swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Extension of therapeutic indication

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:	extension of therapeutic indication approved on 12 May 2026

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.

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1 Terms, definitions, abbreviations

ABCB11	ATP-binding cassette, sub-family B member 11, also known as BSEP
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
ATP8B1	ATPase phospholipid transporting 8B1
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
BA	Bile acids
BID	Twice daily
BSEP	Bile salt export pump, also known as ABCB11
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
EU	European Union
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IBAT	Ileal bile acid transporter
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
PEBD	Partial external biliary diversion
PFIC	Progressive familial intrahepatic cholestasis
PG	Propylene glycol
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
QD	Once daily
RMP	Risk management plan
SAE	Serious adverse event

sBA	Serum bile acids
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)
UDCA	Ursodeoxycholic acid
US	United States

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved indication in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status for the indication of treatment of progressive familial intrahepatic cholestasis (PFIC) in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 17 September 2024.

2.2 Indication and dosage

2.2.1 Requested indication

Livmarli is indicated for the treatment of patients 3 months of age and older:
- Progressive familial intrahepatic cholestasis (PFIC).

2.2.2 Approved indication

Livmarli is indicated for the treatment of cholestatic pruritus in patients with:
- Progressive familial intrahepatic cholestasis (PFIC) aged 12 months and older.

2.2.3 Requested dosage

Summary of the requested standard dosage:

The starting dose is 285 µg/kg once daily (QD) and may be increased to 285 µg/kg twice daily (BID, morning and evening) or to 570 µg/kg twice daily, respectively, as tolerated. The maximum daily dose volume for patients above 50 kg is 6 mL (57 mg).

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	27 November 2024
Formal objection	13 December 2024
Response to formal objection	24 January 2025
Formal control completed	7 February 2025
List of Questions (LoQ)	23 May 2025
Response to LoQ	22 July 2025
2nd list of Questions (LoQ)	19 September 2025
Response to 2nd LoQ	18 November 2025
Preliminary decision	23 January 2026
Response to preliminary decision	24 March 2026
Labelling corrections and/or other aspects	20 April 2026
Response to labelling corrections and/or other aspects	24 April 2026
Final decision	12 May 2026
Decision	approval

3 Medical context

- **Progressive familial intrahepatic cholestasis (PFIC)**

PFIC is a rare group of autosomal recessive liver disorders characterised by impaired bile acid (BA) secretion and transport. It typically manifests in early childhood, leading to progressive liver damage and potential liver failure. The estimated prevalence is 1 in 50,000–100,000 live births, with equal incidence in males and females. Survival rates without surgical biliary diversion or liver transplantation are poor, with only 50% surviving to age 10 and < 10% to age 20.

PFIC is currently divided into 13 subtypes linked to different gene defects affecting bile secretion, with PFIC1 and PFIC2 being most common. PFIC1 (ATP8B1-related) arises from mutations affecting phospholipid transport, causing not only BA retention, but also systemic symptoms like pancreatitis and hearing loss. PFIC2 (ABCB11-related) results from loss of bile salt export pump (BSEP) function, leading to severe cholestasis, rapid liver damage, and an increased risk of hepatocellular carcinoma. Other PFIC subtypes are (very) rare and less investigated. All subtypes share debilitating symptoms such as intense pruritus and malabsorption of fat-soluble vitamins.

Diagnosis relies on molecular genetic testing: ATP8B1 mutations confirm PFIC1, and ABCB11 mutations confirm PFIC2. Treatment focuses on symptom relief (specifically pruritus), slowing disease progression, and managing complications. Therapies include ursodeoxycholic acid (UDCA), BA sequestrants, and surgical approaches like partial external biliary diversion (PEBD). Liver transplantation is often required, with curative outcomes in PFIC2 but limited effectiveness in PFIC1 due to extrahepatic manifestations.

