Maralixibat (Livmarli™) New Drug Update

October 2021

Nonproprietary Name	maralixibat
Brand Name	Livmarli
Manufacturer	Mirum
Form	Oral solution (grape flavor)
Strength	9.5 mg/mL
FDA Approval	September 29, 2021
Market Availability	Available
FDA Approval Classification	Orphan Drug, Priority Review
FDB Classification- Specific Therapeutic Class (HIC3)	Ileal Bile Acid Transporter (IBAT) Inhibitor (D7F)

INDICATION[1]

Maralixibat (Livmarli), an ileal bile acid transporter (IBAT) inhibitor, is indicated for the treatment of cholestatic pruritus in patients ≥ 1 year of age with Alagille syndrome (ALGS).

PHARMACOKINETICS

Maralixibat is minimally absorbed, and overall exposure and maximum concentration appear dose dependent. Following a single oral administration of up to 500 mg in healthy adults, plasma concentrations of maralixibat were below the limit of quantification; thus, reliable estimates of pharmacokinetic parameters were not available. No accumulation was noted following dose up to 100 mg once daily with repeat administration in healthy adults. The impact of food on systemic absorption is not clinically significant, but a high-fat meal can decrease the rate and extent of absorption. Maralixibat is highly protein-bound (91%) and has a mean half-life of 1.6 hours. No metabolites of maralixibat have been detected in plasma but have been detected in elimination; it is primarily eliminated via the feces (73% of the dose; 94% unchanged).

CONTRAINDICATIONS/WARNINGS

Maralixibat has no contraindications.

Warnings associated with maralixibat include liver test abnormalities, gastrointestinal (GI) adverse reactions, and fat-soluble vitamin deficiency. In clinical evaluation for approval, patients had abnormal liver tests at baseline, although treatment-emergent worsening did occur. Providers should obtain baseline liver tests and monitor patients during treatment. Treatment interruption or a dose reduction may be considered for abnormalities in the absence of other causes, and treatment discontinuation

should be considered in patients with recurrent or persistent liver test abnormalities. Maralixibat has not been evaluated in ALGS patients with cirrhosis; a risk versus benefit assessment should occur in these patients prior to initiating therapy. Maralixibat should be permanently discontinued in patients who progress to portal hypertension or experience a hepatic decompensation event.

GI adverse reactions, including abdominal pain, diarrhea, and vomiting, were reported in clinical trials, with 3% requiring hospitalization or intravenous (IV) fluid administration due to vomiting. If these symptoms occur without another etiology, a dose reduction or treatment interruption can be considered. Patients should also be monitored for dehydration. Treatment interruption should also be considered in patients with persistent or severe symptoms (e.g., blood stool, fever, dehydration requiring treatment). Once resolved, treatment can be resumed at 190 mcg/kg/day and titrated as tolerated. If symptoms recur upon rechallenge, treatment discontinuation should be considered.

Patients with ALGS can have deficiencies in fat-soluble vitamins (A, D, E, and K), and maralixibat may impact this (treatment-emergent cases in 10% of patients in a clinical trial). Providers should obtain serum fat-soluble vitamin levels at baseline and monitor these and any clinical manifestations during treatment. Supplementation may be needed, and treatment discontinuation should be considered in patients with worsening or persistent deficiency despite supplementation.

DRUG INTERACTIONS

Maralixibat may bind to bile acid binding resins (e.g., cholestyramine, colesevelam, colestipol) in the gut; bile acid binding results should be administered ≥ 4 hours before or after maralixibat.

Maralixibat is an OATP2B1 inhibitor and may impact the oral absorption of OATP2B1 substrates (e.g., statins) in the GI tract. Additional monitoring may be needed.

COMMON ADVERSE EFFECTS

The most common adverse reactions (incidence ≥ 5%) reported in clinical trials with maralixibat were diarrhea (55.8%), abdominal pain (53.5%), vomiting (40.7%), fat-soluble vitamin deficiency (25.6%), increased transaminases (18.6%), GI bleeding (10.4%), bone fractures (9.3%), and nausea (8.1%).

