swissmedic

Date: 11 November 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Livmarli

International non-proprietary name: maralixibat chloride
Pharmaceutical form: oral solution
Dosage strength(s): 9.5 mg/mL
Route(s) of administration: oral
Marketing authorisation holder: Mirum Pharmaceuticals AG
Marketing authorisation no.: 69201
Decision and decision date: approved on 18 July 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALGS	Alagille syndrome
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for maralixibat chloride in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 31 March 2023.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 3 months of age and older.

2.2.2 Approved indication

Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 3 months of age and older.

2.2.3 Requested dosage

The recommended dosage is 380 µg/kg once daily, taken 30 minutes before a meal in the morning. Dosing starts at 190 µg/kg administered orally once daily, increasing after one week to 380 µg/kg once daily, as tolerated. The maximum daily dose volume for patients above 70 kg is 3 mL or 28.5 mg per day. Refer to the dosing by weight guidelines presented in Table 1.

Table 1: Individual dose volume by patient weight

Patient weight (kg)	**Days 1-7 (190 µg/kg once daily)**		**From Day 8 (380 µg/kg once daily)**	
	Volume once daily (mL)	Dosing dispenser size (mL)	Volume once daily (mL)	Dosing dispenser size (mL)
5 to 6	0.1	0.5	0.2	0.5
7 to 9	0.15		0.3	
10 to 12	0.2		0.45	
13 to 15	0.3		0.6	1
16 to 19	0.35		0.7	
20 to 24	0.45		0.9	
25 to 29	0.5		1	
30 to 34	0.6	1	1.25	3
35 to 39	0.7		1.5	
40 to 49	0.9		1.75	
50 to 59	1		2.25	
60 to 69	1.25	3	2.5	
70 or higher	1.5		3	

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	21 April 2023
Formal control completed	2 May 2023
List of Questions (LoQ)	29 August 2023
Response to LoQ	27 November 2023
Preliminary decision	23 February 2024
Response to preliminary decision	23 April 2024
Final decision	18 July 2024
Decision	approval

Swissmedic has only assessed parts of the primary data submitted with this application. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority, the FDA. This SwissPAR relates to the publicly available assessment report Livmarli “Integrated Review” from 23.09.2021 (Reference ID: 4863362) issued by the FDA.

3 Medical context

Alagille syndrome (ALGS) is rare (prevalence of 1:30,000 to 1:70,000), but is the most common cause of inherited cholestasis in children. ALGS presents with clinical features of chronic cholestasis, cardiovascular abnormalities, butterfly vertebrae, posterior embryotoxon, renal anomalies, vascular abnormalities, and characteristic facies. The phenotypic expression of the disease is variable, ranging from individuals with minimal phenotypic evidence of the disease to others who have end-stage liver disease, require liver transplantation, and die of liver failure, cardiac disease, or vascular dysfunction. However, a common feature of ALGS is severe cholestasis and related unremitting pruritus. The pathophysiological mechanism of cholestatic pruritus has not been identified. However, a pruritogen that accompanies bile acids (BAs) may be a culprit. Cholestatic pruritus is associated with a significantly negative impact on quality of life, causes sleep deprivation resulting in fatigue, and exerts negative effects on mood, such as suicidal ideation. Due to these negative effects on affected patients, pruritus is an indication for liver transplantation, even in the absence of liver failure.

The most common presenting signs are jaundice and pruritus, occurring in 80% of patients. Pruritus occurs earlier in patients who had neonatal jaundice than in patients who are anicteric. The hepatic manifestations of ALGS consist of hepatomegaly, cholestasis, bile duct paucity, hypercholesterolaemia, hypertriglyceridaemia, xanthomas, cirrhosis, oesophageal varices, and hepatocellular carcinoma. It is noteworthy that patients with ALGS have a higher level of bilirubin and a higher paediatric end-stage liver disease score than age-matched patients with biliary atresia. Although hepatic involvement is present in most patients with ALGS, it is a multisystem disorder. The natural history of ALGS is variable due to differences in end-organ involvement. However, cholestasis usually presents in the first 3 months, and pruritus in the first year of life.

The diagnosis of ALGS is made on the basis of both genetic testing and clinical parameters. Mutations/deletions in two genes associated with the Notch signalling pathways are known to cause ALGS: JAGGED1 (in approximately 90% of ALGS cases) and NOTCH2 in a small minority of ALGS cases. Although most patients are diagnosed during the first year of life, the age of the first presentation ranges from 16 weeks to 10 years. Cholestatic pruritus accompanying ALGS is a clinical diagnosis based on the presence of cholestasis and pruritus without skin lesions.

The prognosis of ALGS depends heavily on the extent of the symptoms and the number and severity of the affected organs, especially the liver. Reliable figures regarding life expectancy and mortality are not found in the literature; individual studies, some of them older, report an overall mortality rate of 17%. The chance of reaching the age of 20 years is described as 75% overall, 80% in patients without liver transplantation and 60% in patients who require transplantation[1]. Up to 76% of those affected require transplantation before reaching adulthood[2].

Cholestasis and associated pruritus are primarily treated conservatively with medication. In Switzerland, Quantalan (colestyramine) and Ursofalk (ursodeoxycholic acid) or similar agents are at least theoretically available for this purpose. It is not clear to what extent these two substances are actually used, possibly off label, in patients with ALGS. Potentially, rifampicin might be used off label in Switzerland to treat itching. Antihistamines and topical basic care could, in principle, also be considered for the treatment of pruritus, but it is unclear to what extent these are actually effective or have found their way into practice in the supportive treatment of ALSG. The drug therapy options are therefore severely limited. In 40% of patients there is treatment-refractory pruritus, which ultimately leads to liver transplantation. Hence a therapeutic gap exists for pruritus in ALGS — the most common cause of disabling cholestatic pruritus in children.