Emerging therapies, such as ileal bile acid transporter (IBAT) inhibitors (e.g. odevixibat, maralixibat), aim to alleviate pruritus by reducing BA reabsorption via interruption of the enterohepatic BA circulation, but they may risk exacerbating cholestasis via potential induction of BA synthesis in hepatocytes, which may result in hepatotoxicity in some cases.

- **Maralixibat (Livmarli)**

Maralixibat is an oral, minimally absorbed, selective IBAT inhibitor. IBAT plays a crucial role in the enterohepatic circulation, actively transporting over 95% of the circulating BA pool back to the liver. Maralixibat-mediated blockade of intestinal BA reabsorption interrupts the enterohepatic circulation, thereby increasing faecal BA excretion and lowering serum BA (sBA) levels. Reducing sBA levels has been proposed as an approach to the treatment of cholestatic pruritus. The impact on intrahepatic BA levels is unclear.

4 Nonclinical aspects

The applicant did not submit new nonclinical studies in support of their application for the new indication and the associated changes in posology, which consist of higher dose recommendations (up to 3-fold) for the PFIC indication compared to the approved ALGS indication. This was considered acceptable from a nonclinical perspective, because there are still sufficient safety margins to the NOAEL doses in the nonclinical safety studies, the patient age range for the PFIC indication is approved for the ALGS indication, and the intended mechanism of action of maralixibat (inhibition of bile acid re-absorption) applies to both indications. The Information for healthcare professionals contains appropriate information regarding the excipient propylene glycol, including measures for risk mitigation.

Based on the ERA, the extension of the indication will not be associated with a significant risk to the environment.

From the nonclinical point of view, there are no objections to the approval of the proposed indication extension.

5 Clinical aspects

5.1 Clinical pharmacology

There were no new aspects regarding the PK and PD of maralixibat.

5.2 Dose finding and dose recommendation

No dedicated dose-finding study has been conducted for maralixibat in PFIC.

The maximum recommended dose and BID regimen were evaluated in study SHP625-101 in healthy volunteers. This study demonstrated dose-dependent increases in faecal bile acid levels at doses up to 100 mg QD and 50 mg BID, with no clinically meaningful effects on safety or tolerability. These doses correspond to approximately 700 µg/kg BID in a 70-kg adult. Twice-daily dosing is hypothesised to provide more sustained target inhibition at the level of the distal ileum throughout the day.

In open-label study LUM001-501 in patients with PFIC, 6 of 19 participants with non-truncating BSEP mutations (PFIC2) achieved an sBA response at a maralixibat dose of 280 µg/kg QD. Doubling this dose resulted in an sBA response in one additional participant, yielding an overall response rate of 37% (7/19). These findings suggest that higher maralixibat doses may improve response rates in some patients who require greater IBAT inhibition. On this basis, and to maximise treatment effect, dose escalation up to a maintenance dose of 570 µg/kg BID was evaluated in the pivotal phase 3 study MRX-502. However, post hoc analysis demonstrated that 33% of patients achieved a clinically relevant sBA response (sBA level < 102 µmol/L or a ≥ 75% reduction from baseline) while receiving half of this maralixibat dose (285 µg/kg BID). At the full dose, the corresponding response rate was 45%. In addition, 57% of patients achieved at least 80% of their individual sBA reduction on half dose, compared with 63% on full dose. These findings indicate that maralixibat maintenance doses below 570 µg/kg BID may be effective in a subset of patients with PFIC.

Weaver *et al.* (1991)[1] reported a wide interindividual variability in intestinal length from birth, with up to 100% variation observed from early childhood onwards. This substantial variability may contribute to differences in the dosing requirements needed to achieve a therapeutic response to IBAT inhibitors in paediatric patients. Consequently, individualised dose titration is likely to be necessary to determine the optimal maralixibat dose for each patient and to minimise unnecessary exposure to propylene glycol (see below).

The proposed regimen, with a starting dose of 285 µg/kg once daily (QD) and escalation up to 570 µg/kg twice daily (BID), is consistent with the dosing used in the pivotal MRX-502 and infant MRX-801 studies.

