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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2 Medicinal product overview

Does the request concern a new active substance?	Yes
Trade name	To be confirmed following European Medicines Agency (EMA) approval
Generic name	Elafibranor
Marketing authorisation in Norway	Ipsen Pharma SAS
ATC code	A05AX06
Mode of administration	Film-coated tablet for oral use
Pharmacotherapeutic group and mechanism of action *Briefly describe*	Other drugs for bile therapy (A05AX). Elafibranor is a novel, first-in-class peroxisome proliferator-activated receptor (PPAR) α/δ co-agonist. PPARs are ligand-activated nuclear transcription factors, which play a key role in bile acid metabolism and inflammation. There are three PPAR isotypes (α, δ and γ), of which elafibranor specifically activates two: PPARα and PPARδ [1,2]. Due to its unique dual mechanism of action, elafibranor acts upon complementary pathways in primary biliary cholangitis (PBC): - Activation of PPARα results in detoxification and excretion of bile acids, as well as inhibition of bile acid synthesis [2]. Together, these mechanisms reduce the concentration of bile acids in the liver and thereby reduce the level of hepatic damage due to cholestasis in patients with PBC [2,3]. - Activation of PPARδ leads to beneficial effects on bile homeostasis, including regulation of transport and absorption of bile compounds, and provides anti-fibrotic activity [4]. Moreover, PPARα and PPARδ activation has anti-inflammatory effects by acting on nuclear factor kappa B (NF-κB) and B-cell lymphoma 6 (BCL6) pathways [2,5,6]. In summary, elafibranor decreases both bile output, bile toxicity, inflammation and fibrosis.
Expected indication relevant to the request *Expected indication must be written in Norwegian*	Treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults with inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. Behandling av primær biliær kolangitt; enten i kombinasjon med ursodeoksykolsyre (UDCA) hos voksne med en utilstrekkelig respons på UDCA, eller som monoterapi hos voksne som ikke tåler UDCA.

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
Are you aware of other medicinal products assessed by Nye metoder for the same indication? *If yes, enter the Nye metoder ID number*	No

4 Expected timeline	
Procedure number for the marketing authorisation assessment in EMA	EMEA/H/C/0006231
Expected date (month/year) of CHMP positive opinion	September 2024
Expected date (month/year) of marketing authorisation in Norway	November 2024
Expected date (quarter/year) for submission of documentation to Norwegian Medicines Agency *Dates must be stated*	Q3 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*	N/A
Do you know whether diagnostics can be performed by the public health service or whether it must be performed by an external supplier?	N/A
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.*	N/A

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)?	No
Description of reading of results including data analysis program if necessary.	N/A
Which patient groups need to be tested, and what is the expected proportion of findings that provide treatment options?	N/A

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*	PBC is a rare, progressive, chronic autoimmune disease of the liver, characterised by the slow destruction of small intrahepatic bile ducts [3,7]. This prevents the flow of bile, causing it to build up in the liver in a process known as cholestasis, which leads to scarring of the liver (fibrosis) and can progress to severe scarring (cirrhosis), liver failure and death [3]. Many patients with PBC are asymptomatic at diagnosis, but usually accumulate a range of symptoms and comorbidities as the disease progresses [3,8,9]. These include pruritus, fatigue, bone ache, depression and cognitive dysfunction, with pruritus (itching) and fatigue being the most common symptoms and affecting up to 70% and 80% of patients, respectively [10-13]. End-stage PBC is associated with progressive jaundice, malnutrition, portal hypertension and liver failure, which can lead to premature death in the absence of a liver transplant [14]. Patients with PBC experience a significant humanistic burden from diagnosis through to end-stage disease, and the high symptom burden can significantly impact both patients' health-related quality of life (HRQoL) as well as the ability to perform activities of daily living [15,16].
Therapeutic area *Specify which field best describes the method*	Kreftsykdommer (velg kreftområde i neste kolonne)* Lunge- og luftveissykdommer Mage- og tarmsykdommer Muskel-, skjelett- og bindevevssykdommer Nevrologi
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*	UDCA is the only available first-line treatment for PBC, and the backbone of later lines of treatment. Several qualitative scoring systems have been developed to assess biochemical response to treatment in patients with PBC, of which both the Paris-II and Toronto scoring systems are used in Norway [3]. In some hospitals, response is assessed using other sets of criteria (which are all in accordance with the European Association for the Study of the Liver [EASL] Clinical Practice Guidelines for PBC) [3]. There is no consensus definition for an "inadequate response", but regardless of the response criteria/definition used, the response assessment is generally done after 1 year. If the patient's response to UDCA is evaluated positive, the patient continues with regular follow-up visits. However, up to 5% of patients are intolerant to UDCA, and about 30-40% of PBC patients in Norway would be assessed to have an inadequate response to first-line UDCA (depending on the response definition used) [17-19]. For patients who have an inadequate response to or do not tolerate UDCA, the only currently licensed second-line therapy for PBC is obeticholic acid (Ocaliva), which can be prescribed on H-prescription in Norway [18,20]. In patients who have an inadequate response to UDCA, Ocaliva is administered in combination with UDCA, while it is used as monotherapy in patients intolerant to UDCA [18]. Regardless of the treatment line, for patients with PBC who do not respond adequately to treatment and so progress to cirrhosis and liver failure, liver transplantation is currently the only treatment option available to prevent premature death [21].