[1] Emerick KM, Rand EB, Goldmuntz E, et al., *Features of Alagille syndrome in 92 patients: frequency and relation to prognosis*, Hepatology, 1999 Mar;29(3):822-9, doi: 10.1002/hep.510290331.

[2] Kamath BM, Ye W, Goodrich NP, Loomes KM, et al., Childhood Liver Disease Research Network (ChiLDReN), *Outcomes of Childhood Cholestasis in Alagille Syndrome: Results of a Multicenter Observational Study*, Hepatol Commun. 2020;4(3):387. Epub 2020 Jan 22

Maralixibat is an inhibitor of the ileal bile acid transporter (IBAT). Due to the large molecular weight (710.41 Da) and the positively charged quaternary nitrogen atom, maralixibat is only slightly absorbed, maximising its local exposure at the receptor and minimising unnecessary systemic exposure. Bile acids (BA) are synthesised from cholesterol in the liver. The primary function of BA is to solubilise lipids into micelles, aiding digestion and absorption of fat and fat-soluble vitamins (FSV). Approximately 95% of the BA secreted in the lumen of the gastrointestinal (GI) tract are reabsorbed in the terminal ileum via IBAT. Inhibition of IBAT reduces the re-absorption of BA in the terminal ileum, thereby interfering with the enterohepatic circulation and decreasing the serum BA (sBA) pool. Reducing BA is proposed as an approach to treat cholestatic pruritus.

4 Quality aspects

4.1 Drug substance

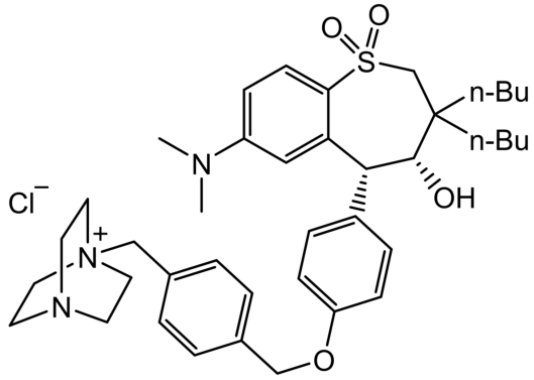
INN: Maralixibat chloride

Chemical name: 1-[[4-[[4-[(4R,5R)-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-azabicyclo [2.2.2]octan-1-ium chloride

Molecular formula: $C_{40}H_{56}ClN_3O_4S$

Molecular mass: 710.42 g/mol

Molecular structure:



Physicochemical properties: The drug substance is a white to light yellow, slightly hygroscopic solid which is soluble in water, methanol and propylene glycol. Maralixibat chloride is a Class III compound according to the Biopharmaceutical Classification System with high solubility and low permeability.

The drug substance has two chiral centres and is manufactured as the R,R-enantiomer.

Maralixibat chloride shows polymorphism and is manufactured in the thermodynamically stable polymorphic form II.

Synthesis: The synthesis of the drug substance has been adequately described, and the process is controlled with appropriate in-process controls and tests for isolated intermediates.

Structure elucidation: The structure of maralixibat chloride has been fully elucidated using several spectroscopic techniques.

Specification: The active substance specification includes tests for: appearance, identity (IR, HPLC), polymorphic form (XRPD), assay (HPLC), impurities (HPLC, GC-MS), chiral purity (HPLC), water content (Ph. Eur.), chloride identity (Ph. Eur.), residual solvents (GC HS), and residue on ignition (Ph. Eur.)

Stability: The bulk drug substance is packaged in two LDPE bags placed in a secondary HDPE container. Appropriate stability data have been generated, resulting in a suitable retest period when packaged in the packaging type described above.

4.2 Drug product

Description and composition: Livmarli 9.5 mg/mL is an oral solution. The solution is clear and colourless to light yellow.
All excipients are widely used in pharmaceutical preparations for oral use and meet the standards as defined in the current Ph. Eur. with the exception of the grape flavour. The flavour fulfils relevant standards for food additives.

Propylene glycol is an excipient with a known physiological effect; respective warnings are included in the product information.

Pharmaceutical development: Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process. In view of the fact that the product is indicated for chronic use in paediatric patients suffering from a liver disease, the development of a stable propylene glycol-free formulation is ongoing in order to improve the safety profile of the drug product.

Manufacture: The drug product is manufactured by a standard dissolution and filling process. Process parameters and in-process controls are defined. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Specification: Adequate tests and acceptance criteria for release and at shelf-life are established for the control of the finished product. The specifications include the parameters description, identity (HPLC, UV), active substance assay (HPLC), degradation products (HPLC), propylene glycol assay (HPLC), disodium edetate assay (HPLC), uniformity of mass of delivered doses from multidose container (Ph. Eur.), deliverable volume (USP), pH (Ph. Eur.), microbial enumeration (Ph. Eur.), and specified microorganisms (Ph. Eur.). Weight loss is controlled during stability testing as an additional parameter. All the analytical procedures are adequately described, and non-compendial methods are validated according to the current requirements of ICH Q2 (R1). Batch analysis data have been provided. The results are within the specifications and consistent from batch to batch.

Container closure system: The drug product is filled into a 30 mL amber coloured PET bottle with a preinstalled LDPE adapter and an HDPE child-resistant closure with a foam liner. Three sizes of CE-marked oral syringes (0.5 mL, 1 mL and 3 mL) are co-packaged as repeated-use dosing dispensers. Extractable and leachable studies were performed with the container closure system.

