**CONTRAINDICATIONS**

- Pregnancy

**5 WARNINGS AND PRECAUTIONS**

**5.1 Liver Test Abnormalities**

Patients treated 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 in 70%, 15%, and 19% of patients treated with ALGS, ALT, or AST, respectively. In the ALGS clinical development program, increases in ALT >2.5 times the upper limit of normal (ULN) occurred in 3% of patients treated with LIVMARLI, compared to none treated with placebo. In a pooled analysis of patients with ALGS (N=86) administered LIVMARLI, increases in ALT >3 times ULN occurred in 24% of patients treated with LIVMARLI and increases in AST >3 times ULN occurred in 11% of patients treated with LIVMARLI, and to more than twice the upper limit of normal (ULN) in 1% of LIVMARLI patients.

- Gastrointestinal Adverse Reactions

- Diarrhea
- Abdominal pain
- Vomiting

- Fat-Soluble Vitamins (FSV) Deficiency

- Oral solution: 9.5 mg of maralixibat per mL as a clear, colorless to yellow solution. [see Drug Interactions (7.1)]

- 3.10 Drug-Drug Interactions

- Drug absorption was not altered by food, and the original dosing schedule should be resumed. If a dose is missed, it should be taken as soon as possible within 12 hours of the time it was missed, and the scheduled dose should be taken at the next regularly scheduled time. If more than 12 hours have elapsed since the missed dose, the dose can be omitted and the original dosing schedule resumed. If diarrhea, abdominal pain, and vomiting recur (or persist more than 12 hours) after re-challenge with LIVMARLI, then consider stopping LIVMARLI treatment.
8.5.5 The safety and effectiveness of LIVMARLI for the treatment of pruritus in ALGS in adult patients, 50 years of age and older, have not been established.

8.7 Hepatic Impairment
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 Studies (16), Dosage and Administration (2.4), and Warnings and Precautions (5.5)].

10. OVERDOSAGE
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 overdose occurs, discontinue LIVMARLI, monitor the patient for any signs and symptoms and institute general supportive measures if needed.

LIVMARLI contains propylglycol (0.5-5.0%) as an excipient. Oral doses of propylglycol up to 50 mg/kg/day (1 month to <5 years of age) and 500 mg/kg/day (≥5 years of age) are generally considered safe. Exposures of propylglycol may result in hyperglycemia, CNS, cardiovascular, and respiratory effects and may subside with the elimination of propylglycol.

11. DESCRIPTION
LIVMARLI (maralixibat oral solution) is an ionic bile acid transport inhibitor (BIT) inhibitor. Maralixibat is present as a chloride salt with the chemical name 1-(3,5-dimethylphenyl)-3-(1,3-dimethylbutyl)-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl phosphate(mono)hydrogen phosphate(4-1)-apamine (2,2'2'2'-bistetrahydrochalcone). The molecular formula of maralixibat chloride is C₄₀H₅₆ClN₃O₄S with a molecular weight of 710.42.

12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Maralixibat is a reversible inhibitor of the ileal bile acid transporter (IBAT). It decreases the reabsorption of bile acids primarily by the small intestine.[See Clinical Pharmacology (12.3).]

Pruritus is a common symptom in patients with ALGS and the pathophysiology of pruritus in ALGS patients is unknown, it may involve inhibition of bile acid reabsorption of bile acids (primarily the salt forms) from the terminal ileum.

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Maralixibat inhibits OATP1B1, OATP1B3, OATP2B1, and OATP2B2, with IC₅₀ values of 10⁻¹⁴ M or lower. At concentrations up to 10⁻⁸ M, maralixibat does not reduce expression of either simvastatin, or lovastatin in the evening, did not have a clinically relevant effect on the pharmacokinetics of these substances and did not reduce hepatic bile acid synthesis. However, the effect of maralixibat on the pharmacokinetics of OATP1B1 substrates at higher doses has not been evaluated in a clinical study.

13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No drug-related tumors were observed following oral administration of maralixibat chloride to TanRats mice at doses up to 525 (males) or 75 (females) mg/kg for 26 weeks.

