Nye metoder - Request for assessment of medicinal product

To request an assessment of a new medicinal product or a new indication for an existing medicinal product through Nye metoder, health technology developers should complete this form. By submitting a request for assessment, the developer signals that it plans to submit documentation for such an assessment.

Please send the completed form to Nye metoder by e-mail: nyemetoder@helse-sorost.no.

A request for assessment may not be submitted prior to day 120 of the European Medicines Agency (EMA) marketing authorisation assessment process for new medicinal products under regular approval procedure, or prior to day 1 for variation/extension assessments and for medicinal products under accelerated assessment.

This form must be completed in its entirety. Nye metoder will plan the assessment process based on the information provided in the request form.

At the time of request for assessment, the health technology developer must have a plan for when it intends to submit documentation for assessment.

Information about Nye metoder can be found online (nyemetoder.no). Please contact Sekretariatet for Nye metoder if you have any questions.

Please note: The form will be published in its entirety.

The submitter is aware that the form will be published in its entirety (**tick**): ☑

1 Contact information	
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External representation Name/Organization Phone/E-mail *PLEASE NOTE: For external representation, please attach an authorisation/power of attorney*	

2 Medicinal product overview

Does the request concern a new active substance?	Yes
Trade name	Uplizna
Generic name	Inebilizumab
Marketing authorisation in Norway	Yes (through central EMA procedure)
ATC code	L04AA47
Mode of administration	Intravenous injection
Pharmacotherapeutic group and mechanism of action *Briefly describe*	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.
Expected indication relevant to the request *Expected indication must be written in Norwegian*	As monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive. Som monoterapi for behandling av voksne pasienter med neuromyelitis opticaspektrumforstyrrelser (NMOSD) som er anti-akvaporin-4 immunglobulin G (AQP4-IgG)-seropositive

3 Assessment history

Has the medicinal product previously been assessed by Nye metoder for other indications? *If yes, enter the Nye metoder ID number*	No, it has not.
Are you aware of other medicinal products assessed by Nye metoder for the same indication? *If yes, enter the Nye metoder ID number*	Yes, there have been two previous assessments: 1) ID2020_013 satralizumab (Enspryng) 2) ID2019_043 ekulizumab (Soliris)

4 Expected timeline	
Procedure number for the marketing authorisation assessment in EMA	EMEA/H/C/005818/0000
Expected date (month/year) of CHMP positive opinion	CHMP positive opinion issued in 11/2021
Expected date (month/year) of marketing authorisation in Norway	EMA marketing authorisation issued in 04/2022
Expected date (quarter/year) for submission of documentation to Norwegian Medicines Agency *Dates must be stated*	April 2024

5 Diagnostics and resource use Fill inn where relevant	
Will the new method require diagnostic testing for biomarker analysis?	No.
Which biomarker(s) are relevant and which publications describe this? *Please refer to publications*	Not applicable.
Do you know whether diagnostics can be performed by the public health service or whether it must be performed by an external supplier?	Not applicable.
Will introduction of the new method require establishment of other/new infrastructure? *For example, custom analysis machine, digital pathology/ AI-based analysis, proteomics, functional tests etc.?*	No.
Pre-analytical requirements *For example, biopsies, other sampling, sample processing etc. are required.*	Not applicable.

Test execution: is there a need to establish one specific test or is a biomarker already established in the health service (e.g. in gene panels)?	Not applicable.
Description of reading of results including data analysis program if necessary.	Not applicable.
Which patient groups need to be tested, and what is the expected proportion of findings that provide treatment options?	Not applicable.

