4 June 2024
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EMADOC-1700519818-1465989
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Livmarli (maralixibat)
Treatment of progressive familial intrahepatic cholestasis
EU/3/13/1216

Sponsor: Mirum Pharmaceuticals International B.V.

Note

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

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1. Product and administrative information

Product	
Designated active substance(s)	(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane Chloride
Other name(s)	Livmarli, (maralixibat chloride)
International Non-Proprietary Name	Maralixibat
Tradename	Livmarli
Orphan condition	Treatment of progressive familial intrahepatic cholestasis
Sponsor's details:	Mirum Pharmaceuticals International B.V. Kingsfordweg 151 1043 GR Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Lumena Pharma UK Limited
COMP opinion	6 November 2013
EC decision	18 December 2013
EC registration number	EU/3/13/1216
Post-designation procedural history	
Transfer of sponsorship	Transfer from Lumena Pharma UK Limited to Shire Pharmaceuticals Ireland Limited – EC decision of 05 September 2016 Transfer from Shire Pharmaceuticals Ireland Limited to SFL Regulatory Services GmbH – EC decision of 25 March 2019 Transfer from SFL Regulatory Services GmbH to Granzer Regulatory Consulting & Services – EC decision of 18 December 2019 Transfer from Granzer Regulatory Consulting & Services to FGK Representative Service GmbH – EC decision of 22 April 2020 Transfer from FGK Representative Service GmbH to Mirum Pharmaceuticals International B.V. – EC decision of 26 November 2021
Type II variation procedural history	
Rapporteur / Co-rapporteur	Martina Weise / Thalia Marie Estrup Blicher
Applicant	Mirum Pharmaceuticals International B.V.
Application submission	3 April 2023
Procedure start	22 April 2023

Procedure number	EMA/H/C/005857/II/0003/G
Invented name	Livmarli
Therapeutic indication	Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older. Further information on Livmarli can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/livmarli
CHMP opinion	30 May 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook/ Armando Magrelli
Sponsor's report submission	1 May 2023
COMP discussions	7-9 November 2023 and 21-23 May 2024
COMP opinion (adoption via written procedure)	4 June 2024

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2013 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido- 1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride was considered justified based on preclinical data showing reduction of serum bile acids in a cholestasis model, accompanied by some reduction of liver enzymes levels. The reduction of biliary acid levels is known to be linked to reduction of pruritus in cholestatic diseases. Since pruritus is an important and chronically debilitating symptom of progressive familial intrahepatic cholestasis, the Committee considered that preliminary evidence of reduction of biliary acid levels supports the intention to treat the condition with the supposed product;
- the condition is life-threatening and chronically debilitating due to progressive severe liver dysfunction, accompanied by portal hypertension, liver failure, cirrhosis, and higher incidence of hepatocellular carcinoma. Symptoms develop very early, around 2 months of life. The disease ultimately leads to cirrhosis by age 10-20 years. Most affected subjects do not survive beyond 20 years of age;
- the condition was estimated to be affecting not more than 0.2 in 10,000 persons in the European Union, at the time the application was made, based on available literature.

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

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

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 (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido- 1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride, as an orphan medicinal product for the orphan indication: treatment of progressive familial intrahepatic cholestasis.

3. Review of criteria for orphan designation at the time of type II variation

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

The sponsor is proposing that progressive familial intrahepatic cholestasis continues to be an orphan condition.

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of rare autosomal recessive liver disorders of childhood characterized by mutations in genes encoding proteins involved in the hepatocellular transport system.

Three main subtypes of PFIC (PFIC1, PFIC2, PFIC3) have been identified.

- PFIC1, also known as Byler's disease, is caused by mutations in the ATPase phospholipid transporting 8B1 gene (ATP8B1), located on chromosome 18, which encodes a phospholipid transporting transmembrane P-type adenosine triphosphatase known as FIC1. This 'flippase' is involved in maintaining an asymmetric distribution of phospholipids across the canalicular membrane bilayer of hepatocytes, thereby protecting the canalicular membrane from hydrophobic bile acids and maintaining its integrity.
- PFIC2 is caused by mutations in the ATP binding cassette subfamily B member11 gene (ABCB11), located on chromosome 2, which encodes the bile salt export pump (BSEP), the main transporter of bile acids from hepatocytes to the canalicular lumen.
- PFIC3 is caused by mutations in the ATP binding cassette subfamily B member 4 gene (ABCB4), located on chromosome 7, which encodes multidrug-resistance protein 3 (MDR3/ABCB4); this protein transports phospholipids into the canalicular lumen to neutralize bile salts and prevent injury to biliary epithelia and bile canaliculi.