Stability: Appropriate stability data have been generated in the packaging material for commercial use and following the relevant international guidelines. Based on these studies, an appropriate shelf-life was established. The storage recommendation is “Do not store above 30°C. Store in the original packaging in order to protect from light.” Once the bottle has been opened, the medicinal product must be used within 130 days and stored below 30°C. After this period, the bottle and any remaining contents must be discarded.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the FDA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Livmarli “Integrated Review” from 23.09.2021 (Reference ID: 4863362) issued by the FDA.

6 Clinical aspects

Swissmedic has only assessed the primary data relating to clinical aspects of maralixibat (Livmarli) use in patients aged 3 to 11 months. The assessment relating to the clinical and clinical pharmacology aspects for older patients relies on the assessment of the foreign reference authority, the FDA. Therefore, some clinical aspects in this SwissPAR refer to the publicly available assessment report for Livmarli “Integrated Review” from 23.09.2021 (Reference ID: 4863362) issued by the FDA.

6.1 Efficacy

Patients aged 3 to 11 months

For patients aged 3 to 11 months, Swissmedic carried out its own in-depth assessment initially based on the interim report of the MRX-801 study (cut-off date 4 May 2022), which was expected to be completed in December 2024. In its response to the LoQ, the company submitted updated data (cut-off date September 28, 2023) based on 16 of the 17 included patients with ALGS (mean age 6.5 months) who had been treated with maralixibat for at least 13 weeks (primary analysis).

The MRX-801 study is an open-label, multi-centre phase 2 study that included male and female patients up to 12 months of age with cholestatic liver disease including ALGS. Similar to the pivotal study LUM001-304, the dose was titrated in the MRX-801 study, but the titration scheme comprised only 2 steps: start with the dose of 190 µg/kg/day for 7 days, with subsequent dose escalation to the target dose of 380 µg/kg once daily. The dose could be reduced to a minimum of 190 µg/kg/day in case of intolerance, but if this lower dose could not be tolerated, the patient was excluded. The FDA assessment of the pivotal study and the dose used were endorsed, therefore the dose and the escalation scheme in the study MRX-801 were considered acceptable. At the end of the study (Week 14), patients were given the opportunity to transfer to the LTE. The primary study endpoint was focused on safety and tolerability. The change in fasting sBA at Week 13 compared to baseline was defined as one of the secondary endpoints. Among the exploratory endpoints, the change from baseline in the Clinician Scratch Scale (CSS) score was determined. The CSS was obtained at baseline and at Week 6 and 13. Like the ItchRO scale, the CSS is based on a 5-point scale from 0 to 4 with higher scores representing worse outcomes, as determined by the physician.

The clinical response (according to CSS) was heterogeneously distributed, although in 47% of patients a CSS reduction was reported by Week 13. However, in 24% of patients an increase and in another 24% no change in CSS were reported. The laboratory response (according to sBA) was compromised by numerous missing data sets, but in patients with a complete data set, the improvements (reduction in sBA over time) were clear and considered clinically relevant (-15% to -77%, with 2 patients showing a minimal increase of up to +4.5%).

In summary, despite the basic difficulties of recording pruritus in infants and the numerous missing values, the interim data from the MRX-801 study, updated with 16/17 patients, showed clinical improvement in pruritus in 47% of patients as well as a numerically clear benefit with regard to sBA levels over the observation period, which justifies the clinical benefit of maralixibat for infants aged 3 months and older.

Efficacy in this young age group is supported by the data from the placebo controlled study performed in older children (LUM001-304), based on comparable disease manifestation and progression, and as no different response to maralixibat is expected given its mechanism of action.

6.2 Safety

Maralixibat is minimally absorbed with low systemic exposure in patients at the recommended doses. In the pivotal study (LUM001-304) 14 subjects experienced 33 SAEs, none of which were attributed to the study drug. No differences were observed in SAEs compared to placebo in the RWD period of the pivotal trial. However, a 4-week randomised withdrawal placebo-controlled period is limited in its ability to detect any differences. Also, there was no difference in AEs leading to discontinuation of the study drug for maralixibat (0) versus placebo (0) and AEs leading to dose modification for maralixibat (0) versus placebo (1/16, 6.2%). In addition, the difference in AEs between maralixibat and placebo was not substantial, as shown by a risk difference (RD) and a 95% CI of -21.2 (-55.6, 13.3). Most common GI adverse reactions such as diarrhoea, abdominal pain, and vomiting were reported but could be addressed by treatment interruption or treatment discontinuation. No deaths were reported in this study.

In the MRX-801 study 14 patients (82.4%) reported at least one TEAE, 4 patients (23.5%) reported at least one grade 3 TEAE (diarrhoea, fever, viral infection, pneumonia, COVID-19, varicella, colic, crying). Five patients (29.4%) reported an SAE, and 1 TEAE led to discontinuation of medication and this study. The most common SOC was infections and infestations (10 patients, 58.8%), although not more common than in the pooled placebo arm (refer to the paragraph below for details), followed by GI complaints (10 patients, 58.8%). The most common PT were diarrhoea (7 patients, 41.2%), nasopharyngitis (5 patients, 29.4%) and upper respiratory tract infection (4 patients, 23.5%). No deaths or AESI were reported in this study.

