NEW DRUG APPROVAL

Brand Name	Livmarli™
Generic Name	maralixibat
Drug Manufacturer	Mirum Pharmaceuticals, Inc

New Drug Approval

FDA Approval Date: September 29, 2021
Review Designation: Priority; Orphan
Type of Review: Type 1 - New Molecular Entity; New Drug Application (NDA): 214662
Dispensing Restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Cholestasis is seen with many hepatobiliary disorders that produce extrahepatic biliary obstruction and/or intrahepatic biliary disruption. One particularly troublesome symptom associated with cholestasis is pruritus, which can range in severity from mild, to moderate (in which sleep is disturbed), and to extreme (in which the lifestyle of the patient is completely disrupted).

Pruritus may develop in patients with cholestasis due to any cause. It may be seen with primary biliary cholangitis (previously referred to as primary biliary cirrhosis), primary sclerosing cholangitis, intrahepatic cholestasis of pregnancy, biliary obstruction, chronic viral hepatitis, cirrhosis, prolonged drug-induced cholestasis, and inherited cholestasis syndromes (eg, progressive familial intrahepatic cholestasis and benign recurrent intrahepatic cholestasis.

Between 23 and 44 million Americans are estimated to suffer from chronic pruritus in the setting of both cutaneous and systemic conditions. Patients with chronic pruritus suffer extreme detriment to their ability to function, including but not limited to deranged sleep patterns, mood disturbances, increased levels of anxiety and depression, and reduced levels of overall quality of life. Indeed, chronic pruritus is now known to be as debilitating as chronic pain. For these reasons, chronic pruritus represents a serious public health concern that must be adequately addressed by clinicians. We present an up-to-date summary of the epidemiology of chronic itch in different cutaneous and systemic conditions. While we have endeavored to discuss some of the most common causes of chronic pruritus, this review does not encompass all of the myriad different diseases in which chronic pruritus can occur.

Efficacy

The efficacy of Livmarli™ was assessed in Trial 1 (NCT02160782), consisted of an 18-week open-label treatment 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 mcg/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 mcg/kg once daily for an additional 26 weeks.

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 reductions 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. 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: 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.

Safety

ADVERSE EVENTS

Most common adverse reactions (≥5%) are diarrhea, abdominal pain, vomiting, fat-soluble vitamin deficiency, liver test abnormalities, gastrointestinal bleeding, and bone fractures.

WARNINGS & PRECAUTIONS

- Liver Test Abnormalities: Obtain baseline liver tests and monitor during treatment. Dose reduction or treatment interruption may be considered if abnormalities occur. For persistent or recurrent liver test abnormalities, consider Livmarli™ discontinuation.
- Gastrointestinal Adverse Reactions: Consider interrupting Livmarli™ treatment if a patient experiences persistent diarrhea, abdominal pain, vomiting, or has diarrhea with bloody stool, vomiting, dehydration requiring treatment, or fever. If diarrhea, abdominal pain, or vomiting persists and no alternate etiology is identified, consider stopping Livmarli™ treatment.
- Fat-Soluble Vitamin (FSV) Deficiency: Obtain baseline levels and monitor during treatment. Supplement if deficiency is observed. If FSV deficiency persists or worsens despite FSV supplementation, consider discontinuing Livmarli™ treatment.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS 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.

Dose & Administration

ADULTS

- The recommended dosage is 380 mcg/kg once daily, taken 30 minutes before the first meal of the day.
- Starting dose is 190 mcg/kg orally once daily and should be increased to 380 mcg/kg once daily after one week, as tolerated.

PEDIATRICS

The safety and effectiveness of Livmarli™ have not been established in patients less than 1 year of age.

GERIATRICS

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.

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

The efficacy and safety in ALGS patients with clinically significant portal hypertension and in patients with decompensated cirrhosis have not been established.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Oral solution: 9.5 mg of maralixibat per mL.