6 Description of the disease and current treatments

Description of the disease *<u>Brief</u> description of the pathophysiology and clinical presentation/symptoms, possibly including references*	Neuromyelitis optica spectrum disorder (NMOSD) is a rare, chronic, autoimmune, inflammatory disorder of the central nervous system (CNS) [Uplizna EPAR report 2021]. Clinical manifestations of NMOSD are variable but are, in 80-90% of cases, unified by the detection of AQP4-IgG autoantibodies in serum or cerebrospinal fluid [Jacob et al. 2013, Jarius et al. 2010]. The disease is characterised by attacks of predominantly optic neuritis and longitudinally extensive transverse myelitis, and, less frequently, affecting the brain and brainstem. Commonly reported symptoms include ocular pain, unilateral and bilateral loss of visual acuity that can reach blindness, loss of sensation, weakness including paraplegia, bladder and bowel dysfunction, paroxysmal tonic spasms of the trunk and limbs, and Lhermitte's phenomenon [Wingerchuk et al, 2006]. Women are more often affected than men [Uplizna EPAR report 2021].
Therapeutic area *Specify which field best describes the method*	Immunologi Infeksjonssykdommer Kreftsykdommer (velg kreftområde i neste kolonne)* Lunge- og luftveissykdommer Mage- og tarmsykdommer
Cancer *If the method applies to the medical field of cancer, specify which type of cancer is relevant*	* Ingen Kreftsykdom Bein- og bløtvevskreft Blod- beinmargs- og lymfekreft Brystkreft Mage- og tarmkreft
Current treatment *Current standard treatment in Norway, including references*	Current treatments for NMOSD are aimed at prevention of attacks, acute management of attacks, and amelioration of persistent symptoms [Kessler et al. 2016]. The prevention of attacks is an important aspect as disability in patients with NMOSD is mainly a result of poor and incomplete recovery from clinical attacks [Kumpfel et al. 2023]. Patients with NMOSD have been treated prophylactically for attack prevention with off-label IST such as azathioprine, mycophenolate mofetil, daily prednisone, or rituximab. High-dose steroids and plasmapheresis are generally used for the acute management of attacks. Symptomatic treatments are used to address symptoms, which can include general and neuropathic pain (e.g, anti-epileptics, anti-spasmodics, anti-depressants, or analgesics), bowel (e.g, laxatives), bladder (e.g, bethanechol), and fatigue and depression (e.g, psychotherapy or medication) disorders [Kessler et al, 2016]. Norwegian treatment guidelines on NMOSD are described in NevroNEL

Prognosis *Describe the prognosis with current treatment options, including references*	The severity of initial and subsequent attacks, and the number of subsequent attacks, are key prognostic factors in NMOSD. If patients are untreated, early and severe disability is common. Timely diagnosis and treatment are essential to improve prognosis [Huda et al. 2019]. Patients with NMOSD have a twelve-fold higher risk of death than that of patients with multiple sclerosis [Bichuetti et al. 2013]. Estimates of mortality due to NMOSD have varied considerably, from 9% to 32%, and depend on age, relapse rate, and recovery from attacks.
The new medicinal product's placement in the treatment algorithm	In line with its indication, inebilizumab is intended as monotherapy for the treatment of adult patients with NMOSD who are AQP4-IgG seropositive. Although there are currently no official Norwegian treatment guidelines available, it is anticipated that due to its mechanism of action (CD19+ depletion compared to CD20+ depletion [Chen et al. 2016, Forsthuber et al. 2018]) and its demonstrated long-term efficacy and safety [European Medicines Agency 2021, Cree et al. 2019, Nie et al. 2022, Rensel et al. 2022], inebilizumab will be a relevant treatment alternative in this patient group.
Patient population *Description, incidence and prevalence of the patient population covered by the relevant indication* in Norway, including references.* *Number of Norwegian patients assumed to be relevant for new method* ** The entire patient group covered by the indication in question is to be described*	The relevant patient population are adult patients with NMOSD. NevroNEL states the prevalence of NMOSD is around 1 per 100,000 [https://legehandboka.no]. From Danish cohort studies, the prevalence is estimated to be between 1.09-1.68 per 100,000 and incidence to be between 0.7-1.5 per million [Asgari et al. 2019, Papp et al. 2018, Dale et al. 2018]. A Swedish cohort study estimated the prevalence and incidence in Sweden to be 10.4 per million and 0.79 per million, respectively [Jonsson et al. 2019].

7 Comparability to other medicinal products and inclusion in tender

Are there existing procurements or tenders in the therapeutic area?	No
Are there other medicinal products with a similar mechanism of action and/or similar effect (for the same indication)?	No
Does the supplier consider the medicinal product to be comparable to other medicinal products?	No.