Impairment of fertility
Maralixibat chloride was negative in vivo (bacterial reverse-mutation, chromosomal aberration, sister chromatid exchange, and in vivo mouse marrow micronucleus assays).

Effect of other Drugs on Maralixibat
In vitro, maralixibat inhibits OATP1B1, OATP1B3, OATP2B1, and OATP2B2; therefore, concomitant drug products are not predicted to affect the pharmacokinetics of maralixibat.

Effect of maralixibat on Other Drugs
In vitro, maralixibat did not induce CYP isoenzymes 1A2, 2C8, 2D6, 2E1, 2C9, 2C19, 2C29, or 3A4 at clinically relevant concentrations. Maralixibat inhibits OATP1B1, OATP1B3, OATP2B1, and OATP2B2 with IC₅₀ values of 10⁻¹⁴ M or lower. In vivo, maralixibat did not inhibit the in vitro activities of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2C9, CYP27, CYP2E1, CYP3A4, PTP1B, CYP7A1, POT1, OCT1, OCT2, OCT3, OCTN1, OCTN2, ABCB1, ABCG2, MRP2, MATE1, or MATE2 at clinically relevant concentrations.

Maralixibat does not inhibit the transporter transporter OATP1B1 in vitro, which can potentially result in reduced absorption of drugs that rely on OATP1B1 mediated uptake in the ileum. In vitro studies characterization of 4.2 mg/mL maralixibat did not show any daily doses of either simvastatin, or lovastatin in the evening, did not have a clinically relevant effect on the pharmacokinetics of these substances and did not reduce hepatic bile acid synthesis. However, the effect of maralixibat on the pharmacokinetics of OATP1B1 substrates at higher doses has not been evaluated in a clinical study.

14. CLINICAL STUDIES
14.1 LIVMARLI in ALGS
A dose-ranging trial in 16 pediatric ALGS patients with cholestasis and pruritus was performed in Trial 1. The highest concentrations of maralixibat in pediatric ALGS patients following treatment with LIVMARLI were 380 mcg/kg once daily for 13 weeks after an initial 5-week dose-escalation period; two additional ALGS patients received LIVMARLI at 380 mcg/kg once daily for an additional 26 weeks. Thirty-one pediatric ALGS patients with cholestasis and pruritus were enrolled, with 90.3% of patients receiving maralixibat after an initial 5-week dose-escalation period; two additional ALGS patients received LIVMARLI at 380 mcg/kg once daily for an additional 26 weeks. Thirty-one pediatric ALGS patients with cholestasis and pruritus were enrolled, with 90.3% of patients receiving maralixibat after an initial 5-week dose-escalation period; two additional ALGS patients received LIVMARLI at 380 mcg/kg once daily for an additional 26 weeks.

The efficacy of LIVMARLI in ALGS was assessed in Trial 1 (NCT01276490), which consisted of an 18-week open-label extension period, 6-week randomized, double-blind, placebo-controlled treatment 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 maralixibat after an initial 5-week dose-escalation period; two additional ALGS patients received LIVMARLI at 380 mcg/kg once daily for 10 weeks after an initial 5-week dose-escalation period; two additional ALGS patients received LIVMARLI at 380 mcg/kg once daily for 10 weeks after an initial 5-week dose-escalation period; two additional ALGS patients received LIVMARLI at 380 mcg/kg once daily for 10 weeks after an initial 5-week dose-escalation period; two additional ALGS patients received LIVMARLI at 380 mcg/kg once daily for 10 weeks after an initial 5-week dose-escalation period; two additional ALGS patients received LIVMARLI at 380 mcg/kg once daily for 10 weeks after an initial 5-week dose-escalation period; two additional ALGS patients received LIVMARLI at 380 mcg/kg once daily for 10 weeks after an initial 5-week dose-escalation period.

The safety and efficacy of LIVMARLI as measured by mean difference in pruritus score was assessed at an average visit (visit 22). Select demographic and clinical characteristics are provided in Table 1. All patients enrolled in this trial were ≥6 years of age.

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