Prognosis *Describe the prognosis with current treatment options, including references*	Delayed diagnosis, which occurs in approximately 25% of cases, negatively impacts PBC prognosis, as patients with a delayed diagnosis are likely to have later-stage PBC than those with an earlier diagnosis, and may therefore be more difficult to treat [22]. About 30-40% of PBC patients in Norway would be assessed to have an inadequate response to first-line UDCA (depending on the response definition used), leaving them at increased risk of disease progression and further complications [18,19]. Studies have shown that UDCA does not improve outcomes such as all-cause mortality, liver transplantation, or serious complications or comorbidities [8,23,24]. Ocaliva, the only currently licensed second-line therapy for PBC patients, has limitations in its efficacy, and in addition to this, has a significant side effect burden, increasing both pruritus and fatigue in patients with PBC, with exacerbated pruritus leading to discontinuation in 10% of Ocaliva-treated patients in the POISE trial [25]. For patients who do not adequately respond to currently available treatments and progress to cirrhosis and severe disease, or suffer with severe medically-resistant pruritus, liver transplant is required [3]. The outcome of liver transplant is usually favourable, with 5-year patient survival rates of 80–85%. However, symptoms of PBC, including fatigue, often persist after transplant. Recurrence of PBC has also been reported in patients receiving a liver transplant; following orthotopic liver transplant, recurrent PBC is estimated to occur in 9–35% of individuals within 1.6–6.5 years [26]. As PBC advances, patients may also develop complications such as hepatocellular carcinoma (HCC), for which there are very limited effective treatments to improve survival [27]. Data from an historical UK cohort (N=770) suggests that the average survival of patients with PBC receiving no or suboptimal treatment is approximately 10 years from presentation, with 26% of patients developing liver failure within 10 years of diagnosis [28]. Overall 5-year survival and transplant-free survival was also lower in people with cirrhosis compared with those without (80% vs. 93% for both estimates) [29]. A variety of biochemical markers are used to assess treatment response and disease progression in PBC, including [3]:
The new medicinal product's placement in the treatment algorithm	Elafibranor is expected to be placed as the first-choice second-line treatment for PBC (in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults who are intolerant to UDCA).
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*	Most patients present with PBC between 40–60 years of age; however, cases have been reported in individuals as young as 15 years [10,33]. PBC is more common in female individuals than males (9:1 female:male ratio); however, male patients tend to have more advanced disease at diagnosis, likely due to delayed presentation [3,8,10]. PBC is a rare disease. In Norway, the prevalence of PBC is estimated to be 216/million (1,166 patients) and the incidence is estimated to be 18/million/year (97 patients/year), calculated using average prevalence and incidence estimates from Sweden, Finland and Denmark [34-36]. The size of the patient population covered by the second-line PBC indication for elafibranor depends on the criteria used to assess the response to first-line treatment, as described in the "Current treatment" section. Assuming that the Toronto scoring system is the one used (in accordance with the inclusion criteria used in the pivotal clinical trial for elafibranor), about 88 patients in the prevalent patient pool would be expected to receive elafibranor treatment. This estimate is based on first-line treatment response rates reported with the Toronto scoring system in Sweden and assuming that not all prevalent non-responders will actually receive second-line treatment [19]. About 7 new patients would be expected to receive elafibranor treatment each year based on the same assumptions.

