09 December 2022
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Livmarli (maralixibat chloride)
Treatment of Alagille syndrome
EU/3/13/1214

Sponsor: Mirum Pharmaceuticals International B.V.

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Un on

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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)	Maralixibat chloride,
International Non-Proprietary Name	Maralixibat chloride
Tradename	Livmarli
orphan condition	Treatment of Alagille syndrome
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/3/13/1214
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 Mirum Pharmaceuticals International B.V.– EC decision of 23 September 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Martina Weise/ Kirstine Moll Harboe
Applicant	Mirum Pharmaceuticals International B.V.
Application submission	8 September 2021
Procedure start	30 September 2021
Procedure number	EMA/H/C/005857/0000
Invented name	Livmarli

Proposed 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	13 October 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Olimpia Neagu
Sponsor's report submission	20 December 2021
COMP discussions	6-8 September 2022 4-6 October 2022
COMP opinion (adoption via written procedure)	18 October 2022

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 Alagille syndrome, 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 hepatic and cardiac dysfunction. Portal hypertension develops in up to one third of patients. Life expectancy is in most cases around 20 years and death is associated with liver failure, cardiac problems and blood vessel abnormalities;
- the condition was estimated to be affecting not more than 0.3 in 10,000 persons in the European Union, at the time the application was made, based on the current available literature;
- 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.

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

Alagille syndrome is a highly heterogenous, autosomal dominant multisystem condition and is caused by mutations in one of two genes: JAG1 and NOTCH2. It was initially described as a hepatic disease, but molecular testing has shown that individuals with ALGS and JAG1 or NOTCH2 mutations may present without overt liver disease.

Table 1. Summary of molecular genetic testing used in ALGS

Gene	Proportion of ALGS attributed to mutation of this gene	Test method	Mutations detected
JAG1	89%	Sequence analysis/mutation scanning	Sequence variants
	~5%–7%	Deletion/duplication analysis (including FISH and MLPA)	Deletion and duplication of exon(s) and entire gene deletion
NOTCH2	1%–2%	Sequence analysis	Sequence variants
	Unknown	Deletion/duplication analysis	Unknown, none reported

ALGS is a multisystem disorder with a wide spectrum of clinical signs and symptoms ranging from life-threatening liver or congenital cardiac defects to only subclinical manifestations, such as mildly abnormal liver enzymes, a heart murmur, butterfly vertebrae, posterior embryotoxon (a thickening of the Schwalbe's line of the cornea), or characteristic facial features. This variability is present even among individuals from the same family sharing the same mutation.

Table 2. A summary of the clinical features and the frequency reported among individuals with ALGS

Common system involved in ALGS	Feature	Overall frequency in ALGS	Frequency of finding in *JAG1*(+) ALGS	Frequency of finding in *NOTCH2* (+) ALGS
Hepatic	Paucity of biliary duct, conjugated hyperbilirubinemia, and liver failure	Up to 100%	100%	100%
Cardiac	Structural changes, pulmonary stenosis, and tetralogy of Fallot	90%–97%, 60%–67%, and 7%–16%	100%	60%
Facial features	Prominent forehead, deep-set eyes with moderate hypertelorism, pointed chin, and saddle or straight nose with a bulbous tip	20%–97%	97%	20%
Eye	Posterior embryotoxon	78%–89%	75%	60%
Skeletal	Vertebral anomalies (hemivertebra and butterfly vertebra)	33%–93%	64%	10%
Renal	Ureteropelvic obstruction and renal tubular acidosis	39%	40%	40%