In addition, at least 3 other subtypes have been described in the literature (PFIC4-6).

The main clinical features of PFIC include cholestasis, jaundice, and pruritus, with symptoms typically appearing in infancy or early childhood. PFIC is associated with a range of potentially fatal complications of the liver, including portal hypertension, liver failure, cirrhosis, and hepatocellular carcinoma (HCC; PFIC2), as well as extrahepatic manifestations (PFIC1). The biochemical features of PFIC1 and PFIC2 are low levels of γ-glutamyl transferase (GGT) with elevated serum bile acid and decreased primary bile acid concentrations, while PFIC3 is associated with high levels of GGT.

The diagnosis of PFIC is based on a combination of clinical and laboratory or biochemical approaches, and genetic testing (Clinics and Research in Hepatology and Gastroenterology (2019) 43, 20—36).

The COMP continues to designate this condition as an orphan condition.

The new proposed therapeutic indication "*Livmarli is indicated in patients 3 months of age and older for the treatment of progressive familial intrahepatic cholestasis (PFIC)"* falls within the scope of the designated orphan condition "Treatment of progressive familial intrahepatic cholestasis".

Intention to diagnose, prevent or treat.

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature.

Symptoms of the disease develop early, median time of onset of symptoms being 2 months and 78% of PFIC patients develop jaundice. Icterus (itching) is often seriously debilitating and could lead to auto-mutilation of the skin, irritability and sleeplessness. Several complications of hepatic dysfunction (portal hypertension, liver failure, cirrhosis) and hepatocellular carcinoma are associated with the condition. Due to malabsorption of fat and in fat soluble vitamins, young patients commonly show signs of "failure to thrive".

PFIC can lead to death secondary to complications of end-stage liver disease. In general, without treatment, PFIC 1 and 3 will lead to end-stage liver disease by age 10-20 years, and even earlier in PFIC 2. The survival in patients not receiving a liver transplant is 50% at the age of 10 and almost none at the age of 20 years. The rates of liver transplant (LT) for patients with PFIC1 and PFIC2 (40—100%) suggest that the highest reported mortality figure (87%) is probably most representative of the natural history of untreated PFIC.

Reasons for death included infections, bleeding (cerebral, gastrointestinal, splenic), liver failure, liver transplant-related complications, hepatocellular carcinoma, and complications secondary to cholestasis, including acute infections, dehydration and gastrointestinal bleeding (Clinics and Research in Hepatology and Gastroenterology (2019) 43, 20—36).

Number of people affected or at risk.

The sponsor proposes three different approaches to estimating the prevalence of the condition for the review of the maintenance of the orphan designation.

The first approach was to conduct a literature search to see if there were any new publications since their initial orphan designation back in 2013. Table 1 below summarises all the publications.

Table 1. Publications Related to Determination of Prevalence of PFIC

Reference	Study design	Study population	N	No. of PFIC cases	Genetic diagnosis	Country/ Region	Study period	PFIC epidemiology reported (calculated)	PFIC subtype
Davit-Spraul et al. 2009	Review	PFIC	NA	NA	NA	France	NR	Incidence (I): 1/50,000 - 1/100,000 births	PFIC1,2: 67% PFIC3: 33%
Henriksen et al. 1981*	Retrospective chart review	Infants with cholestatic jaundice	124	60	No	Norway	1955-1974	I: 1:18,000 live births	NR
Fischler et al. 2001*	Retrospective study	Infants with neonatal cholestasis	85	11	Yes	Sweden	1988-1995	Prevalence (P): 12.9% (P: 0.02/100,000[a])	PFIC2: 91% PFIC1/3: NR
Englert et al. 2007*	Retrospective chart review	Patients with PFIC treated with UDCA+ PEBD or LT	42	42	Yes	Germany (1 center)	NR	NR (P: 0.05/100,000[b])	PFIC1: 62% PFIC2: 38%
Davit-Spraul et al. 2010*	Retrospective chart review	Children with hepatocellular cholestasis, pruritus, elevated bile acid and normal serum GGT activity	62	62	Yes	France (1 center)	1978-2007	NR (P: 0.004/100,000[c])	PFIC1: 21% PFIC2: 63% PFIC3: NR
Wanty et al. 2004*	Retrospective chart review	Patients with PFIC (based on chronic cholestasis)	49	49	Yes	Belgium (1 center)	The 15 years before publication	NR (P: 0.03/100,000[d])	PFIC1/2: 61% PFIC3: 39%
Yang et al. 2009	Retrospective chart review	Children with PFIC who underwent PEBD	11	11	Partial	Netherlands (1 center)	2000-2005	NR (P:0.01/100,000[e])	PFIC2: 73% Others: NS