SPECIAL POPULATIONS

Pregnancy

At recommended doses, maternal use is not expected to result in measurable fetal exposure *in utero* due to limited systemic absorption; however, maralixibat may indirectly impact the fetus due to its potential for inhibiting fat-soluble vitamin absorption, and supplementation may be needed. No developmental effects have been seen in animal studies, but there are insufficient data on use in pregnant women.

Pediatrics

Safety and effectiveness of maralixibat have been established in patients as young as 1 year of age.

Geriatrics

Safety and effectiveness of maralixibat have not been established in patients ≥ 65 years of age.

Hepatic Impairment

Clinical studies included patients with hepatic impairment at baseline; however, its safety and efficacy have not been established in ALGS patients with clinically significant portal hypertension or decompensated cirrhosis.

Renal Impairment

Maralixibat has not been studied in patients with impaired renal function.

DOSAGES

Maralixibat should be initiated at 190 mcg/kg once daily for 1 week, then increased to 380 mcg/kg once daily, as tolerated. All doses should be administered 30 minutes prior to the first meal of the day. The maximum daily dose of maralixibat in patients > 70 kg is 28.5 mg (3 mL) daily. Detailed dosing by weight is described in the table below.

Patient Weight (kg)	Days 1 to 7 (based on 190 mcg/kg/day)		Day 8 and Thereafter (based on 380 mcg/kg/day)	
	Once Daily Volume (mL)	Recommended Dosing Dispenser	Once Daily Volume (mL)	Recommended Dosing Dispenser
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	1.5		3	

Dose modifications following adverse reactions are described in the warnings above. Maralixibat should be stored at room temperature, discarding any remaining solution 45 days after opening the bottle.

CLINICAL TRIALS[2,3]

A literature search was performed using "maralixibat," "pruritus," and "Alagille syndrome."

ICONIC (NCT02160782), a 48-week multinational study, assessed the efficacy of maralixibat in 31 pediatric patients with ALGS who had cholestasis and pruritis who weighed up to 50 kg. The trial consisted of an 18-week open-label treatment period, followed by a 4-week randomized, double-blind, placebo-controlled treatment-withdrawal period, and then followed by a 26-week open-label treatment period. Patients were then able to continue treatment in an open-label, long-term extension period. Patients were required to have ≥ 1 of the following: total serum bile acid > 3 times the upper limit of normal (ULN) for age, conjugated bilirubin > 1 mg/dL, gamma glutamyl transferase (GGT) > 3-times ULN for age, fat soluble vitamin deficiency not otherwise explained, and/or intractable pruritus only explained by liver disease. Included patients also had an average score of > 2 (moderate) on the worst daily Itch Reported Outcome Instrument (ItchRO[Obs]) score, as assessed by the caregiver (due to child age) in the 2 weeks prior to baseline. The pruritis score was based on a 5-point ordinal response, ranging

from 0 (no observed/reported pruritis) to 4 (very severe observed/reported pruritus). Patients were excluded if they had decompensated cirrhosis or other concomitant liver disease or if they had used bile acid or lipid binding resins within 28 days prior to screening. Use of these agents was not permitted during the trial as well. Other notable exclusion factors revolved around other GI or liver conditions (e.g., chronic diarrhea requiring fluid or nutrition therapy, gallstones, liver transplant).

In the 18-week open-label treatment period, patients received 13 weeks of 380 mcg/kg/day following a 5 week dose titration. At baseline, 28 patients (90.3%) had received ≥ 1 medication for pruritis, and all had a *JAGGED1* mutation. During the initial 18-week phase, 2 patients discontinued treatment. The mean (standard deviation [SD]) baseline worst daily ItchRO(Obs) pruritus score was 3.1 (0.5). The mean (SD) post-18-week (pre-randomization) worst daily ItchRO(Obs) pruritus score was 1.4 (0.9).

The 29 remaining patients were then randomized to either continue treatment or to placebo for weeks 19 through 22 (13 assigned maralixibat, 16 to placebo). Randomized patients (66% male) had a median age of 5 years and a baseline mean (SD) serum bile acid level of 280 (213) µmol/L, aspartate aminotransferase (AST) of 158 (68) U/L, alanine aminotransferase (ALT) of 179 (112) U/L, GGT of 498 (399) U/L, and total bilirubin (TB) of 5.6 (5.4) mg/dL.