8 Relevant clinical trials
(pivotal trial(s) and clinical studies relevant for establishing relative efficacy)

	Study 1	Study 2	Study 3
Study ID *Study name, NCT number, hyperlink*	N-MOmentum trial (NCT02200770, available from: https://clinicaltrials.gov/study/NCT02200770?cond=NMOSD&term=inebilizumab&rank=2)		
Study type and design	Multicentre, double-blind, randomised, placebo-controlled phase 2/3 trial with an open-label extension period (OLP)		
Objective	The aim of the N-MOmentum study was to assess the efficacy and safety of B-cell depletion with inebilizumab as a monotherapy in reducing the risk of attacks and disability in NMOSD		
Population *Important inclusion and exclusion criteria*	Inclusion: - Adults (18 years and older) with an EDSS score ≤ 7.5 (≤ 8.0 if the Investigator and medical monitor agreed that the subject was reasonably able to participate in the study) - A diagnosis of NMOSD at the time of screening - A documented history of ≥ 1 NMOSD attacks that required rescue therapy in the previous year or ≥ 2 NMOSD attacks that required rescue therapy in the preceding 2 years Exclusion: - Use of background IST while on trial was not permitted		
Intervention (n) *Dosage, dosing interval, duration of treatment*	Inebilizumab, given as 300mg dose on Day 1 and Day 15 of the randomised period. During open-label period, inebilizumab was given on Day 1 and placebo on Day 15 (to maintain masking) followed by inebilizumab every 26 weeks .		
Comparator (n) *Dosage, dosing interval, duration of treatment*	Placebo, given on Day 1 and Day 15 of the randomised period. During open-label period, patients could switch to inebilizumab and receive a dose of 300mg on Day 1 and Day 15, followed by one dose every 26 weeks.		
Endpoints *Primary, secondary and exploratory endpoints, including definition, measurement method and, if applicable, time of measurement*	The primary efficacy endpoint was time (days) from Day 1 to onset of an Adjudication Committee (AC)-determined NMOSD attack on or before Day 197. Secondary endpoints included: - Worsening from baseline in EDSS at last visit during the RCP. A subject will be considered to have a worsening in overall EDSS score if one of the following criteria is met: o Worsening of 2 or more points in EDSS score for subjects with baseline score of 0. o Worsening of 1 or more points in EDSS score for subjects with baseline score of 1 to 5. o Worsening of 0.5 points or more in EDSS score for subjects with baseline score of 5.5 or more. - 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 magnetic resonance imaging (MRI) lesions (new Gd-enhancing or new/enlarging T2) during the RCP. - Number of NMO/NMOSD-related in-patient hospitalisations. In-patient hospitalisation is defined as more than an overnight stay. Hospitalisations for the administration of NMO-related medications or procedures only were not counted when measuring this variable. - Annualised relapse rate (ARR, total number of AC-determined NMO/NMOSD attacks normalised by person-years) during any exposure to		
Relevant subgroup analyses *Description of any relevant subgroup analyses*	Sex (male vs female), baseline EDSS (< 5 vs ≥ 5), number of prior NMOSD relapses (< 2 vs ≥ 2), disease duration category (< 5 years vs ≥ 5 years), AQP4-IgG serostatus (positive vs negative) as determined at screening were the five subgroup analyses which were performed for the intention-to-treat (ITT) population on the efficacy endpoints. Per the US FDA's request, subgroup analyses by race, site region, and previous treatment for the prevention of NMO attacks on the primary endpoint were performed.		

	Study 1	Study 2	Study 3
Follow up time *If the study is ongoing, indicate the follow-up time for the data expected to be available for assessment by the Norwegian Medicines Agency as well as the expected/planned total follow-up time for the study*	The randomised controlled period for each participant was up to 197 days or until the occurrence of an adjudicated attack (2, 3). All participants were followed-up for 12 months after the last dose as safety follow-up.		
Time perspective results *Ongoing or completed study? Available and future data cut-offs*	Completed study		
Publications *Title, author, journal, year. Expected date of publication*	Cree BAC, Bennett JL, Kim HJ, Weinshenker BG, Pittock SJ, Wingerchuk DM, Fujihara K, Paul F, Cutter GR, Marignier R, Green AJ, Aktas O, Hartung HP, Lublin FD, Drappa J, Barron G, Madani S, Ratchford JN, She D, Cimbora D, Katz E; N-MOmentum study investigators. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Lancet. 2019 Oct 12;394 (10206):1352-1363. Fujihara K, Kim HJ, Saida T, Misu T, Nagano Y, Totsuka N, Iizuka M, Kido S, Terata R, Okumura K, Hirota S, Cree BAC. Efficacy and safety of inebilizumab in Asian participants with neuromyelitis optica spectrum disorder: Subgroup analyses of the N-MOmentum study. Mult Scler Relat Disord. 2023 Aug 20;79:104938. Flanagan EP, Levy M, Katz E, Cimbora D, Drappa J, Mealy MA, She D, Cree BAC.		

9 Ongoing and planned studies

Are there ongoing or planned studies for the medicinal product within the same indication that may provide further information in the future? *If yes, state the expected time perspective for data availability*	There are four ongoing studies: 1) NCT05909761, expected completion date is August 2023 2) NCT05549258, expected completion date is April 2027 3) NCT06068829, expected completion date is June 2025 4) NCT05891379, expected completion date is July 2025
Are there ongoing or planned studies for the medicinal product for other indications?	There are four ongoing studies: 1) NCT04540497, expected completion date is October 2028 2) NCT04524273, expected completion date is March 2029 3) NCT05198557, expcted completion date is July 2026 4) NCT04372615, expected completion date is August 2026