There was a concern that a short 4-week randomised withdrawal placebo-controlled period in the pivotal study (LUM001-304) and the lack of a placebo arm in the MRX-801 study limited the ability to detect potential safety signals. A requested pooled safety analysis of all ALGS patients who participated in maralixibat studies (LUM001-302/302/304 and MRX-801) confirmed the safety profile of maralixibat. This analysis included 87 patients from all maralixibat treatment arms and 18 patients from all placebo arms. In the pooled verum arm compared to placebo arm an increased incidence of ear problems (2.3% vs 0%), abdominal pain (28.7% vs 16.7%), cough (14.9% vs 0%), and nasopharyngitis (17.2% vs 5.6%) but not infections in general (55.2% vs 55.6%) was detected. More falls with corresponding subsequent injuries (4 vs 0 cases, 4.6% vs 0%) as well as laboratory abnormalities (14.9% vs 5.6%) were observed in the pooled maralixibat arm. Furthermore, pruritus (4.6% vs 0%) and central nervous disorders such as headache (12.6% vs 0%) and lethargy (3.4% vs 0%) were more frequent with maralixibat, with zero cases being documented in the placebo pool in each case.

Treatment-emergent liver test abnormalities, FSV deficiency and bone fractures were observed in open-label portions of the pivotal trial and in supportive studies. However, these adverse events commonly occur in ALGS (e.g. the presence of FSV deficiency is one criterion that can support the diagnosis of ALGS). Therefore, the extent to which maralixibat may affect the frequency and severity of these events is unclear. Careful review of liver test abnormalities, for example, suggests that most are unrelated to maralixibat, although several are potentially related to maralixibat exposure, with improvement after drug discontinuation or a decrease in dose. These observations of liver test abnormalities, gastrointestinal adverse reactions, and FSV deficiency are properly addressed in the Information for healthcare professionals to alert clinicians to carefully follow patients who experience these adverse reactions.

Consequently, this approval of maralixibat was bound to the post-approval requirement to submit the final clinical study reports of the ongoing long-term open-label trial (MRX-800), the MRX-801, and the MRX-310 trials.

6.3 Final clinical benefit-risk assessment

The FDA assessment for patients aged 12 months and older was endorsed by Swissmedic. The data submitted showed that the benefits of maralixibat outweigh the risks in the treatment of cholestatic pruritus in patients with Alagille syndrome.

The efficacy and safety of maralixibat in the treatment of cholestatic pruritus in patients younger than 12 months with Alagille syndrome was assessed based on interim data from the MRX-801 study. This interim report included 16 out of 17 enrolled patients treated for at least 13 weeks (primary analysis). The estimated efficacy in this population can be considered sufficient while further supported by the data from the placebo controlled study performed in older children. The safety is comparable to that in patients aged 12 months and older without prohibitive signals, but due to the small number of cases and relatively short exposure time, it must also be regarded as limited. In the overall context of ALGS being an orphan disease with limited treatment options, the benefit-risk assessment for patients aged 3 to 11 months is positive.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Livmarli was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

LIVMARLI®

Composition

Active substances

Maralixibat (as maralixibat hydrochloride).

Excipients

Edetate disodium, grape flavor (contains propylene glycol(E 1520)), propylene glycol (E 1520), sucralose (E 955), purified water.
1 ml of the oral solution contains 0.124 mg of sodium and 364.55 mg of propylene glycol.

Pharmaceutical form and active substance quantity per unit

Oral solution: 9.5 mg of maralixibat per ml (equivalent to 10 mg of maralixibat chloride per ml) as a clear, colorless to yellow solution.

Indications/Uses

LIVMARLI is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 3 months of age and older.

Dosage/Administration

Usual dosage

The recommended dosage is 380 µg/kg once daily, taken 30 minutes before a meal in the morning. Start dosing at 190 µg/kg administered orally once daily; after one week, increase to 380 µg/kg once daily, as tolerated. The maximum daily dose volume for patients above 70 kg is 28.5 mg. The efficacy of a therapy with 190 µg/kg has not been investigated. Refer to the dosing by weight guidelines presented in Table 1.

Table 1: Individual Dose Volume by Patient Weight

Patient Weight (kg)	**Days 1-7 (190 µg/kg once daily)**		**Beginning Day 8 (380 µg/kg once daily)**	
	Volume per day (ml)	Syringe size (ml)	Volume per day (ml)	Syringe size (ml)
5 to 6	0.1	0.5	0.2	0.5

7 to 9	0.15		0.3	
10 to 12	0.2		0.45	
13 to 15	0.3		0.6	1
16 to 19	0.35		0.7	
20 to 24	0.45		0.9	
25 to 29	0.5		1	
30 to 34	0.6	1	1.25	3
35 to 39	0.7		1.5	
40 to 49	0.9		1.75	
50 to 59	1		2.25	
60 to 69	1.25	3	2.5	
70 or higher	1.5		3	

Special dosage instructions

Patients with hepatic disorders

LIVMARLI has not been studied in patients with hepatic decompensation. Discontinue LIVMARLI permanently if a patient experiences a hepatic decompensation event (e.g., variceal hemorrhage, ascites, hepatic encephalopathy).
Clinical studies of LIVMARLI included ALGS patients with impaired hepatic function at baseline. The efficacy and safety in ALGS patients with clinically significant portal hypertension and in patients with decompensated cirrhosis have not been established (see “Clinical efficacy”, and “Warnings and precautions”).

Patients with renal disorders

The safety and efficacy of LIVMARLI in patients with renal disorders have not been investigated.

Elderly patients

The safety and effectiveness of LIVMARLI for the treatment of pruritus in ALGS in adult patients, 65 years of age and older, have not been established.

Children and adolescents

LIVMARLI is not authorised for use in patients less than 3 months of age.