The primary outcome, the weekly average worst daily ItchRO(Obs) score, as assessed by the caregiver and evaluated using an analysis of covariance model, was generally maintained in the treatment group and returned to baseline in the placebo group. At week 22, the mean weekly average worst daily ItchRO(Obs) score was 1.6 (95% confidence interval [CI]; 1.1 to 2.1) in the maralixibat group compared to 3 (95% CI, 2.6 to 3.5) in the placebo group. The mean change from week 18 to week 22 in the weekly average worst daily ItchRO(Obs) score was 0.2 (95% CI, -0.3 to 0.7) in the maralixibat group compared to 1.6 (95% CI, 1.2 to 2.1), with a mean difference between the groups of -1.4 (95% CI, -2.1 to -0.8).

All patients completed the randomized, treatment-withdrawal phase and continued on to the 26-week, open-label treatment period. Upon reentry to open-label treatment, both groups had similar pruritis scores by week 28.

OTHER DRUGS USED FOR CONDITION[4,5,6]

Maralixibat is the only drug approved for the treatment of cholestatic pruritus in patients with ALGS.

While not specifically indicated for use in patients with ALGS, ursodeoxycholic acid (ursodiol) and cholestyramine may provide relief of cholestatic pruritus. Ursodiol (Urso 250®, Urso Forte®) is indicated for the treatment of adult patients with primary biliary cholangitis, and cholestyramine (Prevalite®, Questran®) is approved for the relief of pruritus in patients, including pediatrics, with partial biliary obstruction. Off-label use of other therapies noted in the literature for the symptomatic relief of pruritus include antihistamines, rifampin, and opioid antagonists (e.g., naloxone, naltrexone).

In July 2021, odevixibat (Bylvay™), another IBAT inhibitor, was approved for the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC).

PLACE IN THERAPY[7,8,9,10,11]

Alagille syndrome (ALGS), a spontaneous or heritable autosomal dominant genetic disorder, occurs in approximately 1 in every 30,000 to 45,000 live births and affects both genders equally and with no known racial or ethnic association. Mutations in the *JAG1* gene are responsible for > 90% of cases, although it may also be caused by mutations in the *NOTCH2* gene. A paucity of interlobular bile ducts and hepatic

manifestations characterize ALGS, although other findings include cardiac murmur or anomalies, butterfly vertebrae, distinct facial features, short stature or failure to thrive, and ocular and renal manifestations. Chronic cholestasis and pruritus occur in 87% to 100% and 59% to 88% of ALGS patients, respectively. The pathogenesis of cholestatic pruritus is not well defined, but theories include a relation to bile acid accumulation, endogenous opioids, and specific phospholipids. Diagnosis of ALGS is generally made following symptoms and can be confirmed or differentiated from other diagnoses with similar presentations via genetic testing, although genetic testing is not required for diagnosis. Management of ALGS is based on presenting symptoms, with pruritis commonly treated with agents approved for pruritus or cholangitis or off-label agents, as described above; however, up to 40% of cases may be refractory to treatment. As an IBAT, maralixibat decreases reabsorption of bile acids from the terminal ileum; however, the complete mechanism by which it improves pruritus, a symptom of ALGS, is unknown.

There are no guidelines that specifically address the treatment of cholestatic pruritus in patients with ALGS. Guidelines from the American Association for the Study of Liver Diseases (AASLD; 2018) regarding pruritus associated with primary biliary cholangitis (PBC) state that bile acid/anion-exchange resins may be used in patients with pruritus due to PBC. For treatment refractory patients, they state rifampicin, opiate antagonists, or sertraline may be used.