5.3 Efficacy

The efficacy of maralixibat in PFIC was evaluated in a single 1:1 randomised, double-blind, placebo-controlled, multicentre, 6-month study (MRX-502) and its open-label, single-arm extension study (MRX-503). Patients aged 1 to 17 years with a diagnosis of PFIC, persistent pruritus (> 6 months), and biochemical abnormalities, but without severe hepatic impairment, were enrolled.

The primary endpoint of study MRX-502 was the change in pruritus severity, assessed using the caregiver-reported ItchRO(Obs) instrument, a 5-point scale ranging from 0 (no itch) to 4 (very severe itch), with a ≥ 1.0-point reduction considered clinically meaningful. ItchRO(Obs) responders were defined as participants with a ≥ 1.0-point decrease from baseline in the 4-week average morning ItchRO(Obs) score or an average score of ≤ 1.0. The key secondary endpoint was change in sBA levels. sBA responders were defined as participants with an average sBA level < 102 µmol/L (if baseline sBA was ≥ 102 µmol/L) or a ≥ 75% average reduction from baseline.

[1] Weaver LT, Austin S, Cole TJ. Small intestinal length: a factor essential for gut adaptation. Gut. 1991 Nov;32(11):1321-3. doi: 10.1136/gut.32.11.1321. PMID: 1752463; PMCID: PMC1379160

Maralixibat demonstrated a statistically significant and clinically meaningful improvement in pruritus compared with placebo, with a least-squares mean difference in average morning ItchRO(Obs) score between baseline and weeks 15–26 of −1.20 points (95% CI: −1.727, −0.674; $p < 0.0001$). The difference in mean change in total sBA levels from baseline to the average of weeks 18, 22, and 26 between maralixibat and placebo was −160.4 µmol/L (95% CI: −220.8, −100.0; $p < 0.0001$). These findings were confirmed in the per-protocol population and sensitivity analyses.

Subgroup analyses by PFIC type suggested improvements in pruritus and reductions in sBA levels in patients with PFIC1, nt-PFIC2 and PFIC3. Patients with PFIC4 and PFIC6 also showed positive trends in pruritus improvement and sBA reduction, although patient numbers were limited. No improvement in pruritus or sBA levels was observed in patients with truncating PFIC2 (BSEP3), consistent with the anticipated lack of efficacy in this subgroup. No patients with PFIC5 were enrolled.

As of the interim analysis, the effects observed in study MRX-502 were largely replicated in patients who switched from placebo to maralixibat in the open-label extension study MRX-503. Patients who continued maralixibat treatment showed, on average, sustained reductions in sBA and bilirubin levels, as well as sustained improvement in pruritus.

Hard clinical endpoints (e.g. liver disease progression, death) were collected in study MRX-502, but data analysis was not informative owing to the very low number of events. Only one participant in the full cohort experienced a liver-associated event (“listing for liver transplantation followed by liver transplantation”) due to their cholestasis worsening during maralixibat treatment. As at data cut-off in MRX-503, 13 participants had experienced liver-associated events (6 previously treated with maralixibat and 7 from the placebo arm of MRX-502), with “listing for liver transplantation” being the most frequent event. No clear conclusion can be drawn regarding a causal association with maralixibat. Importantly, a trend towards a reduced incidence of liver-associated events with maralixibat treatment, supporting a disease-modifying effect in PFIC, was not evident.

Uncertainties remain regarding the clinical relevance of sBA levels, as their correlation with pruritus severity and liver injury is not fully established and sBA levels are not routinely used as a clinical biomarker. The long-term clinical benefit of sustained sBA reduction with maralixibat is therefore unknown. In addition, sBA levels do not reliably reflect bile acid exposure within hepatocytes or bile ducts, which are more directly linked to liver-related clinical outcomes. Consequently, it remains uncertain whether maralixibat can slow disease progression in PFIC.