Delayed administration

If a dose is missed, it should be taken as soon as possible within 12 hours of the time it is usually taken, and the original dosing schedule should be resumed. If a dose is missed by more than 12 hours, the dose can be omitted and the original dosing schedule resumed.

Mode of administration

Administer LIVMARLI 30 minutes before a meal in the morning (see “Pharmacokinetics”).
For patients taking bile acid binding resins, take LIVMARLI at least 4 hours before or 4 hours after taking a bile acid binding resin (see ”Interactions”).
Mixing LIVMARLI oral solution directly into food or drink prior to administration has not been studied and should be avoided.
Three sizes of oral syringe (0.5 ml, 1 ml and 3 ml) are provided with each bottle of LIVMARLI. In table 1 the correct size of oral syringe is shown for each dosing volume.

Contraindications

Hypersensitivity to the active substance or to any of the excipients (see “Composition”).

Warnings and precautions

Liver Test Abnormalities

Establish the baseline pattern of variability of liver tests prior to starting LIVMARLI, so that potential signs of liver injury can be identified. Monitor liver tests (e.g., ALT [alanine aminotransferase], AST [aspartate aminotransferase], TB [total bilirubin]), DB [direct bilirubin] and International Normalized Ratio [INR]) during treatment with LIVMARLI. Interrupt LIVMARLI if new onset liver test abnormalities occur in the absence of other causes. Once the liver test abnormalities either return back to baseline values or stabilize at a new baseline value, consider restarting LIVMARLI at 190 µg/kg, and increase to 380 µg/kg as tolerated. Consider discontinuing LIVMARLI permanently if liver test abnormalities recur or symptoms consistent with clinical hepatitis are observed.

Patients enrolled in Trial 1 had abnormal liver tests at baseline. During Trial 1, treatment-emergent elevations of liver tests or worsening of liver tests, relative to baseline values, were observed. Most abnormalities included elevation in ALT, AST, or T/DB. In Trial 1, one patient (TB elevated at baseline) discontinued LIVMARLI due to increased TB above baseline after 28 weeks. Four patients had ALT increases that led to dose modification (n=1), dose interruption (n=2), or permanent discontinuation (n=2) of LIVMARLI during the long-term, open-label extension period of Trial 1(see ”Undesirable effects”)

LIVMARLI was not evaluated in ALGS patients with cirrhosis. Monitor patients during treatment with LIVMARLI for elevations in liver tests and for the development of liver-related adverse reactions. Weigh the potential risks against the benefits of continuing treatment with LIVMARLI in patients who have experienced persistent or recurrent liver tests abnormalities. Discontinue LIVMARLI permanently if a patient progresses to portal hypertension or experiences a hepatic decompensation event.

Gastrointestinal Adverse Reactions

Diarrhea, abdominal pain, and vomiting were reported as the most common adverse reactions in patients treated with LIVMARLI (see ”Undesirable effects”). Three patients (3%) experienced vomiting as a serious adverse event requiring hospitalization or intravenous fluid administration.

If diarrhea, abdominal pain, and/or vomiting occur and no other etiologies are found, consider reducing the dose of LIVMARLI or interrupting LIVMARLI dosing~~interrupt the therapy with LIVMARLI.~~ For diarrhea or vomiting, monitor for dehydration and initiate an adequate treatment if necessary. Consider interrupting LIVMARLI dosing if a patient experiences persistent diarrhea or has diarrhea with accompanying signs and symptoms such as bloody stool, vomiting, dehydration requiring treatment, or fever. A dose reduction or an interruption of treatment were not investigated in a controlled manner in the studies relevant for the authorisation.

When diarrhea, abdominal pain, and/or vomiting resolve, restart LIVMARLI at 190 µg/kg/day and increase the dose as tolerated. If they recur upon re-challenge with LIVMARLI, then consider stopping LIVMARLI treatment.

Fat Soluble Vitamin (FSV) Deficiency

Fat-soluble vitamins (FSV) include vitamin A, D, E, and K (measured using INR levels). ALGS patients can have FSV deficiency at baseline. LIVMARLI may affect absorption of fat-soluble vitamins. In Trial 1, treatment emergent FSV deficiency was reported in 3 (10%) patients during 48 weeks of treatment.

Obtain serum FSV levels at baseline and monitor during treatment, along with any clinical manifestations. If FSV deficiency is diagnosed, supplement with FSV. Consider discontinuing LIVMARLI if FSV deficiency persists or worsens despite adequate FSV supplementation.

This medicinal product contains 364.5 mg propylene glycol per ml. The concomitant use with a substrate of alcohol dehydrogenase - such as ethanol - can cause serious undesirable effects in newborns.
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium-free”.

Interactions

Bile acid binding resins

Bile acid binding resins may bind to maralixibat in the gut. Administer bile acid binding resins (e.g., cholestyramine, colesevelam, or colestipol) at least 4 hours before or 4 hours after administration of LIVMARLI.

Effect of Other Drugs on Maralixibat

Maralixibat is not a substrate of the drug transporters MDR1 (P-gp), BCRP, OATP1B1, OATP1B3, or OATP2B2; therefore, concomitant drug products are not predicted to affect the disposition of maralixibat.

Effect of Maralixibat on Other Drugs

In vitro, maralixibat did not induce CYP isoforms 1A2, 2B6, or 3A4, nor inhibit CYP isoforms 1A2, 2B6, 2C8, 2C9, 2C19 or 2D6 at clinically relevant concentrations. Maralixibat inhibits CYP3A4 *in vitro.* An increase of plasma levels of CYP3A4 substrates (e.g., midazolam, simvastatin) can therefore not be excluded. Caution is advised when administering such medicinal products concomitantly. *In vitro,* maralixibat did not inhibit the transporters MDR1 (P-gp), BCRP, OAT1, OAT3, OATP1B1, OATP1B3, PEPT1, OCT1, OCT2, OCT3, OCTN1, OCTN2, MRP2, MATE1, or MATE2-K at clinically relevant concentrations.