Maralixibat (Livmarli) offers a novel treatment option for patients ≥ 1 year of age with ALGS. While there are no comparative studies, it has demonstrated efficacy in pruritus symptoms in a key clinical trial but may be limited by GI adverse effects. Maralixibat provides a specific treatment option for patients who may otherwise be treated with general symptomatic treatments (e.g., bile acid resins) or non-FDA-approved agents.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Bile Salts
Clinical Edit	**Initial Approval Criteria** ▪ Patient is ≥ 1 year of age; **AND** ▪ Patient is diagnosed with Alagille syndrome; **AND** ▪ Patient has evidence of cholestasis, as evidenced by ≥ 1 of the following: – Serum bile acid > 3 times upper limit of normal (ULN) for age; **OR** – Conjugated bilirubin > 1 mg/dL; **OR** – Gamma glutamyl transferase (GGT) > 3 times ULN for age; **OR** – Fat soluble vitamin deficiency not otherwise explained; **OR** – Intractable pruritus only explained by liver disease; **AND** ▪ Patient experiences persistent moderate to severe pruritus; **AND** ▪ Patient does NOT have any of the following: – Chronic diarrhea requiring ongoing intravenous fluid or nutritional intervention; **AND** – Prior hepatic decompensation event; **AND** – Significant portal hypertension; **AND** – Decompensated cirrhosis; **AND** – Another concomitant liver disease; **AND** ▪ Maralixibat is prescribed by or in consultation with a specialist (e.g., gastroenterologist, hepatologist, dermatologist); **AND** ▪ Patient has failed an adequate trial, or is intolerant to, or has a contraindication to at least 1 pruritus treatment (e.g., ursodeoxycholic acid [ursodiol], cholestyramine, rifampin, naloxone, naltrexone, antihistamine). ***Note: use of these agents are off-label.*** **Renewal Criteria** ▪ Patient must continue to meet the above criteria; **AND** ▪ Patient has experienced a reduction in serum bile acids from baseline; **AND** ▪ Patient must experience improvement in pruritus; **AND** ▪ Patient has NOT experienced any treatment-restricting adverse effects (e.g., persistent diarrhea; persistent fat-soluble vitamin deficiency despite vitamin A, D, E, K supplementation; persistent or recurrent worsened liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), direct bilirubin (DB)]); **AND** ▪ Patient has NOT developed decompensated cirrhosis; **AND** ▪ Patient has NOT developed significant portal hypertension.
Quantity Limit	855 mg/90 mL per 30 days (28.5 mg/3 mL per day)

Suggested Utilization Management (continued)

Duration of Approval	Initial: 6 months Renewal: 1 year
Drug to Disease Hard Edit	None

REFERENCES

1 Livmarli [package insert]. Foster City, CA; Mirum; September 2021.
2 Livmarli [package insert]. Foster City, CA; Mirum; September 2021.
3 NCT02160782. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/home. Accessed October 11, 2021.
4 Drugs@FDA. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed October 11, 2021.
5 Clinical Pharmacology. Available at: https://www.clinicalkey.com/pharmacology/. Accessed October 11, 2021.
6 Poupon R, Chopra S. Pruritus associated with cholestasis. Updated February 16, 2021. Available at: https://www.uptodate.com/contents/search. Accessed October 11, 2021.
7 Alagille syndrome. American Liver Foundation. Available at: https://liverfoundation.org/for-patients/about-the-liver/diseases-of-the-liver/alagille-syndrome/#facts-at-a-glance. Accessed October 12, 2021.
8 Alagille syndrome. National Organization for Rare Disorders (NORD). Available at: https://rarediseases.org/rare-diseases/alagille-syndrome/. Accessed October 12, 2021.
9 Erlichman J, Loomes KM. Causes of cholestasis in neonates and young infants. Updated January 29, 2021. Available at: https://www.uptodate.com/contents/search. Accessed October 11, 2021.
10 Poupon R, Chopra S. Pruritus associated with cholestasis. Updated February 16, 2021. Available at: https://www.uptodate.com/contents/search. Accessed October 11, 2021.
11 Lindor KD, Bowlus CL, Boyer J, et al. Primary biliary cholangitis: 2018 practice guideline from the American Association for the Study of Liver Diseases. Hepatology. 2019;69(1):394-419. DOI: 10.1002/hep.30145. Available at: https://www.aasld.org/publications/practice-guidelines. Accessed October 12, 2021.