As the long-term extension of the pivotal study lacked a placebo control, no conclusions regarding the potential disease-modifying or liver-protective effects of maralixibat can be drawn. Furthermore, PFIC patients without pruritus were not enrolled in the submitted studies, and potential benefits in this subgroup remain unknown. Accordingly, the indication was restricted to the treatment of cholestatic pruritus.

5.4 Safety

Safety data for maralixibat in the PFIC population are limited to 47 patients aged ≥ 12 months enrolled in pivotal study MRX-502 and its open-label extension MRX-503.

Consistent with the known safety profile of IBAT inhibitors, gastrointestinal adverse drug reactions were most frequently reported, including diarrhoea (57.4%) and abdominal pain (21.3%). Most events were mild to moderate, transient, and resolved without intervention. Overall, the safety profile was similar to that observed in patients with ALGS, taking into account the heterogeneity of both populations.

Elevations in alanine aminotransferase (ALT) were observed in some PFIC patients during treatment. However, the available data do not allow firm conclusions regarding the hepatotoxic potential of maralixibat. Hepatotoxicity has already been identified as an important potential risk in the ALGS population and requires post-approval monitoring in PFIC patients. Regular monitoring of liver function tests is recommended, with maralixibat discontinuation if a drug-induced liver injury is suspected.

Two deaths were reported in participants previously enrolled in study MRX-503. One death occurred 19 days after discontinuation of maralixibat following a respiratory tract infection, and the second

occurred three months after treatment discontinuation due to liver decompensation that developed during maralixibat treatment. A causal relationship with maralixibat is uncertain in either case.

The proposed maintenance dose of maralixibat in PFIC is approximately three-fold higher than the dose approved for ALGS. Although the higher dose appears to be similarly tolerated, concerns remain regarding increased exposure to propylene glycol (PG), which may reach up to 50 mg/kg/day at the highest recommended dose of the marketed Livmarli formulation. Safety data for PG exposure exceeding 26 mg/kg/day in the target population are lacking. While PG intake of up to 50 mg/kg/day is generally considered safe, the risk of PG-related toxicity may be increased in vulnerable populations, including children under 5 years of age and patients with hepatic or renal impairment. For these patients, a lower maximum maralixibat dose of 570 µg/kg/day (corresponding to approximately 25 mg/kg/day PG) is therefore recommended. Maralixibat is contraindicated in patients with severe hepatic or renal impairment.

Overall, the safety profile of maralixibat in PFIC appears comparable to that observed in ALGS. However, the limited size of both safety populations precludes reliable detection of infrequent or rare adverse events, and safety assessment is complicated by the overlap between disease-related manifestations and treatment-emergent adverse events. Long-term safety of maralixibat remains uncertain and will require continued post-approval monitoring.

5.5 Final clinical benefit risk assessment

PFIC is a rare, heterogeneous genetic disorder in which cholestatic pruritus represents the most common and most debilitating symptom with limited treatment options. The efficacy of maralixibat in reducing pruritus severity has been demonstrated in PFIC patients one year of age and older. The safety profile was considered acceptable, with no prohibitive safety signals identified, but active monitoring of liver functional tests recommended. Overall, the benefit-risk balance for the treatment of cholestatic pruritus with maralixibat in patients with PFIC aged 12 months and older is considered positive.

6 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.

7 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 chloride).

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) aged 3 months and older,
- Progressive familial intrahepatic cholestasis (PFIC) aged 12 months and older.

Dosage/Administration

Special attention should be given to calculating the dose of LIVMARLI precisely and to communicating the dosage instructions to caregivers and patients clearly in order to minimise the risk of an incorrect dose or overdose.
An alternative treatment should be considered for patients who do not show any response to treatment after 3 months of uninterrupted daily treatment with maralixibat.