OATP2B1 substrates

Maralixibat is an OATP2B1 inhibitor based on *in vitro* studies. A decrease in the oral absorption of OATP2B1 substrates (e.g., statins) due to OATP2B1 inhibition in the GI tract cannot be ruled out. In clinical studies coadministration of 4.75 mg maralixibat (once daily in the morning) with daily doses of either simvastatin, or lovastatin in the evening, did not have a clinically relevant effect on the pharmacokinetics of these statins and their metabolites. Coadministration of 4.75 mg maralixibat did not affect pharmacokinetics of atorvastatin. However, the effect of maralixibat on the pharmacokinetics of OATP2B1 substrates at higher doses has not been evaluated in a clinical study. Consider monitoring the drug effects of OATP2B1 substrates (e.g. statins) as needed.

Bile acids

Maralixibat inhibits the absorption of bile acids. The interaction potential with the bile acid ursodeoxycholic acid has not been fully evaluated.

Pregnancy, lactation

Pregnancy

Maternal use at the recommended clinical dose of LIVMARLI is not expected to result in measurable fetal exposure because systemic absorption following oral administration is low (see “Pharmacokineticcs”). Maralixibat may inhibit the absorption of fat-soluble vitamins (see “Warnings and precautions and below section on “Clinical Considerations”). In animal reproduction studies, no developmental effects were observed (see “Preclinial data”).
The estimated background risk of major birth defects for the indicated population is higher than the general population because Alagille syndrome is an autosomal dominant condition. The estimated background risk of miscarriage for the indicated population is unknown..

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Maralixibat may inhibit the absorption of fat-soluble vitamins (FSV). Monitor for FSV deficiency and supplement as needed. Increased supplementation of FSVs may be needed during pregnancy (see “Warnings and precautions”).

Lactation

LIVMARLI has low absorption following oral administration, and breastfeeding is not expected to result in exposure of the infant to LIVMARLI at the recommended dose (see ”Pharmacokinetics”). There are no data on the presence of LIVMARLI in human milk, the effects on the breastfed infant, or the effects on milk production. Patients with ALGS can have FSV deficiency as part of their disease. Maralixibat may reduce absorption of fat-soluble vitamins (see “Warnings and precautions). Monitor FSV levels and supplement FSV intake, if FSV deficiency is observed during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother’s need for LIVMARLI and any potential adverse effects on the breastfed child from LIVMARLI or from the underlying maternal condition.

Fertility

There is currently no experience of the effects of maralixibat on fertility in humans.
Animal studies have not shown any direct or indirect harmful effects on fertility.

Effects on ability to drive and use machines

No corresponding studies have been performed.

Undesirable effects

Summary of the safety profile

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In the Alagille syndrome clinical development program, which includes five clinical studies comprising 86 patients, patients received doses of LIVMARLI up to 760 µg/kg per day with a median duration of exposure of 32.3 months (range: 0.03 - 60.9 months). In Trial 1, the 4-week placebo control period occurred after 18 weeks of LIVMARLI treatment. In two supportive studies that included long-term open-label extensions, only 13 weeks of placebo-controlled treatment occurred which evaluated doses lower than 380 µg/kg/day. The majority of LIVMARLI exposure in the development program occurred without a placebo control in open-label trial extensions.

The most common adverse reactions (≥5%) for ALGS patients treated with LIVMARLI are presented in Table 2 below. Treatment interruptions or dose reductions occurred in 5 (6%) patients due to diarrhea, abdominal pain, or vomiting.

List of adverse reactions

Adverse drug reactions for LIVMARLI are ranked under the MedDRA frequency classification: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1'000 to <1/100); rare (≥1/10'000 to <1/1'000); very rare (<1/10'000).

Table 2: Adverse Reactions Occurring in Patients Treated with LIVMARLI in the ALGS Clinical Development Program

LIVMARLI (n=86)			
System organ class Adverse Reaction	**Frequency**	**Any Grade n (%)**	**Number of events per 100 person-years[1]**
Infections and infestations			
Nasopharyngitis	Very common	37 (35.9%)	20.8
Ear infection	Very common	23 (22.3%)	11.1
Metabolism and nutrition disorders			
Fat-Soluble Vitamin deficiency*	Very common	22 (21.4%)	10.4
Nervous system disorders			
Headache	Very common	27 (26.21%)	13.3
Respiratory, thoracic, and mediastinal disorders			
Cough	Very Common	40 (38.9%)	24.8
Gastrointestinal disorders			
Diarrhea	Very common	55 (53.4%)	44.2
Abdominal pain*	Very common	49 (47.6%)	37.9
Vomiting	Very common		19.7
Gastrointestinal bleeding*	Common	9 (8.7%)	3.6
Nausea	Common	7 (8.1%)	2.9
Hepatobiliary disorders			
Transaminases increased (ALT, AST)*	Very common	17 (16.5%)	7.0
Musculoskeletal and connective tissue disorders			
Bone fractures*	Common	8 (7.77%)	3.2

* Terms were defined as:
Fat-Soluble Vitamin deficiency includes: A, D, E, or K deficiency, or INR increase
Abdominal pain includes: abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper
Gastrointestinal bleeding includes: hematochezia, hematemesis, gastrointestinal hemorrhage, melena
Transaminases increased includes: ALT abnormal, ALT increased, AST abnormal, AST increased
Bone fracture includes: tibia fracture, rib fracture, hand fracture, humerus fracture, pathological fracture, forearm fracture, clavicle fracture
[1] Exposure adjusted incidence rate for each adverse reaction type was calculated using the first occurrence of this adverse reaction per patient

