29 July 2024
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Iqirvo (Elafibranor)
Treatment of primary biliary cholangitis
EU/3/19/2182

Sponsor: Ipsen Pharma

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted

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Table of contents

1. Product and administrative information

Product	
Designated active substance(s)	Elafibranor
Other name(s)	Elafibranor
International Non-Proprietary Name	Elafibranor
Tradename	Iqirvo
Orphan condition	Treatment of primary biliary cholangitis
Sponsor's details:	Ipsen Pharma 65 Quai Georges Gorse 92100 Boulogne Billancourt France
Orphan medicinal product designation procedural history	
Sponsor/applicant	Genfit
COMP opinion	20 June 2019
EC decision	25 July 2019
EC registration number	EU/3/19/2182
Post-designation procedural history	
Transfer of sponsorship	Transfer from Genfit to Ipsen Pharma – EC decision of 02 September 2022
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Patrick Vrijlandt / Paolo Gasparini
Applicant	Ipsen Pharma
Application submission	09 October 2023
Procedure start	26 October 2023
Procedure number	EMA/H/C/006231/0000
Invented name	IQIRVO
Proposed therapeutic indication	Treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. Further information can be found in the European public assessment report (EPAR) on the Agency's website:https://www.ema.europa.eu/en/medicines/human/EPAR/IQIRVO
CHMP opinion	25 July 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Joao Rocha
Sponsor's report submission	26 March 2024
COMP discussion	18-20 June 2024
Oral explanation	N/A
COMP opinion (adoption via written procedure)	29 July 2024

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2019 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing elafibranor was considered justified based on preliminary clinical data demonstrating that treatment can reduce alkaline phosphatase levels in patients affected by the condition;
- the condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular cancer. Common findings include pruritus, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopenia;
- the condition was estimated to be affecting less than 3.9 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing elafibranor will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating that treatment can reduce alkaline phosphatase levels in patients affected by the condition after failing one line of treatment. Indirect comparisons suggest that the proposed product might have improved efficacy compared to the product that is currently authorised for second line therapy. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing elafibranor as an orphan medicinal product for the orphan condition: treatment of primary biliary cholangitis.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Primary Biliary Cholangitis (PBC) is an auto-immune condition manifesting with chronic, progressive liver disease. PBC is characterised by cholestasis caused by autoimmune destruction of biliary ductules with progressive impairment of bile flow in the liver. This results in increased hepatocellular bile acid

concentrations toxic to the liver. Such hepatocellular injury is associated with a local inflammatory response resulting early on in an abnormal elevation of serum alkaline phosphatase (ALP) levels, a hallmark of the disease.

The clinical features and natural history of PBC vary greatly between patients, ranging from asymptomatic and slowly progressive to symptomatic and rapidly evolving. It affects primarily (90%) women of middle-age. Many asymptomatic patients will, however, develop symptomatic liver disease within 5 years of diagnosis, although a third could remain symptom-free for many years. In untreated patients or in inadequate responders to existing therapies, the disease may progress to hepatic fibrosis, cirrhosis, hepatic decompensation, and death unless they receive a liver transplant. [Kuiper 2010, Kumagi 2008]. PBC has also been identified as an important risk factor for hepatocellular carcinoma [Ali 2015]. In early stage, patients present with ALP (alkaline phosphatase) elevation, and in advanced stage cirrhosis and conjugated hyperbilirubinemia. Symptoms commonly include fatigue, abdominal pain, pruritus, hepatic encephalopathy ("brain fog") and jaundice.

The aetiology of PBC remains largely unknown, although there is an association with anti-mitochondrial antibodies, and disease-specific anti-nuclear antibodies targeting sp100 and gp210 (Rigopoulou EI and Bogdanos DP, World J Gastroenterol. 2023 Mar 28;29(12):1795-1810).

The expected therapeutic indication "*Iqirvo is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA"* falls within the scope of the designated orphan condition "Treatment of Primary Biliary Cholangitis".

Intention to diagnose, prevent or treat

The medical plausibility is expected to be confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

PBC is a progressive inflammatory autoimmune cholestatic liver disease. Without treatment, it leads to further liver injury with potential progression to fibrosis, cirrhosis, and its complications, including end-stage liver disease and potentially death. If left untreated, the median duration of survival for symptomatic patients ranges from 5 to 8 years from the onset of symptoms [Al-Harthy 2012]. The use of UDCA in the 1990s changed the natural history of PBC, and has resulted in decreased histological progression of disease, and lower rates of liver transplantation and death. UDCA is also associated with a lower risk of hepatic decompensation. Patients from the Globe PBC Study Group diagnosed after the year 2000 had a 10-year incidence rate of cirrhotic decompensation (defined as ascites, esophageal varices bleeding, or hepatic encephalopathy) of 5.8% versus 13.7% in the 1980s. The degree of the biochemical response to UDCA is strongly associated with clinical outcomes [Trivedi 2016].