Usual dosage

Alagille syndrome (ALGS)

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 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: ALGS

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	

Progressive familial intrahepatic cholestasis (PFIC)

The starting dose is 285 µg/kg orally once daily (QD) and, if there is no response to treatment or the response is inadequate, this may be increased to 285 µg/kg twice daily (BID, morning and evening) or, depending on how well it is tolerated, to 570 µg/kg twice daily. In patients under 5 years of age, the maximum dose is 285 µg/kg twice daily due to the propylene glycol content. Table 2 provides the dose in ml of solution to be given for each weight range. In case of poor tolerability, dose reduction or treatment interruption should be considered. Renewed dose escalation can be attempted as tolerated. The maximum daily dose volume for patients above 50 kg is 6 ml (57 mg).

Table 2: Individual dose volume by patient weight: PFIC

Patient Weight (kg)	285 µg/kg		570 µg/kg	
	Volume Per dose (ml)	Dosing dispenser size (ml)	Volume Per dose (ml)	Dosing dispenser size (ml)
3	0.1	0.5	0.2	0.5
4	0.1		0.25	
5	0.15		0.3	
6 to 7	0.2		0.4	
8 to 9	0.25		0.5	
10 to 12	0.35		0.6	1
13 to 15	0.4		0.8	
16 to 19	0.5		1	
20 to 24	0.6	1	1.25	3
25 to 29	0.8		1.5	
30 to 34	0.9		2	
35 to 39	1.25	3	2.25	
40 to 49	1.25		2.75	
50 to 59	1.5		3	
60 to 69	2		3	
70 to 79	2.25		3	
80 or higher	2.5		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 patients with impaired hepatic function at baseline. The efficacy and safety in patients with clinically significant portal hypertension and in patients with decompensated cirrhosis have not been established (see “Clinical efficacy”, and “Warnings and precautions”).

ALGS: No dose adjustment is required for patients with hepatic impairment. Close monitoring is, however, advised for patients with end-stage liver disease or progression to decompensation.

PFIC: The maximum recommended dose of LIVMARLI in patients with moderate hepatic impairment is 285 µg/kg twice daily because of the propylene glycol content. LIVMARLI should not be used in patients with PFIC and severe hepatic impairment (see sections “Contraindications”, and “Warnings and precautions”).

Patients with renal disorders

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

ALGS: Maralixibat has not been studied in patients with renal impairment or end-stage renal disease (ESRD) requiring haemodialysis.

ALGS: No dose adjustment is required.

PFIC: The maximum recommended dose of LIVMARLI in patients with moderate renal impairment (creatinine clearance CrCl ≥ 30 and < 60 ml/min) is 285 µg/kg BID, due to propylene glycol content. LIVMARLI should not be used in patients with PFIC and severe renal impairment (creatinine clearance CrCl < 30 ml/min; (see “Contraindications” and “Warnings and precautions”).

Elderly patients

The safety and effectiveness of LIVMARLI in patients, 65 years of age and older, have not been established.

Children and adolescents

LIVMARLI is not authorised for use in ALGS patients less than 3 months of age and PFIC patients less than 12 months of age. The maximum recommended dose of LIVMARLI in PFIC patients below 5 years of age is 285 µg/kg twice daily because of the propylene glycol content. The safety and efficacy of LIVMARLI in infants less than 3 months of age in ALGS, or less than 12 months of age in PFIC, have not been established. Currently available data are described in “Undesirable effects”, ”Pharmacodynamics” and “Pharmacokinetics”, and no recommendation on a posology can be made in these age groups.
Special attention should be paid to accurate calculation of the LIVMARLI dose and clear communication of dosing instructions to caregivers and patients to minimise the risk of erroneous dosing and overdose.

Delayed administration

If a dose is missed, the dose should be omitted, and the original dose schedule resumed with the next scheduled intake.

Mode of administration

Administer LIVMARLI 30 minutes before a meal (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. Tables 1 and 2 provide 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”).

Previous or existing hepatic decompensation (e.g. variceal bleeding, ascites, hepatic encephalopathy).

Patients with PFIC who have severe hepatic and/or renal impairment because of the potential risk of toxicity from the excipient propylene glycol (see section “Warnings and precautions”).