Description of specific adverse reactions and additional information

Liver Test Abnormalities

Increase in Transaminases

In a pooled analysis of patients with ALGS (N=86) administered LIVMARLI, increases in hepatic transaminases (ALT) were observed. Seven (8.1%) patients discontinued LIVMARLI due to ALT increases. Three (3.5%) patients had a decrease in dose or interruption of LIVMARLI in response to ALT increases. In the majority of cases, the elevations resolved or improved after discontinuation or dose modification of LIVMARLI. In some cases, the elevations resolved or improved without change in LIVMARLI dosing. Increases to more than three times baseline in ALT occurred in 24% of patients treated with LIVMARLI and increases to more than five times baseline occurred in 2%. AST increases to more than three times baseline occurred in 14% of patients treated with LIVMARLI, and an increase to more than five times baseline occurred in one patient. Elevations in transaminases were asymptomatic and not associated with bilirubin elevations or other laboratory abnormalities.

Increases in Bilirubin

Four (4.6%) patients in the pooled analysis experienced bilirubin increases above baseline, and LIVMARLI was subsequently withdrawn in two of these patients, who had elevated bilirubin at baseline.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Single doses of maralixibat up to 500 mg, approximately 18-fold higher than the recommended dose, have been administered in healthy adults and were tolerated without a meaningful increase in

adverse effects when compared to lower doses. If an overdose occurs, discontinue LIVMARLI, monitor the patient for any signs and symptoms and institute general supportive measures if needed.

Properties/Effects

ATC code

A05AX04

Mechanism of action

Maralixibat is a reversible inhibitor of the ileal bile acid transporter (IBAT). It decreases the reabsorption of bile acids (primarily the salt forms) from the terminal ileum.
Pruritus is a common symptom in patients with ALGS and the pathophysiology of pruritus in patients with ALGS is not completely understood. Although the complete mechanism by which maralixibat improves pruritus in ALGS patients is unknown, it may involve inhibition of the IBAT, which results in decreased reuptake of bile salts, as observed by a decrease in serum bile acids (see “Pharmacodynamics”).

Pharmacodynamics

In Trial 1, pediatric patients with ALGS were administered open-label treatment with LIVMARLI 380 µg/kg once daily for 13 weeks after an initial 5-week dose-escalation period (see “Clinical efficacy). At baseline, serum bile acids were highly variable among patients ranging from 20 to 749 µmol/L and mean (SD) serum bile acid level was 283 (210.6) µmol/L. Serum bile acid levels decreased from baseline in the majority of patients as early as at Week 12 and the reduction in serum bile acids was generally maintained for the treatment period.

Clinical efficacy

The efficacy of LIVMARLI was assessed in Trial 1 (NCT02160782), which consisted of an 18-week open-label treatment period; a 4-week randomized, double-blind, placebo-controlled drug-withdrawal period; a subsequent 26-week open-label treatment period; and a long-term open-label extension period.
Thirty-one pediatric ALGS patients with cholestasis and pruritus were enrolled, with 90.3% of patients receiving at least one medication to treat pruritus at study entry. All patients had JAGGED1 mutation. Patients were administered open-label treatment with LIVMARLI 380 µg/kg once daily for 13 weeks after an initial 5-week dose-escalation period; two patients discontinued treatment during this first 18 weeks of open-label treatment. The 29 patients who completed the open-label treatment phase were then randomized to continue treatment with LIVMARLI or receive matching placebo during the 4-week drug withdrawal period at Weeks 19-22 (n=16 placebo, n=13 LIVMARLI). All 29 patients completed the randomized, blinded drug withdrawal period; subsequently, patients received open-label LIVMARLI at 380 µg/kg once daily for an additional 26 weeks.

Randomized patients had a median age of 5 years (range: 1 to 15 years) and 66% were male. The baseline mean (standard deviation [SD]) of liver test parameters were as follows: serum bile acid levels 280 (213) µmol/l, AST 158 (68) U/l, ALT 179 (112) U/l, Gamma Glutamyl Transferase (GGT) 498 (399) U/l, and TB 5.6 (5.4) mg/dl.

Given the patients' young age, a single-item observer-reported outcome was used to measure patients' pruritus symptoms as observed by their caregiver twice daily (once in the morning and once in the evening) on the Itch Reported Outcome Instrument (ItchRO[Obs]). Pruritus symptoms were assessed on a 5-point ordinal response scale, with scores ranging from 0 (none observed or reported) to 4 (very severe). Patients were included in Trial 1 if their average pruritus score was greater than 2.0 (moderate) in the 2 weeks prior to baseline.

The average of the worst daily ItchRO(Obs) pruritus scores was computed for each week. For randomized patients, the mean (SD) at baseline (pre-treatment) was 3.1 (0.5) and the mean (SD) at Week 18 (pre-randomized withdrawal period) was 1.4 (0.9). On average, patients administered LIVMARLI for 22 weeks maintained pruritus reduction whereas those in the placebo group who were withdrawn from LIVMARLI after Week 18 returned to baseline pruritus scores by Week 22. Results from the placebo-controlled period are presented in Table 3. After re-entering the open-label treatment phase, both randomized treatment groups had similar mean pruritus scores by Week 28, the first week placebo patients received the full dosage of LIVMARLI after withdrawal. These observer-rated pruritus results are supported by similar results on patient-rated pruritus in patients 5 years of age and older who were able to self-report their itching severity.