The most common and burdensome symptoms described in patients with PBC include fatigue and pruritus, which can have a significant negative impact on a patient's quality of life.

In recent decades, patients are being diagnosed earlier and thus are presenting with milder disease severity [Murillo Perez 2018]. Up to 60% of the newly diagnosed cases are asymptomatic with the majority of those diagnosed becoming symptomatic within 10 years [Kumagi 2008].

In conclusion, the condition is considered to be chronically debilitating due to progressive hepatic dysfunction, pruritus, fatigue and abdominal pain and life-threatening due to hepatic failure, cirrhosis and esophageal varices bleeding, and the increased risk of developing hepatocellular cancer.

Number of people affected or at risk

The sponsor proposes a prevalence estimate of 2.6 per 10,000 persons.

This is lower than at the time of the original orphan designation (OD) for this product in 2019, where the prevalence was estimated to less than 3.9 per 10,000 persons. Notably at the time of marketing authorisation of Ocaliva in 2016, another orphan product for the treatment of PBC, the COMP also accepted a prevalence of less than 3.9 per 10,000 persons.

The sponsors estimate of 2.6 per 10,000 is mainly based on a meta-analysis by Gazda, 2021 of the prevalence estimates, based on 18 articles from the literature from 11 member states (search 2000-2020). Gazda et al estimated summary point-prevalence rate of 22.27 cases per 100,000 inhabitants (95% CI: 17.98–27.01).

The Sponsor provided an estimate of the prevalence for all EU member states. When there was no source available for an individual member state, the estimated pooled value from the meta-analysis by Gazda was implemented (Table 1).

Table 1. Calculation of Estimated Point Prevalence of PBC in the EU

Country	Population[1]	Prevalence Rate (per 10K)[2]	Estimated Prevalence[3]	Reference for Prevalence Rates
Austria	8,958,960	2.227	1,995	Gazda 2021
Belgium	11,686,140	2.227	2,603	Gazda 2021
Bulgaria	6,687,717	2.227	1,489	Gazda 2021
Croatia	4,008,617	1.25	501	Madir 2019
Republic of Cyprus	1,260,138	2.227	281	Gazda 2021
Czech Republic	10,495,295	2.227	2,337	Gazda 2021
Denmark	5,910,913	1.22	721	Lleo 2016
Estonia	1,322,765	2.69	356	Remmel 1995
Finland	5,545,475	1.8	998	Rautiainen 2007
France	64,756,584	2.43	15,736	Dahlvqvist 2017
Germany	83,294,633	3.689	30,727	Sebode 2020
Greece	10,341,277	5.82	6,019	Gatselis 2017
Hungary	10,156,239	2.227	2,262	Gazda 2021
Ireland	5,056,935	1.0	506	Gazda 2021
Italy	58,870,762	2.79	16,425	Marzioni 2019
Latvia	1,830,211	2.227	408	Gazda 2021
Lithuania	2,718,352	2.227	605	Gazda 2021
Luxembourg	654,768	2.227	146	Gazda 2021
Malta	535,064	2.227	119	Gazda 2021
Netherlands	17,618,299	1.32	2,326	Boonstra 2014
Poland	41,026,067	2.227	9,137	Gazda 2021
Portugal	10,247,605	2.227	2,282	Gazda 2021
Romania	19,892,812	2.227	4,430	Gazda 2021
Slovakia	5,795,199	1.488	862	Drazilova 2020
Slovenia	2,119,675	2.227	472	Gazda 2021
Spain	47,519,628	2.02	9,599	Parés 2018
Sweden	10,612,086	3.46	3,672	Marschall 2019

Computed estimate for EU	**448,922,216**	**2.61[4]**	**117,013**	

[1]Population values obtained from https://worldpopulationreview.com (Accessed: 31 Dec 2023)
[2]Where country-specific prevalence rates were not available, published pooled prevalence value was used
[3]Prevalence rate applied to population values
[4]Computed by dividing estimated prevalence by total population

In Greece the reported prevalence exceeded the threshold acceptance level for rarity of 5/10,000 (Gatselis, 2017), however, the other EU sources reported prevalence values well below the acceptance limit. In Crete the prevalence was estimated to 3.7/10,000 (Koulentaki, 2014). Similar high prevalence values (around 3.6/10,000) were also reported in Sweden and Germany, but these are still below the acceptance criterion of 5/10,000. In contrast, in Ireland, Croatia, Denmark, Netherlands, and Slovakia, the prevalence was reported to be rather low (range 1.0-1.48/10,000).