Warnings and precautions

Enterohepatic circulation

LIVMARLI acts by inhibiting the ileal bile acid transporter (IBAT) and disrupting enterohepatic circulation of bile acids. Therefore, conditions, medicinal products or surgical procedures that impair either gastrointestinal motility or enterohepatic circulation of bile acids, including bile salt transport to biliary canaliculi, may reduce the efficacy of maralixibat.
For this reason, patients with PFIC2 who have a complete absence or lack of function of bile salt export pump (BSEP) protein (i.e. patients with the BSEP3 subtype of PFIC2) are not expected to respond to maralixibat. The efficacy of LIVMARLI has not been studied in patients with PFIC5.

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. Reduce the dose or 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 the last tolerated dose. Consider discontinuing LIVMARLI permanently if liver test abnormalities recur or symptoms consistent with clinical hepatitis are observed.

Patients with ALGS 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 treatment is associated with a potential for drug-induced liver injury. In the PFIC trial, treatment-emergent hepatic decompensation events and elevations of liver tests or worsening of liver tests occurred. Two patients experienced drug-induced liver injury (DILI) attributable to LIVMARLI. Two additional patients experienced DILI in the open-label extension portion of the trial. Of these four patients, one patient required liver transplant and another patient died.

LIVMARLI was not evaluated inpatients with cirrhosis. Monitor patients during treatment with LIVMARLI for elevations in liver tests and for the development of liver-related adverse reactions. Dose reduction or treatment interruption should be considered if abnormalities occur in the absence of other causes. 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

In ALGS, diarrhea abdominal pain and vomiting were reported as the most common adverse reactions in patients treated with LIVMARLI (see ”Undesirable effects”).

If diarrhea abdominal pain, and/or vomiting occur and no other etiologies are found, consider reducing the dose of LIVMARLI or interrupting LIVMARLI dosing. For diarrhea or vomiting, monitor for dehydration and initiate an adequate treatment if necessary. Consider interrupting LIVMARLI dosing if

a patient experience 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 was not investigated in a controlled manner in the studies relevant for the authorisation.

When diarrhea or abdominal pain, and/or vomiting resolve, restart LIVMARLI at the last tolerated dose. If they recur upon re-challenge with LIVMARLI, then consider stopping LIVMARLI treatment. LIVMARLI has not been studied in PFIC patients with chronic diarrhea who required intravenous fluids.

Fat Soluble Vitamin (FSV) Deficiency

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

In PFIC patients in Trial 2, treatment-emergent FSV deficiency was reported in 13 (28%) of LIVMARLI-treated patients versus 16 (35%) of placebo-treated patients during 26 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.

Toxicity risk of propylene glycol:

This medicinal product contains 364.5 mg propylene glycol (E 1520) per ml.

ALGS: Administration of a dose of 380 µg/kg LIVMARLI once daily will result in propylene glycol exposure of up to 17 mg/kg/day.

PFIC: Administration of a dose of 285 µg/kg LIVMARLI twice daily will result in propylene glycol exposure of up to 26 mg/kg/day, and a dose of 570 µg/kg LIVMARLI twice daily will result in propylene glycol exposure of up to 50 mg/kg/day.

The total amount of propylene glycol in all medicinal products and food supplements, including LIVMARLI oral solution, should be taken into account when assessing the potential risk of toxicity from propylene glycol, especially in patients with limited ability to metabolise or excrete propylene glycol (e.g. patients below 5 years of age or patients with reduced renal or hepatic function) (see ‘Dosage/Administration” and “Contraindications”). Co-administration with a substrate for alcohol

dehydrogenase such as ethanol may increase the risk of propylene glycol toxicity. The adverse events associated with possible propylene glycol toxicity include, for example: hyperosmolality (with or without lactic acidosis), renal impairment (acute tubular necrosis), acute kidney injury; cardiotoxicity (arrhythmia, hypotension); central nervous system depression (depression, coma, seizures), respiratory depression, dyspnoea; hepatic impairment; haemolytic reaction (intravascular haemolysis) and haemoglobinuria; multiple organ failure. Patients should be monitored for signs and symptoms of possible propylene glycol toxicity.