10 Expected health economic documentation

Enter information about the expected health economic analysis

Type of health economic analysis *E.g. cost-per-QALY analysis or cost minimisation analysis* *(Justify the proposal)*	The health economic analysis is planned to be presented in form of a cost-utility analysis. This is based on the observation from the clinical trial that inebilizumab has shown better efficacy compared to placebo.
The patient population on which the health economic analysis is based, including any subgroups. *The main analysis (base case) shall include the entire patient population covered by the indication sought.*	The model will include adult patients with NMOSD who are AQP4-seropositive based on the patient population from the pivotal inebilizumab trial (the N-MOmentum trial).
What type of documentation will form the basis for estimating relative efficacy? *(Direct or indirect evidence)*	The efficacy calculations will be based on direct evidence from the N-MOmentum trial.
What type of documentation will form the basis for health-related quality of life data?	Health state utility values in the model is envisioned to be based on patient-level data from the N-MOmentum trial. The N-MOmentum trial collected HRQoL data via the SF-36v2 Health Survey at regular 12-week intervals and immediately following the occurrence of an adjudicated NMOSD attack. The SF-36v2 measure of HRQoL will be converted into estimates of health utility. In the model, the measures derived from the Rowen algorithm are planned to be applied.
Expected pharmaceutical budget impact per year, in the 5-year period following a potential approval	Will be submitted with the application.

11 Suitable for FINOSE?

Can the method be appropriate for assessment through FINOSE (yes/no) *If no, why not?*	No.

12 Other relevant information

Disclose other aspects that Nye metoder should be aware of.

Have you been in contact with clinicians at Norwegian health trusts about this medicinal product/ indication? Yes/no *If so, who have you been in contact with and what have been their contribution?* *(Relevant information in connection with the recruitment of experts in the field at Nye metoder)*	No
Are there specific circumstances related to the medicinal product implying that a plain discount may not be appropriate for fulfilment of the priority criteria (yes/no)? *If yes, a separate form must be completed and sent nyelegemidler@sykehusinnkjop.no at the same time as documentation is sent to the Norwegian Medicines Agency for a health technology assessment.* *Information and form:* https://www.sykehusinnkjop.no/om-oss/informasjon-og-opplering/	No
Any other relevant information?	References: Asgari N, Lillevang ST, Skejoe HPB, Kyvik KO. Epidemiology of neuromyelitis optica spectrum disorder in Denmark (1998-2008, 2007-2014). Brain Behav. 2019;9(7):e01338. Bichuetti DB, Oliveira EM, Souza NA, Tintore M, Gabbai AA. Patients with neuromyelitis optica have a more severe disease than patients with relapsingremitting multiple sclerosis, including higher risk of dying of a demyelinating disease. Arq Neuropsiquiatr. 2013;71(5):275-9. Cree BAC, Bennett JL, Kim HJ, Weinshenker BG, Pittock SJ, Wingerchuk DM, Fujihara K, Paul F, Cutter GR, Marignier R, Green AJ, Aktas O, Hartung HP, Lublin FD, Drappa J, Barron G, Madani S, Ratchford JN, She D, Cimbora D, Katz E; N-MOmentum study investigators. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Lancet. 2019 Oct 12;394(10206):1352-1363. Cree BA, Bennett JL, Kim HJ, Weinshenker BG, Pittock SJ, Wingerchuk D, Fujihara K, Paul F, Cutter GR, Marignier R, Green AJ, Aktas O, Hartung HP, Williams IM, Drappa J, She D, Cimbora D, Rees W, Ratchford JN, Katz E. Sensitivity analysis of the primary endpoint from the N-MOmentum study of inebilizumab in NMOSD. Mult Scler. 2021 Nov;27(13):2052-2061. Dale GH, Svendsen KB, Gjelstrup MC, Christensen T, Houen G, Nielsen E, et al. Incidence of neuromyelitis optica spectrum disorder in the Central Denmark Region. Acta Neurol Scand. 2018;137 (6):582-8. European Medicines Agency. EPAR assessment report - Uplizna (EMEA/H/C/005818/0000). 2021. Flanagan EP, Levy M, Katz E, Cimbora D, Drappa J, Mealy MA, She D, Cree BAC. Inebilizumab for treatment of neuromyelitis optica spectrum disorder in patients with prior rituximab use from the N-MOmentum Study. Mult Scler Relat Disord. 2022 Jan;57:103352. Fujihara K, Kim HJ, Saida T, Misu T, Nagano Y, Totsuka N, Iizuka M, Kido S, Terata R, Okumura K, Hirota S, Cree BAC. Efficacy and safety of inebilizumab in Asian participants with neuromyelitis optica spectrum disorder: Subgroup analyses of the N-MOmentum study. Mult Scler Relat Disord. 2023 Aug 20;79:104938.