The COMP considered that the point prevalence of 2.6 per 10,000 persons is acceptable as it likely reflects the average prevalence of PBC throughout the EU.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are two authorised medicinal products in the EU for the treatment of PBC: ursodeoxycholic acid (UDCA) and Ocaliva (obeticholic acid, OCA).

Ursodeoxycholic acid (UDCA)

UDCA is a hydrophilic, noncytotoxic bile acid and represents the universal first-line standard of care treatment for PBC [Corpechot 2005]. UDCA is currently approved nationally or decentralised in EU member states for the treatment of of primary biliary cirrhosis. In international treatment guidelines, its use is recommended as a first-choice treatment option, based on long-term experience and evidence of slowing disease progression, and improve transplant-free survival [Corpechot 2011]. Nevertheless, up to 40 percent of patients have persistent elevation of AP and/or bilirubin despite UDCA administration and are considered inadequate responders [Rudic 2012].

The COMP considers that UDCA is not a satisfactory method for the purpose of this orphan maintenance procedure, as Iqirvo is intended for a different target patient population, i.e. as second-line treatment option in in combination with UDCA, in PBC patients with inadequate response to prior UDCA therapy or as monotherapy in patients unable to tolerate UDCA.

The pivotal randomised trial with Iqirvo (319-1) enrolled a population representative of a typical population of patients with PBC in need of second-line therapy (i.e., with an inadequate response and/or intolerance to UDCA). Approximately 95% of participants remained on treatment with UDCA throughout the study (i.e. Iqirvo + UDCA / placebo + UDCA). Treatment with Iqirvo for 52 weeks resulted in a statistically significant higher proportion of participants achieving the primary endpoint of cholestasis response (defined as ALP $<1.67 \times$ ULN, TB $\leq$ULN, and $\geq$15% ALP reduction from baseline) in the Iqirvo 80 mg group (50.9%) compared to placebo (3.8%); $p<0.0001$. A statistically significant improvement in ALP normalization at Week 52 was also seen in the Iqirvo group (14.8%) compared to placebo (0); $p=0.0019$. This data confirms that Iqirvo allows the treatment of a PBC patient sub-

population which cannot achieve sufficient control or is intolerant to the existing authorized treatment UDCA.

Obeticholic acid (OCA)

Ocaliva (obeticholic acid) is the only approved second-line therapy for the treatment of PBC (conditional approval has been granted in the EU in 2016 under the Centralised Procedure). Ocaliva is indicated in the same setting as Irqivo, i.e. for the treatment of PBC either in combination with UDCA in patients with an inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA. OCA is a bile acid analogue, which activates the nuclear hormone receptor farnesoid X-receptor (FXR), thereby reducing the production of bile in the liver and exposure of the toxic levels of endogenous bile acids [Hirschfield 2015].

Irqivo and Ocaliva have a complete overlap of the 4.1 SmPC indication wording. However, according to section 4.3 of the SmPC, Ocaliva is contra-indicated for PBC patients with decompensated cirrhosis (including progression to Child-Pugh Class B or C) or in patients with a prior decompensation event. Furthermore, according to section 4.4 of the SmPC (special warnings and precautions for use) treatment with obeticholic acid should be permanently discontinued in patients with laboratory or clinical evidence of hepatic decompensation (e.g., ascites, jaundice, variceal bleeding, hepatic encephalopathy), including progression to Child-Pugh Class B or C. No such contraindication and precaution for use exists in the proposed SmPC for elafibranor.

The COMP considers that patients with hepatic impairment including Child-Pugh Class B or C are a relevant patient subset in PBC. While no participants with severe hepatic impairment and cirrhosis were enrolled in the pivotal Study 319-1 with Iqirvo (elafibranor), safety and PK data are available from a phase I study (GFT505-118-14). This study was a single-dose, open label, parallel-group study of 120 mg elafibranor (80mg recommended dose in SmPC) in participantswith mild (Child-Pugh class A; n=7), moderate (Child-Pugh class B; n=7), or severe hepatic impairment (Child-Pugh class C; n=6). Results showed that the total drug exposure of the parent and active metabolite was not significantly different between participants with normal hepatic function and hepatically impaired participants (Child Pugh A, B and C). However, the unbound fraction of elafibranor and its active metabolite increased by approximately 3-fold in the severe (Child Pugh C) hepatically impaired PBC participants. Therefore, section 4.2 of the SmPC (posology) for Iqirvo states that no dose adjustment is required for patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. However, section 4.2 and 5.2 of the SmPC for Iqirvo state that its use is not recommended for patients with severe hepatic impairment (Child-Pugh C). Nevertheless, this means that Iqirvo can be used in broader patient subset as Ocaliva, which also includes patients with moderate (Child Pugh B) hepatic impairment and patients with a prior hepatic decompensation event. The COMP considers that this patient subset is relevant for the specific target population of Iqirvo in PBC patients with inadequate response to UDCA.