While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the fetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis (see "Pregnancy, lactation").

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium-free”.

Interactions

Maralixibat is not metabolized and is minimally absorbed; therefore, other drugs are not expected to impact the disposition of maralixibat.

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 “Pharmacokinetics”). 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 “Preclinical data”). Because of the propylene glycol content, the use of LIVMARLI during pregnancy should preferably be avoided (see "Warnings and precautions").

The estimated background risk of major birth defects for the ALGS population is higher than the general population because Alagille syndrome is an autosomal dominant condition. The estimated background risk of miscarriage for ALGS is unknown. The estimated background risk of birth defects and miscarriage for PFIC 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 and PFIC 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.

Because of the propylene glycol content, the use of LIVMARLI during lactation should preferably be avoided (see "Warnings and precautions").

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

ALGS

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 3 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 3: 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	37 (35.9%)	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 (7.8%)	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 26% of patients treated with LIVMARLI and increases to more than five times baseline occurred in 3%. AST increases to more than three times baseline occurred in 16% 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.

PFIC

In Trial 2, which enrolled 93 patients, patients received doses of LIVMARLI up to 570 µg/kg BID, with a median duration of exposure of 6.0 months (range: 0.3-6.7 months).

Table 4 summarizes the frequency of Adverse Reactions reported in ≥5% of patients and at a rate greater than placebo in patients treated with LIVMARLI in Trial 2. Diarrhea was the most frequent adverse reaction; the majority of episodes were mild and transient with a median duration of 5.5 days. Nineteen (40.4%) of the patients treated with LIVMARLI suffered from diarrhea for at least 7 days. In the patients treated with placebo, the diarrhea lasted for a median period of 3 days, and in two patients (4.3%) it lasted for at least 7 days. There were no severe or serious events reported. The majority of abdominal pain events were mild and transient, and associated with concurrent diarrhea.

One patient with an event of mild diarrhea discontinued treatment. Treatment interruptions or dose reductions occurred in 3 (6.4%) patients due to diarrhea or abdominal pain.

Table 4: Adverse Reactions (any grade) Occurring in ≥5% and at a Rate Greater Than Placebo in Patients Treated with LIVMARLI in the PFIC Trial

LIVMARLI (n = 47)			
System Organ Class **Adverse Reaction** (any grades)	**Frequency**	**Any Grade** **n (%)**	**Number of events per 100 person-years[1]**
Gastrointestinal disorders			
Diarrhea	Very common	27 (57.4%)	221.1
Abdominal pain†	Very common	12 (25.5%)	65.5
Haematochezia or rectal bleeding	Common	4 (8.5%)	17.9
Hepatobiliary disorders			
Increase in transaminases†	Very common	8 (17%)	37.8
Musculoskeletal and connective tissue disorders			
Fractures†	Common	3 (6.4%)	13.1

†Terms were defined as:

Abdominal Pain includes: abdominal pain, abdominal pain upper, flatulence

Increase in transaminases includes: hypertransaminasaemia, ALT abnormal, ALT increased, AST abnormal, AST increased, transaminases increased, liver enzymes increased

Fracture includes: upper limb fracture, lower limb fracture, radius fracture, ulna fracture, femur fracture, foot 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

Increase in transaminases

Elevations in ALT and AST, partly accompanied with increase in bilirubin were mostly transitory and mild or moderate in intensity (see also "Warnings and precautions").

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. LIVMARLI contains propylene glycol; an overdose can lead to an overdose of propylene glycol (see "Warnings and precautions").

If an overdose occurs, discontinue LIVMARLI, monitor the patient for any signs and symptoms of propylene glycol toxicity and institute general supportive measures if needed. In the event of an overdose, propylene glycol can be removed from the body by means of dialysis.

