יולי 2026

UPLIZNA (Inebilizumab 10 mg/mL)
Concentrate for Solution for Infusion

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,
אמג'ן אירופה בי. וי., בעלת הרישום, שמחה לבשר על הרחבת ההתוויה ועדכונים בעלון לרופא לתכשיר UPLIZNA.

השינויים המהותיים מפורטים להלן. קו תחתי מציין תוספת טקסט וקו חוצה מציין מחיקת טקסט.

ההתוויות הרשומות לתכשיר:

Neuromyelitis optica spectrum disorders (NMOSD)

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.

Immunoglobulin G4-related disease (IgG4-RD)

Immunoglobulin G4-related disease (IgG4-RD) Uplizna is indicated for the treatment of adult patients with active IgG4-RD.

העדכונים בעלון לרופא:

4.1 Therapeutic indications

Neuromyelitis optica spectrum disorders (NMOSD)

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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

Maintenance doses

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

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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.

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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). ~~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 section 5.1).~~

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Infections:

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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%).

Progressive multifocal leukoencephalopathy (PML)

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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.

B-cell repletion time

The time to B-cell repletion following administration of inebilizumab is not known (see section 5.1). ~~B-cell depletion below the lower limit of normal was maintained in 94% of patients for at least 6 months following treatment.~~

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 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).

4.6 Fertility, pregnancy, and lactation

Pregnancy

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).

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%), ~~and~~ back pain (13.8%), and lymphopenia (10.7%) across both the randomised controlled period (RCP) and open-label period (OLP).

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Tabulated list of adverse reactions

Adverse reactions reported in ~~the~~ clinical trials and post-marketing experience following treatment with ~~of~~ inebilizumab ~~in NMOSD~~ are listed in ~~Table~~ 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 reported in inebilizumab clinical trials, including patients with NMOSD and IgG4-RD as well as from post-marketing experience

MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**
Blood and lymphatic system disorders	Lymphopenia*		
Musculoskeletal and connective tissue disorders		Myalgia	
General disorders and administration site conditions		Pyrexia	

* 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 ~~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 d~~D~~uring the RCP, no opportunistic infections occurred in either treatment group, and a single ~~Grade~~ 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~~ 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, a~~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~~ 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, a~~A~~fter 6.5 months of treatment, neutrophil counts between 1.0-1.5 × 10^9/L (~~Grade~~ 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 × 10^9/L (~~Grade~~ 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 1.0-1.5 × 10^9/L were observed in 7.5% of inebilizumab-treated patients versus 3% of placebo-treated patients. Neutrophil counts between 0.5-1.0 × 10^9/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 ~~After~~ 6.5 months of treatment, a reduction in lymphocyte counts was observed more commonly in patients treated with inebilizumab than placebo: lymphocyte counts between 500-< 800/mm^3 (~~Grade~~ grade 2) were observed in 21.4% of inebilizumab-treated patients versus 12.5% of placebo-treated patients. Lymphocyte counts between 200-< 500/mm^3 (~~Grade~~ 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-< 800/mm^3 (grade 2) were observed in 26.9% of both inebilizumab-treated and placebo-treated patients. Lymphocyte counts between 200-< 500/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.

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 cytolysis (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 ~~precise~~ mechanism by which inebilizumab exerts its therapeutic effects in these diseases ~~NMOSD~~ is unknown but is presumed to involve B-cell depletion and may include the suppression of antibody secretion, antigen presentation, ~~B~~ B-cell~~-T~~ 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 ~~a~~ 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. ~~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.

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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

Graph was added

[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.

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6.6 Special precautions for disposal

Preparation of infusion solution

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- 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.

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העלון לרופא נשלח לפרסום במאגר התרופות של אתר משרד הבריאות, וניתן לקבלו גם על-ידי פניה למפיץ המקומי של התרופה, חברת מדיסון פארמה.
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בברכה,
אמג'ן אירופה בי. וי.