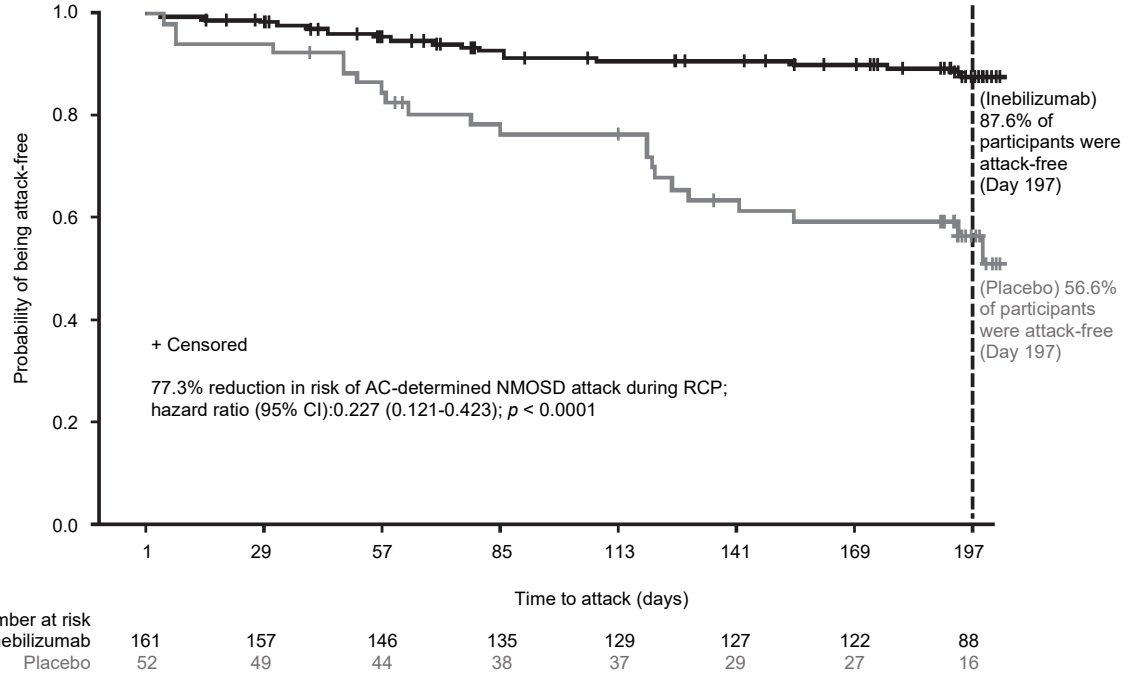
Rescue therapy was initiated as needed for NMOSD attacks. All patients were pre-medicated prior to investigational product administration to reduce the risk of infusion-related reactions.
The primary efficacy endpoint was time (days) from Day 1 to onset of an AC-determined NMOSD attack on or before Day 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 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 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.

Pharmacokinetics

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.

Elimination

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

Kinetics in specific patient groups

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.

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.

Elderly patients

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

Children and adolescents

Inebilizumab has not been studied in adolescents or children.

Gender, race

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

Preclinical 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.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date «EXP» stated on the pack.

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.

Special precautions for storage

Store in a refrigerator (2-8°C).

Do not freeze.
Store in the original packaging in order to protect the contents from light.
For storage conditions after dilution of the medicinal product, see section «Shelf life after dilution».
Keep out of the reach of children.

Instructions for handling

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.
- 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.

Authorisation number

69322 (Swissmedic)

Packs

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. (A)

Marketing authorisation holder

Horizon Therapeutics Switzerland GmbH,
6300 Zug

Date of revision of the text

October 2023