Properties/Effects

ATC code

A05AX04

Mechanism of action

Maralixibat is a minimally absorbed, reversible, selective inhibitor of the ileal bile acid transporter (IBAT). Maralixibat acts locally in the distal ileum, where it reduces the reabsorption of bile acids and increases their clearance via the colon, thereby reducing the concentration of bile acids in the serum.

Pharmacodynamics

ALGS

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.

PFIC

In Trial 2, 64 pediatric patients with PFIC were administered LIVMARLI 570 µg/kg (n = 33) or placebo (n = 31) twice daily for up to 22 weeks after an initial 4–6-week dose escalation period. For the mean change in total serum bile acid level between baseline and average of Weeks 18, 22, and 26, the difference between maralixibat and placebo treatment groups was statistically significant (LS mean change from placebo of -160 µmol/L [95% CI: -220.8, -100.0], p<0.0001.) At the start of the trial, the serum bile acid concentrations were highly variable among the patients and were between 2 and 549 µmol/l (n = 62). The mean (SD) serum bile acid level was 263 µmol/l (143 µmol/l For the mean change in total serum bile acid level between baseline and average of Weeks 18, 22, and 26, the difference between maralixibat and placebo treatment groups was statistically significant (LS mean change from placebo of -160 µmol/L [95% CI: -221, -100], p<0.0001.). Whereas the concentrations fluctuated, the reduction in serum bile acids was generally maintained during the treatment period.

Clinical efficacy

ALGS

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 5. 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 5: 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

PFIC

The efficacy of LIVMARLI was assessed in Trial 2 (NCT03905330), which consisted of a 26-week randomized, placebo-controlled trial.

64 PFIC patients [PFIC1, nt-PFIC2, PFIC3, PFIC4, PFIC6] with persistent pruritus aged > 12 months and < 18 years were included. Persistent pruritus was defined as morning average pruritus score on ItchRO[Obs] equal or greater than 1.5 in the 4 weeks prior to baseline.

Patients with decompensated cirrhosis, history or presence of any condition known to interfere with the absorption, distribution, metabolism or excretion of drugs, including bile salt metabolism in the intestine, and chronic diarrhea requiring intravenous fluid or nutritional intervention were excluded. Patients were randomized 1:1 to receive maralixibat orally 570 µg/kg (n = 33) or placebo (n = 31) twice daily. The 26-week study period was completed by 93.8% of patients (32/33 maralixibat and 28/31 placebo), with 4 discontinuing from the study (3 withdrawal of consent and 1 disease progression).

There were more females (53.1%) and the mean age was 4.6 with a range of 1-15 years. Most patients were on stable ursodeoxycholic acid (89.1%) or rifampicin (51.6%) therapy at baseline. The baseline mean (standard deviation [SD]) of liver test parameters were as follows: serum bile acid levels 263 (143) µmol/L, AST 113 (82) U/L, ALT 107 (87) U/L, and TB 4.1 (4.1) mg/dL, DB 3.0 (3.1) mg/dL. The mean (SD) of the average baseline morning pruritus severity score was 2.8 (0.87) on a 0-4 Itch Reported Outcome Observer scale (ItchRO[Obs]).

Pruritus

Maralixibat demonstrated difference between maralixibat and placebo treatment groups for the average change in morning ItchRO(Obs) score between baseline and weeks 15–26, with a LS mean change from placebo of -1.2 (95% CI: -1.7, -0.7).

Table 6: Proportion of pruritus responders (Trial 2)

Responder Type Category	Maralixibat (n = 33)	Placebo (n = 31)
ItchRO(Obs) responders; average score ≤ 1 OR reduction of at least 1.0 from baseline		
Responder(%)	63.6	25.8
p-value vs. placebo difference (95% CI)	0.0023	37.8 (11.3, 59.4)

p-values comparing maralixibat to placebo treatment groups are calculated using a Barnard's exact test. Exact 95% confidence intervals are based on a score statistic.

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 and PFIC patients were below the limit of quantification (0.25 ng/ml) in the majority of plasma samples.

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

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