Table 3: Weekly Average of Worst Daily ItchRO(Obs) Pruritus Severity Scores in Trial 1

	Maralixibat (N=13)	**Placebo (N=16)**	**Mean Difference**
Week 22, Mean (95% CI)	1.6 (1.1, 2.1)	3.0 (2.6, 3.5)	
Change from Week 18 to Week 22, Mean (95% CI)	0.2 (-0.3, 0.7)	1.6 (1.2, 2.1)	-1.4 (-2.1, -0.8)

Results based on an analysis of covariance model with treatment group and Week 18 average worst daily pruritus score as covariates

Paediatrics

The safety and effectiveness of LIVMARLI for the treatment of cholestatic pruritus in Alagille syndrome are established in pediatric patients aged 12 months of age and older. The use of LIVMARLI in patients aged 3 to 11 months is supported by the results of an open, multicenter study in 16 patients aged 2 months and older. Despite a very small number of cases and heterogeneous variability, the efficacy results show a treatment benefit that is considered clinically relevant and the safety results show a similar safety profile compared to patients aged 12 months and older.

Pharmacokinetics

Because of the low systemic absorption of maralixibat, pharmacokinetic parameters cannot be reliably calculated at the recommended dose. Concentrations of maralixibat in the pediatric ALGS patients were below the limit of quantification (0.25 ng/ml) in the majority of plasma samples. In Trial 1, the highest concentration of maralixibat in pediatric ALGS patients following treatment with LIVMARLI 380 µg/kg once daily was 5.93 ng/ml.
Following single oral administration of maralixibat in healthy adults at doses ranging from 1 mg to 500 mg, plasma concentrations of maralixibat were below the limit of quantification (0.25 ng/ml) at doses less than 20 mg and PK parameters could not be reliably estimated.
Following a single dose administration of 30 mg under fasted condition, median T_{max} was 0.75 and mean (SD) C_{max} and AUC_{last} were 1.65 (1.10) ng/ml and 3.43 (2.13) ng·h/ml, respectively.

Absorption

Maralixibat is minimally absorbed and plasma concentrations are often below the limit of quantification (0.25 ng/ml) after single or multiple doses at recommended doses. Following a single oral administration of maralixibat 30, 45, and 100 mg liquid formulation under fasted condition, AUC_{last} and C_{max} increased in a dose-dependent manner with increase of 4.6-and 2.4-fold, respectively, following a 3.3-fold dose increase from 30 to 100 mg.
No accumulation of maralixibat was observed following repeated oral administration of administration of maralixibat in healthy adults at doses up to 100 mg once-daily.

Effect of Food

Concomitant administration of a high-fat meal with a single oral dose of maralixibat decreased both the rate and extent of absorption. AUC and C_{max} of maralixibat values in the fed state were 64.8% to 85.8% lower relative to oral administration of 30 mg in fasted conditions. The effect of food on the changes of systemic exposures to maralixibat is not clinically significant (see “Dosage/Administration”).

Distribution

Maralixibat shows high binding (91%) to human plasma proteins *in vitro*.

Metabolism

No maralixibat metabolites have been detected in plasma. Three minor metabolites, accounting for <3% of maralixibat-associated fecal radioactivity in total, were identified following oral administration of [^{14}C]maralixibat.

Elimination

Following a single oral dose of 30 mg maralixibat in healthy adults, the mean half-life ($t_{1/2}$) was 1.6 hours.

Fecal excretion was found to be the major route of elimination. Following a single oral dose of 5 mg ^{14}C-maralixibat, 73% of the dose was excreted in the feces with 0.066% excreted in the urine. 94% of the fecal excretion was as unchanged maralixibat.

Kinetics in specific patient groups

Renal impairment

The pharmacokinetics of maralixibat were not studied in patients with impaired renal function, including those with end-stage renal disease (ESRD) or those on hemodialysis.

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date “EXP" stated on the pack.

Shelf life after opening

After the first opening of the bottle, the medicinal product must be stored below 30°C and used within 130 days. Then the bottle and its contents have to be discarded, even if not empty.

Special precautions for storage

Store below 30°C.
Store in the original packaging in order to protect the contents from light.
Keep out of the reach of children.

Instructions for handling

The oral syringes may be rinsed with water, air dried and reused for 130 days.
The instructions for use of the oral syringes are described in the patient information.

Authorisation number

69201 (Swissmedic)

Packs

Each pack contains 1 amber-coloured PET bottle (30 ml) with a preinstalled LDPE adapter, a HDPE child-resistant closure with a foam liner and three oral repeated-use syringes (0.5 ml, 1 ml and 3 ml) with the following graduations. [B]

- 0.5 ml polypropylene syringe with a white plunger: numbers for each 0.1 ml, major hash marks for 0.05 ml increments, and minor hash marks for 0.01 ml increments.
- 1 ml polypropylene syringe with a white plunger: numbers for each 0.1 ml increment.
- 3 ml polypropylene syringe with a white plunger: numbers for each 0.5 ml increment, and hash marks for each 0.25 ml increment between 0.5 ml and 3 ml.

Marketing authorisation holder

Mirum Pharmaceuticals AG, 6300 Zug

Date of revision of the text

July 2024

Revision history

Application ID	Milestone	Created on	Change	Initials
102703256	Initial Submission	March 2023	Initial Application for Marketing Authorisation	Inital MAA
102703256	Response to LoQ	November 2023	Response to LoQ	Response to LoQ
102703256	Response to PD	April 2024	Response to Preliminary Decree	Response to PD