7 Comparability to other medicinal products and inclusion in tender

Are there existing procurements or tenders in the therapeutic area?	Yes, the tender for "Sjeldne sykdommer" includes Ocaliva.
Are there other medicinal products with a similar mechanism of action and/or similar effect (for the same indication)?	No, Ocaliva is a semi-synthetic bile acid and selective farnesoid X receptor (FXR) agonist, whereas elafibranor is a dual PPAR α/δ co-agonist [14].
Does the supplier consider the medicinal product to be comparable to other medicinal products?	No, due to its unique dual mechanism of action, elafibranor acts upon complementary pathways in PBC, resulting in additional therapeutic benefits compared with other treatments on the market.

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*	ELATIVE: A Double-blind, Randomized, Placebo-Controlled Study and Open-label Long Term Extension to Evaluate the Efficacy and Safety of Elafibranor 80 mg in Patients With Primary Biliary Cholangitis With Inadequate Response or Intolerance to Ursodeoxycholic Acid. NCT04526665 https://clinicaltrials.gov/study/NCT04526665		
Study type and design	Phase III, randomised, double-blind, placebo-controlled, parallel group study, followed by open-label long-term extension (LTE). The double-blind period comprised two parts. In part one, patients were randomly assigned to receive elafibranor or placebo for at least 52 weeks. In part two, patients continued their assigned regimen after week 52 until all patients had completed their week 52 assessment or for a maximum of 104 weeks, whichever came first. At the end of the double-blind period, patients could enter an open LTE period and receive elafibranor for up to 5 additional years [37].		
Objective	To evaluate the efficacy and safety of elafibranor in patients with PBC and inadequate response or intolerance to UDCA.		
Population *Important inclusion and exclusion criteria*	A total of 161 patients underwent randomization in a 2:1 ratio (108 patients were assigned to receive elafibranor, 53 were assigned to receive placebo) [37]. Key inclusion criteria [38]: - Males or females aged 18-75 years inclusive - PBC diagnosis - UDCA for at least 12 months prior to screening and at stable dose for ≥3 months, or unable to tolerate UDCA treatment - ALP ≥1.67 x upper limit of normal (ULN) (different ULN values for females		
Intervention (n) *Dosage, dosing interval, duration of treatment*	80 mg elafibranor once daily (patients who were receiving a stable dose of UDCA at baseline were allowed to continue their concurrent UDCA treatment during the study) [37].		
Comparator (n) *Dosage, dosing interval, duration of treatment*	Placebo (patients who were receiving a stable dose of UDCA at baseline were allowed to continue their concurrent UDCA treatment during the study) [37].		
Endpoints *Primary, secondary and exploratory endpoints, including definition, measurement method and, if applicable, time of measurement*	Primary endpoint: biochemical response at week 52, defined as ALP level <1.67 x ULN, with a decrease of ≥15% from baseline, and TB ≤ULN. Key secondary endpoints include [37]: - Normalization of ALP level at week 52. - Pruritus intensity change from baseline through week 52 and through week 24, assessed using the PBC Worst Itch Numeric Rating Scale (WI-NRS) among patients with moderate-to-severe pruritus (defined as a WI-NRS score of ≥4 at baseline); patients are asked to rate their worst itch over the past 24 hours on a scale ranging from zero (no itch) to 10 (worst itch imaginable) [39]. Other secondary endpoints include [37,38]: - Change from baseline to week 52 in 5D-Itch; patients are asked to rate their symptoms in terms of 5 domains: degree, duration, direction (improvement or worsening), disability (effect on daily activities) and distribution of itching over the preceding 2-week period on a 1 to 5 scale, with 5 being the most affected. Total scores range from 5 (no pruritus) to 25 (most severe pruritus), with higher scores indicating worse itch-related quality of life) [40]. - Change from baseline to week 52 in PBC-40; this questionnaire includes 40 questions that evaluate patients' experience across six domains: fatigue, emotional impact, social impact, cognitive function, general symptoms and itch. Each question is scored from 1 to 5, then summed to give a total domain score. High scores represent high impact, and low scores low impact		
Relevant subgroup analyses *Description of any relevant subgroup analyses*	- Age (<65, ≥65) - ALP level at baseline >3 x ULN (Yes/No) - Advanced disease stage, defined as liver stiffness at baseline >10.0 kPa and/or bridging fibrosis or cirrhosis on histology (Yes/No) A full overview of subgroup analyses in the ELATIVE trial is available in reference [38].		

