New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Livmarli™ (maralixibat) [Mirum Pharmaceuticals Inc.]**
Dosage Formulations:	Oral solution: 9.5 mg/mL
FDA Approval Date: **FDB File Date:**	FDA: September 29, 2021 FDB: October 3, 2021
Indication:	Treatment of cholestatic pruritis in patients with Alagille syndrome (ALGS) 1 year of age and older.
Mechanism of Action:	Livmarli is a reversible inhibitor of the ileal bile acid transporter (IBAT), decreasing the reabsorption of bile acids (primarily the salt forms) from the terminal ileum. ALGS cholestasis is associated with increased serum bile acid (sBA), reduction of sBA reduces bile acid-mediated cholestatic symptoms.
Dose/ Administration:	• Livmarli is initiated at a dose of 190 mcg/kg administered orally once daily. • After 1 week, increase to 380 mcg/kg, as tolerated. The maximum daily dose volume for patients weighing above 70 kg is 3 mL or 28.5 mg per day. • The following dosing guideline is provided by the manufacturer:

Patient Weight (kg)	Days 1-7 (190 mcg/kg once daily)		Beginning Day 8 (380 mcg/kg once daily)	
	Volume QDay (mL)	Dosing dispenser size (mL)	Volume QDay (mL)	Dosing dispenser size (mL)
5 to 6	0.1	0.5	0.2	0.5
7 to 9	0.15		0.3	
10 to 12	0.2		0.45	
13 to 15	0.3		0.6	1
16 to 19	0.35		0.7	
20 to 24	0.45		0.9	
25 to 29	0.5		1	
30 to 24	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	

- Missed doses should be taken as soon as possible within 12 hours of the time it is usually taken. If a dose is missed by more than 12 hours the dose can be omitted and the original dosing schedule resumed.
- Livmarli should be taken at least 4 hours before or 4 hours after administration of bile acid resins.
- Livmarli should be stored at room temperature and discarded 45 days after first opening bottle.

Disease State Clinical Highlights:	• ALGS is an autosomal dominant, multisystem disorder associated with abnormalities of the liver, heart, bones, eyes, and kidneys. Presentation of Alagille syndrome can vary greatly between individuals, even among family members sharing the same pathogenic variant. Alagille syndrome is caused by pathogenic variants in the *JAG1* gene (90% of cases) and the *NOTCH2* gene (1% of cases). The estimated incidence of ALGS is 1 in 30,000 to 1 in 45,000 in the United States. • Alagille syndrome most commonly affects the liver with symptoms presenting during the first 3 months of life including cholestasis, jaundice, pruritis, xanthomas, and failure to thrive due to improper fat absorption. Severity can range from asymptomatic elevations

	in liver enzymes to cirrhosis and end-stage liver disease. Approximately 75-90% of patients with ALGS have a reduced number (paucity) of bile ducts often leading to cholestasis. • Severe pruritis often results in scarring, bleeding, excoriations, and discomfort leading to impact on quality of life. The exact mechanism by which cholestasis causes pruritis is not fully understood. Theories implicate elevated venous histamine levels, retention of pruritogenic intermediates in bile acid synthesis, and elevated serum bile acid levels. • Fat-soluble vitamins (FSV) require bile acid to be properly absorbed in the intestines. Patients with ALGS often present with FSV deficiency which can result in vision problems (vitamin A), bone weakness (vitamin D), developmental delay (vitamin E), and clotting problems (vitamin K). • Cardiac abnormalities range from benign heart murmurs to structural defects and occur in 90-97% of patients with ALGS, with stenosis/hypoplasia of the pulmonary arteries being most common. Skeletal abnormalities include a wide range of vertebral anomalies. The most common are butterfly vertebrae, where the anterior arches of vertebrae fail to fuse. Butterfly vertebrae do not result in symptoms but can be useful in diagnosis of ALGS. Distinct facial features are observed in ALGS patients and include a high forehead, deep-set eyes, pointed chin, and a straight nose with a bulbous tip. These facial features appear to occur in the presence of the *JAG1* pathogenic variant. • Diagnosis can be established by genetic testing confirming the presence of *JAG1* or *NOTCH2* pathogenic variants, however a very small percentage of patients with ALGS do not present with one of these variants. Clinical criteria for diagnosis include having three of the following five clinical manifestations: cholestasis, cardiac defects, skeletal abnormalities, ocular abnormalities, and distinctive facial features.

Drug Clinical Highlights:	• Livmarli is a reversible inhibitor of IBAT. Inhibition of IBAT blocks the reabsorption of bile acids from the terminal ileum, facilitating fecal excretion of bile acids. It is the first product approved for the treatment of pruritis associated with Alagille syndrome.
	