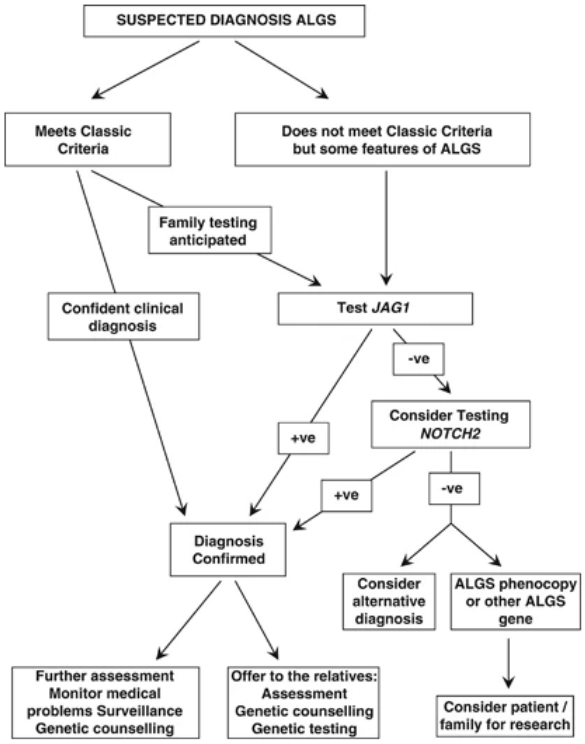
In the majority of cases, individuals with ALGS present in infancy with cholestasis (conjugated hyperbilirubinemia with high GGT, increased serum bile acids, and elevated cholesterol and triglycerides), which manifest as jaundice, intense pruritus, xanthomas (fatty deposits on the extensor surfaces), and failure to thrive due to fat malabsorption. Cardiac findings ranging from benign heart murmurs to significant structural defects occur in 90%–97% of individuals with ALGS. Pulmonic stenosis (peripheral and branch) is the most common cardiac finding (60-67%). The most common complex cardiac defect is tetralogy of Fallot, which is seen in 7%–16% of individuals. Other cardiac malformations include ventricular septal defect, atrial septal defect, aortic stenosis, and coarctation of the aorta (in order of decreasing frequency).

The typical facial features (see Table 2A above) are almost universally present in ALGS due to JAG1 mutations. The typical facial features do not seem to be as prevalent in individuals with ALGS carrying a NOTCH2 mutation.

The mortality is ~10%, with vascular accidents, cardiac disease, and liver disease being the most frequent cause of death (The Application of Clinical Genetics 2016:9 75–82). Alagille syndrome is diagnosed when an individual has three out of seven major clinical features. See Figure 1 below for diagnostic framework. Individuals with an affected first-degree relative and who do not meet full clinical criteria but with the presence of one or more clinical features should be diagnosed with Alagille syndrome. Infants younger than 6 months of age may not present with a marked paucity of the bile ducts or even present with ductal proliferation that could lead to a misdiagnosis of biliary atresia. Traditionally, the clinical diagnostic criteria for ALGS included liver histology showing bile duct paucity (an increased portal tract-to-bile duct ratio) and three of five major clinical features: cholestasis; ophthalmologic abnormalities (commonly posterior embryotoxon); characteristic facial features (see Table 2 A); cardiac defect (see Table 2); and skeletal abnormalities (commonly butterfly vertebrae). The five criteria have been increased to seven which are: Cardiac defects, hepatic manifestation, renal abnormalities, skeletal abnormalities, ophthalmologic manifestations, dysmorphic facies and vasculature abnormalities.

Bile duct paucity on liver histology is no longer considered mandatory for the diagnosis of Alagille syndrome, the presence of cholestasis can be used instead. (*Alagille Syndrome Article - StatPearlshttps://www.statpearls.com › Article Library › view article 14 Aug 2022* https://www.statpearls.com/ArticleLibrary/viewarticle/17321)

Figure 1. Flow diagram of genetic investigations and management for suspected ALGS patients.



European Journal of Human Genetics volume 20, pages251–257 (2012)

The approved therapeutic indication "***Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older***" falls within the scope of the designated orphan condition "Treatment of Alagille syndrome"

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

The condition is chronically debilitating and life threatening due to chronic cholestasis due to paucity of intrahepatic bile ducts, progressing to portal hypertension and liver failure. Pruritus (itching) is reported as the most bothersome symptom of ALGS across all ages by patients and caregivers (Kamath et al. 2018b), which is difficult to treat, leads to cutaneous mutilation, mood disturbances, disruption of sleep and school performance, and has negative impact on physical and psychosocial health (Elisofon et al. 2010; Kamath et al. 2015, Kamath et al. 2018b), as well as overall Quality of Life (Abetz-Webb et al. 2014).