In fact, it has been reported that in the general PBC population, most patients present with mild biochemical stage (75%) at diagnosis and 24% of patients with advanced histology (cirrhosis) (Murillo Perez 2018). The 10-year incidence rate of cirrhotic decompensation in the general PBC population has been estimated to be about 5.8% in more recent years. However, this rate is increased in the target patient population of Iqirvo, i.e. patients with insufficient response to UDCA. In a retrospective cohort study including 501 PBC patients with compensated cirrhosis at baseline and a mean follow-up time of 5.7 years, the rate of hepatic decompensation among UDCA non-responders was higher with 30.4% as compared to UDCA responders which was 20.2% (John, 2021). Liver-related death or transplantation rates were also reported to be higher in UDCA non-responders as compared to UDCA responders. This suggests that the patient subset in which the currently authorized second-line therapy Ocaliva is

contra-indicated is a relevant subset in the target population of Iqirvo, i.e. patients with moderate hepatic impairment (Child Pugh B) and patients with a previous hepatic decompensation event.

In addition to the broader patient population of Iqirvo as compared to Ocaliva, the COMP also considered it relevant, that Iqirvo has shown efficacy in a patient subset of the pivotal study population which had a prior history of inadequate response or intolerance to Ocaliva. In this subgroup of participants with no other alternative approved treatment options, the primary endpoint of cholestasis response was achieved in 37.5% (n=3/8) of patients in the elafibranor group compared to 0% (n=0/5) of participants in the placebo group.

Furthermore, the COMP acknowledged that pruritus is a common and debilitating symptom for patients with PBC, and Ocaliva has been reported to increase pruritus in a dose-dependent manner (SmPC Ocaliva). In the pivotal study with Ocaliva (study 747-301), the overall incidence of pruritus TEAEs was numerically higher in patients treated with Ocaliva 5-10 mg (55.7%) compared to placebo (38.4%). For Iqirvo on the other hand, such increased trends have not been observed during the pivotal licensing study 319-1. In contrast, the TEAEs (treatment emergent adverse events) related to pruritus was 20.4% in patients treated with Iqirvo, versus 26.4% for patients who received placebo. A Network Meta-analyses of the indirect comparisons of the pivotal trials of Iqirvo and Ocaliva (using the approved posology of 5-10 mg titrated dose) did not indicate a statistically significant difference in the Odds Ratio's for pruritus TEAEs between both products. It is noted that for a claim of a Safety advantage of Iqirvo, the overall safety profile of the drug should be regarded. Considering the limited experience for Iqirvo thus far, a safety claim was not considered established by the COMP.

As the key secondary endpoint of reduction of PBC Worst Itch NRS score was not met in the pivotal trial for Iqirvo versus placebo, an advantage regarding efficacy on pruritus reduction was neither considered clearly established for Iqirvo by the COMP.

Of note, the benefit-risk balance of Ocaliva is currently under review by the CHMP in an Article 20 referral procedure, initiated in October 2023 by the European Commission.

In conclusion, the COMP considers that neither UDCA nor Ocaliva are satisfactory methods for the purpose of this procedure, as Iqirvo covers a PBC patient subset which is not covered by these two authorized PBC therapies. With regards to UDCA this patient subset comprises patients with inadequate response to prior UDCA therapy or patients unable to tolerate UDCA. With regards to Ocaliva this patient subset comprises patients with decompensated cirrhosis (e.g., Child-Pugh Class B) or a prior decompensation event.

Significant benefit

Not applicable.

4. COMP position adopted on 29 July 2024

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of Primary Biliary Cholangitis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 2.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;

- the condition is chronically debilitating due to progressive hepatic dysfunction and cirrhosis, pruritus, fatigue, abdominal pain and hepatic encephalopathy and life-threatening due to hepatic failure, risk of oesophageal varices bleeding and the increased risk of developing hepatocellular cancer;
- at present, no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Iqirvo.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Iqirvo, elafibranor for treatment of primary biliary cholangitis (EU/3/19/2182) is not removed from the Community Register of Orphan Medicinal Products.