	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*	52 weeks (study is ongoing). In the LTE period, patients can receive elafibranor for up to 5 additional years [37].		
Time perspective results *Ongoing or completed study? Available and future data cut-offs*	Study started: 24-09-2020 Study primary completion: 01-06-2023 Study completion (estimated): December 2028		
Publications *Title, author, journal, year. Expected date of publication*	Efficay and Safety of Elafibranor in Primary Biliary Cholangitis. Kowdley KV, et al. New Engl J Med. 2023 [37,38]		

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*	The ELATIVE trial is ongoing. In addition to ELATIVE, a Phase III study of elafibranor in PBC began in August 2023 (ELFIDENCE; NCT06016842), evaluating the clinical efficacy and safety of elafibranor 80 mg on long-term outcomes [42].
Are there ongoing or planned studies for the medicinal product for other indications?	A Phase II trial is currently ongoing for elafibranor in patients with primary sclerosing cholangitis (PSC) (ELMWOOD; NCT05627362) [43].

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)*	It will not be appropriate to evaluate elafibranor through a cost-minimisation analysis, as the product provides additional therapeutic benefits over existing standard of care, nor through a cost-per-QALY analysis for the following reasons: - As PBC progression is relatively slow, complications associated with the disease progression such as cirrhosis and liver failure may take a long time to develop [44]. Clinical trials of novel PBC therapies would therefore require a prolonged follow-up period to demonstrate a reduction in end-stage clinical outcomes, with trial durations of 8–15 years expected to be needed [45]. It is also difficult to recruit a large enough study population of patients with advanced PBC (i.e. the patients most likely to experience these complications) to provide sufficient statistical power for a clinical trial to demonstrate efficacy on long-term outcomes, as PBC is a rare disease [31,44]. - As an alternative to long-term clinical outcomes, ALP and TB serum levels are surrogate markers of progression in PBC [30]. As described in the "Prognosis" section, these parameters are the most important in evaluating response to treatment in patients with PBC, and when combined, ALP and TB serum levels are powerful predictors of cholestatic injury and liver function, transplant-free survival and the speed of PBC progression [30,31]. A 2014 meta-analysis of data from 4,845 PBC patients demonstrated that levels of both ALP and bilirubin are strongly associated with clinical outcomes, and that any reduction in ALP and bilirubin levels are associated with longer transplant-free survival [31]. Therefore, reduction of ALP and bilirubin levels are goals of treatment for the reduction of cholestasis in patients with PBC [46]. However, even though ALP and TB serum levels are reliable surrogate markers of disease progression in PBC, modeling the disease trajectory of PBC and capturing the clinical benefits of elafibranor vs. standard of care adequately in a cost-per-QALY analysis without having long-term data on end-stage clinical outcomes available will inevitably be associated with uncertainties in estimating several model parameters, with a potentially critical influence on the results. - Due to the rarity of PBC, the sample sizes available for doing utility analyses based on the ELATIVE (and competitor) trials are rather small, which reduces the reliability of utility estimates as lower sample sizes reduces the statistical power of the analyses and the reliability of estimates. This implies also an increased risk of getting inconsistent results that can be difficult to interpret and use in a cost-per-QALY analysis. - The funding responsibility for several orphan drugs, including Ocaliva, was transferred from Folketrygden to the RHFs in 2019. A formal health technology assessment of Ocaliva in the treatment of PBC has not been done by Nye Metoder after the transfer of funding responsibility, as this has not been ordered by Bestillerforum. Based on above, we request that Bestillerforum orders a simplified assessment of relative efficacy and safety for elafibranor in PBC, as performing a cost-per-QALY analysis is not considered to add significant value and reliability to the decision basis in this case. This is supported by the fact that Bestillerforum has not ordered a health technology assessment for Ocaliva in PBC.
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.*	N/A
What type of documentation will form the basis for estimating relative efficacy? *(Direct or indirect evidence)*	Indirect treatment comparison (vs. Ocaliva +/- UDCA) and head-to-head (vs. UDCA monotherapy/no treatment).
What type of documentation will form the basis for health-related quality of life data?	Will depend on the type of assessment to be ordered by Bestillerforum.
Expected pharmaceutical budget impact per year, in the 5-year period following a potential approval	To be included in dossier.