Jankowska et al, 2014	Retrospective chart review	Children with PFIC who underwent ileal exclusion	56	56	Partial	Poland (1 center)	1979-2010	NR (P:0.004/100,000[f])	PFIC1: 7% PFIC2: 63% Other: NR
Ruth et al. 2014*	Prospective study	Infants with cholestasis, acute liver failure or splenomegaly	238	NR	Yes	International (13 centers)	NR	P: 9%	NR
Kamath et al. 2015*	Longitudinal observational study (LOGIC)	Children with chronic intrahepatic cholestasis	214	25	Yes	North America (16 centers)	NR	P: 11.7%	PFIC-1: 24% PFIC-2: 48% PFIC-3: 28%
Malik et al. 2017[#]	Retrospective study	Patients with hepato-biliary disorders admitted to hospital	644	12	No	Pakistan (1 center)	Jan 2013-Dec 2015	P: 1.87%	NR
Flores et al. 2018[#]	Retrospective chart review	Patients with diagnosis of ALGS or PFIC	37	17	Partial	North America (1 center)	Jan 1996 – Dec 2016	P: 46%	PFIC1: 11% PFIC2: 24% PFIC3: 11%
El-Guindi et al. 2021	Retrospective chart review	Patients with diagnosis of neonatal cholestasis	412	51	No	Egypt (1 center)	Jul 2012 – Jun 2015	P: 12%	NR

*Publication mentioned in Baker et al, 2019. [#]Publication mentioned in Jones-Hughes et al. 2021.
[a] Based on an average Swedish population of 8.650 Million between 1988 and 1995 (www.populationpyramid.net). [b] Based on a German population of 81.472 Million in year 2006 (www.populationpyramid.net). [c] Based on an average French population of 57.646 Million between 1978 and 2007 (www.populationpyramid.net). [d] Based on an average Belgian population of 10.000 Million between 1988 and 2003 (www.populationpyramid.net). [e] Based on an average Dutch population of 16.147 Million between 2000 and 2005 (www.populationpyramid.net). [f] Based on an average Polish population of 37.000 Million between 1979 and 2010 (www.populationpyramid.net).

The sponsor proposes two different approaches to estimate the prevalence:

The first approach was to use the number of liver transplantations for PFIC. PFIC represents 10-15% of the indications for liver transplantations in children (Davit Spraul et al. 2009). According to the European Liver Transplant Registry (European Liver Transplant Registry - ELTR), a total of 6171 patients 0–2 years of age and a total of 8673 patients 2–18 years of age received a liver transplantation in the time period from 1988 to June 2020. Based on the upper rate of 15% stated above, a total of 2227 paediatric patients may thus had received liver transplantation for PFIC. Assuming an increase in the rate of yearly liver transplantations and assuming that two-thirds of the transplantations were performed between years 2000 and 2020, then a total of 1485 paediatric patients would have received liver transplantation for PFIC between 2000 and 2020, a yearly rate of 74 patients. Further assuming a European paediatric population of 67 million children <15 years of age (Eurostat [Population structure and ageing - Statistics Explained (europa.eu)]), the rate of paediatric PFIC patients with liver transplantation would be 0.01 in 10,000. Assuming that about half of the patients with PFIC undergo liver transplantation, the prevalence of PFIC would be 0.02 in 10,000.

The second approach was to determine PFIC prevalence using incidence and survival data. According to Davit-Spraul et al. 2009, fibrosis and end-stage liver disease usually develop before adulthood and, in half of patients, liver transplantation is required at a mean age of 7.5 years. One might therefore assume the following:

- Half of patients with PFIC receive a liver transplant at age 10 years, 25% receive a transplant at age 20 years and that 25% do not receive a liver transplant and succumb to liver failure at age 20 years.
- Post-liver transplant, survival is comparable to survival with other liver transplant indications. This can be approximated to 75% 5-year survival (www.mayoclinic.org) and 48% 18-year survival (Jain et al. 2000).
  - Normal life-years for 100 individuals would be 100 x 70 = 7,000 years.
  - 25% of patients with PFIC would live no more than 20 years (500 life-years).
  - The remaining 75% of patients would all survive to at least age 8 years (600 life-years).
  - 50% (i.e., n=50) would have a liver transplant at age 8 years. Of these:

    25% (n=12.5) would survive no more than 5 years post-transplant (62.5 life-years).