Twenty-one percent to 31% of patients require liver transplantation during childhood, including approximately 50% of those diagnosed in infancy. Cardiac dysfunction also occurs due to cardiac defects which are reported in greater than 90% of patients and include peripheral pulmonic stenosis (60-67%), tetralogy of Fallot (7-16%), ventricular septal defect, atrial septal defect, aortic stenosis, and coarctation of the aorta. Associated with cardiac defects are vasculature abnormalities which when present, are often associated with neurovascular abnormalities such as aneurysms, Moyamoya syndrome, abnormalities in cerebral arteries, reno-vascular abnormalities, and middle aortic syndrome.

Intracranial bleeding can also occur. Additional involvement of other systems/organs contributes to the chronically debilitating nature of the disease, including butterfly vertebrae, posterior embryotoxon and/or anterior segment abnormalities of the eyes, pigmentary retinopathy and dysplastic kidney.

The reported mortality is ~10%, with vascular accidents, cardiac disease, and liver disease being the most frequent cause of death. In a retrospective analysis of 1,154 children from 25 countries with a clinically and/or genetically confirmed ALGS diagnosis the 18-year survival was 88.6% (Vandriel et al. 2020). Mortality is high in the very young age because of the concurrent severe cardiac malformations.

Number of people affected or at risk

The sponsor has provided a prevalence estimate based on a literature search. Several publications are mentioned which are derived from the Gala Study (key study in the development of maralixibat chloride (Kamath et al 2020, Vandriel et al 2020 and Kamath et al 2018). This data is supplement with a publication from Australia (Danks et al 1977) and a revision from 2014 (Leonard et al 2014). One publication identified the incidence of the condition, Langlois and Scheuerle 2015 which is derived from a Texas Birth Defects Registry (TBDR) in the USA. Finally, a publication from Kamath et al from 2003 was used to describe the incidence of live births of the condition which is proposed as 1.74 in 100,000.

The sponsor acknowledges in their submission that detection of the condition in Europe is difficult which can compromise the prevalence estimate. The final proposed incidence of the condition is 3.16 in 100,000. Life expectancy is proposed to be slightly less than normal where the sponsor proposed that:

- Normal life-years for 100 individuals would be 100 X 70 = 7,000 years
- 11% of Alagille syndrome patients would live no more than 18 years (198 life-years) and 89% would have a normal lifespan (6,230 life-years)
- Alagille life-years vs normal life-years would be 6,428/7000 = 0.92

Table 3. Adjustment of birth incidence to arrive at prevalence

Estimated birth incidence	Estimated prevalence Adjustment factor 0.92 (Vandriel et al. 2020)
3.16 per 100,000	2.9 per 100,000

The sponsor proposed a final estimate of 0.3 in 10,000 to be the current prevalence in the European Union. This is similar to the prevalence estimate as established at the orphan designation back in 2013. There are no reasons to consider that the prevalence of this hereditary disease has changed much since the orphan designation in 2013.

The COMP accepted this final 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

There are no formal European Guidelines regarding the management and treatment of these patients.

The sponsor indicates that there are no products authorised for the condition in Europe. It appears therefore that nothing has changed since the original orphan designation in 2013. It is noted by the COMP that off-label use of several products is reported like: ursodeoxycholic acid, cholestyramine, rifampicin and naltrexone. These products are tried for the management of pruritus and xanthoma but typically have limited success (Kronsten et al. J Pediatr Gastroenterol Nutr. 2013 Aug;57(2):149-54). Surgical interventions are used to treat cholestatic disease in ALGS and include surgical biliary diversion (SBD) procedures and liver transplantation. SBD procedures may not be fully effective and can lead to electrolyte disturbances and dehydration (Emerick et al. 1999; Kamath et al. 2018). Liver transplantation is associated with considerable safety risks, and donors are limited available.

The COMP concluded that the currently available methods and treatments are not satisfactory.

Significant benefit

Not applicable.

4. COMP position adopted on 18 October 2022

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 Alagille syndrome (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.3 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 severe pruritus, cholestasis, liver failure, and congenital cardiac defects. Life expectancy is in most cases around 20 years and death is associated with blood vessel abnormalities, cardiac failure and end-stage liver disease;
- there is, at present, no satisfactory method for the treatment of Alagillle syndrome that has been authorised in the European Union for patients affected by the condition.

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 chloride for treatment of Alagille syndrome (EU/3/13/1214) is not removed from the Community Register of Orphan Medicinal Products.