11 Suitable for FINOSE?

Can the method be appropriate for assessment through FINOSE (yes/no) *If no, why not?*	No, since there are significant differences in national treatment standards and practices. Given these differences, it is deemed more suitable to tailor the approach to each national agency specifically.

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)*	Yes. Kristin Kaasen Jørgensen, Akershus University Hospital, has participated in an advisory board focused on PBC in Norway.
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: [1] Cariou B, Zair Y, Staels B, et al. Diabetes Care. 2011;34:2008-14. [2] Ye X, Zhang T, Han H. Front Pharmacol. 2022;13:916866. [3] EASL. J Hepatol. 2017;67:145-72. [4] Wetten A, Jones DEJ, Dyson JK. Expert Opin Investig Drugs. 2022;31:1101-7. [5] Lee C-H, Chawla A, Urbiztondo N, et al. Science. 2003;302:453-7. [6] Pawlak M, Baugé E, Bourguet W, et al. Hepatology. 2014;60:1593-606. [7] Lindor KD, Bowlus CL, Boyer J, et al. Hepatology. 2019;69:394-419. [8] Hirschfield GM, Chazouillères O, Cortez-Pinto H, et al. Expert Rev Gastroenterol Hepatol. 2021;15:929-39. [9] Kim KA, Ki M, Choi HY, et al. Aliment Pharmacol Ther. 2016;43:154-62. [10] Galoosian A, Hanlon C, Zhang J, et al. J Clin Transl Hepatol. 2020;8:49-60. [11] Shaheen AA, Kaplan GG, Almishri W, et al. PLoS One 2018;13:e0194839. [12] Jung HE, Jang JY, Jeong SW, et al. Clin Mol Hepatol. 2012;18:375-82. [13] Milovanovic T, Popovic D, Stojkovic Lalosevic M, et al. Dig Dis. 2020;38:515-21. [14] Montano-Loza AJ, Corpechot C. Clin Gastroenterol Hepatol. 2021;19:2241-51 e1. [15] Mells GF, Pells G, Newton JL, et al. Hepatology. 2013;58:273-83. [16] Selmi C, Gershwin ME, Lindor KD, et al. Hepatology. 2007;46:1836-43. [17] Invernizzi P, Floreani A, Carbone M, et al. Dig Liver Dis. 2017;49:841-6. [18] Jørgensen KK. Primær biliær cholangitt – sjelden sykdom med nytt navn. Gastroenterologen. 20 Oct, 2017. Available at: https://gastroenterologen.no/2017/10/primaer-biliaer-cholangitt-sjelden-sykdom-med-nytt-navn/ [19] Henriksson I, Udumyan R, Nilsson E, et al. Scand J Gastroenterol. 2023;58:70-75. [20] Felleskatalogen.no. Ocaliva «Advanz Pharma». 25 Jul, 2022. Available at: https://www.felleskatalogen.no/medisin/ocaliva-advanz-pharma-631817 [21] Harms MH, Janssen QP, Adam R, et al. Aliment Pharmacol Ther. 2019;49:285-295. [22] Terziroli Beretta-Piccoli B, Stirnimann G, Cerny A, et al. Clin Rev Allergy Immunol. 2018;54:295-306