    27% (n=13.5) would survive no more than 18 years post-transplant (243 life-years).

    48% (n=24) would live a normal lifespan of 62 further years post-transplant (1488 life-years).
  - 25% (i.e., n=25) would have a liver transplant at age 20 years. Of these:

    25% (n=6.25) would survive no more than 5 years post-transplant (31.25 life-years).

    27% (n=6.75) would survive no more than 18 years post-transplant (121.5 life-years).
  - 48% (n=12) would live a normal lifespan of a further 50 years post-transplant (600 life-years).

PFIC life-years versus normal life-years would be 3,646.25 / 7,000 = 0.52.

Therefore, the average lifespan of a patient with PFIC (i.e., the average disease duration) would be 36 years.

According to Davit-Spraul et al. (2009), the birth prevalence of PFIC is 1–2 per 100,000 live births. Based on 4.09 million live births in Europe (Eurostat for EU-27, 2021), the total number of newborns with PFIC would be 41 to 82 cases annually. Across an overall EU population of 446.8 million people, the annual incidence would be 0.001–0.002 per 10,000. If patients with PFIC on average live for 30 years, the prevalence would be 0.03 to 0.06/10,000. Table 2 summarizes the birth prevalence and estimated general prevalence based on these calculations.

Table 2. Adjustment of Incidence at Birth to Estimate Prevalence of PFIC

Estimated birth prevalence	**Estimated prevalence**
0.1 per 10,000	0.03 per 10,000
0.1 per 5,000	0.06 per 10,000

In conclusion the sponsor estimated that the prevalence of PFIC was 0.06 per 10,000. The COMP accepted this more conservative estimate.

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

The EASL Clinical Practice Guidelines (2009) recommends UDCA for PFIC 3 and biliary diversion surgery for all types of PFIC (Management of cholestatic liver diseases Journal of Hepatology 51 (2009) 237–267). There has been no recent update of the EASL Clinical Practice Guidelines.

Partial biliary diversion reduces serum bile acids and pruritus and prevent hepatic fibrosis. However, the external stoma may lead to complications, such as cholangitis. Effects of this surgery have been reported to be temporary. Liver transplantation is indicated in case of end-stage liver disease in PFIC. Liver transplantation requires extensive surgery, and life-long immune-suppression thereafter to counterfeit rejection reaction. There is also a shortage of suitable donors.

Non-authorised pharmacological treatments

Supplementation with medium chain triglycerides and fat-soluble vitamins is generally recommended in children with PFIC, but these supplement products are not specifically authorised for the treatment of PFIC and are symptomatic treatments only.

Rifampicin may alleviate pruritus and is widely prescribed in PFIC patients although it is not specifically authorised.

Authorised pharmacological treatments

Ursodeoxycholic acid (UDCA) has national marketing approval for PFIC subtype 3 in France. UDCA has been reported to improve biochemical tests in almost 50% of patients with PFIC3, but generally does not affect PFIC1 and PFIC2, although it is widely prescribed off-label. In fact, 87.5% of the PFIC patients in the Livmarli trials, which mainly consisted of PFIC1 and 2 patients, had been treated with UDCA. UDCA is not considered a satisfactory method as it does not cover the same patient population as Livmarli.

Bylvay (Odevixibat) received a centralised marketing approval in 2021. Its' indication is:

Bylvay is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.

The CHMP has agreed to the following indication for Livmarli:

Livmarli is indicated in patients 3 months of age and older for the treatment of progressive familial intrahepatic cholestasis (PFIC)

Livmarli covers a broader patient population as compared to Bylvay as it is possible to treat patients from the age of 3 months while the indication for Bylvay restricts the use to the age of 6 months and older. Thus significant benefit does not have to be assessed.

Significant benefit

Not applicable

4. COMP position adopted on 4 June 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 progressive familial intrahepatic cholestasis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.06 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to progressive severe liver dysfunction, accompanied by portal hypertension, liver failure, cirrhosis, and higher incidence of hepatocellular carcinoma. Symptoms develop very early, around 2 months of life. The disease ultimately leads to cirrhosis by age 10-20 years with a reduced life expectancy;
- 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 Livmarli.

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 Livmarli, (4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane Chloride, maralixibat for treatment of progressive familial intrahepatic cholestasis (EU/3/13/1216) is not removed from the Community Register of Orphan Medicinal Products.