	<u>Warnings and Precautions</u>
	• Liver Test Abnormalities
	  ○ Baseline liver tests (ALT [alanine aminotransferase], AST [aspartate aminotransferase], TB [total bilirubin], DB [direct bilirubin], and International Normalized Ratio [INR]) should be obtained prior to treatment with Livmarli to establish baseline the pattern of variability.
	  ○ Monitor liver tests during therapy. Interrupt Livmarli treatment if new onset liver test abnormalities occur in the absence of other causes. Once abnormalities either return to baseline or stabilize at a new baseline, consider restarting Livmarli at 190 mcg/kg and increase to 380 mcg/kg as tolerated.
	  ○ Consider discontinuing Livmarli permanently if liver test abnormalities recur, symptoms consistent with clinical hepatitis are observed, or if a patient experiences a hepatic decompensation event (variceal hemorrhage, ascites, hepatic encephalopathy).
	• Gastrointestinal Adverse Reactions
	  ○ Diarrhea, abdominal pain, and vomiting were reported as the most common adverse reactions in patient treated with Livmarli. Three (3%) patients experienced vomiting classified as a serious adverse event requiring hospitalization or intravenous fluid administration.
	  ○ If significant gastrointestinal adverse events occur and no other etiologies are found, consider reducing the dose of Livmarli or interrupting Livmarli treatment. For diarrhea and vomiting, monitor for dehydration and treat promptly.

- After diarrhea, abdominal pain, and/or vomiting resolve treatment can be restarted at 190 mcg/kg and increased as tolerated. If symptoms recur upon re-challenge, consider stopping Livmarli therapy.

- Fat-Soluble Vitamin (FSV) Deficiency
  - Livmarli may affected absorption of FSV (vitamin A, D, E, and K) and ALGS patients can have FSV deficiencies at baseline. Treatment emergent FSV deficiency was reported in 10% of patients during 48 weeks of Livmarli treatment.
  - Obtain serum FSV levels at baseline and monitor during treatment. If FSV deficiency is diagnosed, supplement with FSV therapy. Consider discontinuing Livmarli if FSV deficiency persists or worsens despite FSV supplementation.

Contraindications: none

Pregnancy/Lactation

- 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. In animal reproductive studies, no effects of embryo-fetal development were observed in pregnant rats or in pregnant rabbits treated with Livmarli.
- Due to low systemic absorption of Livmarli, breastfeeding is not expected to result in exposure of the infant to Livmarli at the recommended dose. FSV levels should be monitored, and supplementation is recommended if FSV deficiency is observed during lactation.

Drug Interactions

- Bile acid binding resins may bind to Livmarli in the gut. Administer bile acid resins at least 4 hours before or 4 hours after administration of Livmarli.
- Livmarli 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.

Hepatic Impairment:

- Study participants included ALGS patients with impaired hepatic function at baseline. Efficacy and safety in ALGS patients with clinically significant portal hypertension or decompensated cirrhosis have not been established.

Clinical Studies

- Efficacy of Livmarli was assessed in the ICONIC trial (NCT02160782):
  - Thirty-one pediatric ALGS participants with cholestasis or pruritis were enrolled. 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 during the 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. All 29 patients completed the randomized, blinded drug withdrawal period and subsequently received open-label Livmarli 380 mcg/kg once daily for an additional 26 weeks.
  - Key Inclusion Criteria
    - Age between 12 months and 18 years
    - Diagnosis of ALGS
    - Evidence of cholestasis (one or more of the following):

- Total serum bile acid (sBA) > 3x upper limit of normal (ULN) for age
- Conjugated bilirubin > 1mg/dL
- FSV deficiency otherwise unexplainable
- Gamma-glutamyl transferase (GGT) > 3x ULN for age
- Intractable pruritis explainable only by liver disease

▪ Participant is expected to have a consistent caregiver for the duration of the study
▪ Average daily score > 2 (moderate pruritis symptoms) on the Itch Reported Outcome (ItchRO™) questionnaire for two consecutive weeks in the screening period

○ Key Exclusion Criteria
▪ Previous liver transplant or surgical interruption of the enterohepatic circulation
▪ Pregnancy
▪ Decompensated cirrhosis or other concomitant liver disease
▪ History or presence of gallstones or kidney stones
▪ Chronic diarrhea requiring intravenous fluid or nutritional intervention
▪ Known diagnosis of human immunodeficiency virus (HIV) infection
▪ Cancer, except for in situ carcinoma, or cancers treated at least 5 years prior to screening with no evidence of recurrence
▪ Administration of bile acid or lipid binding resins within 28 days prior to screening and throughout trial
▪ Participants weighing over 50 kg at screening

○ Key Baseline Characteristics
▪ Participant median age was 5 years (range: 1 to 15 years)
▪ 66% of participants were male
▪ 90.3% of participants were receiving at least 1 medication to treat pruritis.
▪ All patients had *JAG1* pathogenic variant.
▪ Baseline mean of liver test parameters were: sBA 280 µmol/L, AST 158 U/L, ALT 179 U/L, GGT 498 U/L, and TB 5.6 mg/dL.

○ Primary Outcome Measure: change from week 18 to week 22 in fasting sBA levels in participants who had a reduction in sBA ≥50% from baseline to week 12 or week 18 (modified intent-to-treat [MITT] population). Five participants in the Livmarli group and 10 participants in the placebo group met the prespecified sBA reduction criteria.

	Livmarli 380mcg/kg/day	Placebo
Number of participants	5	10
Least Square Mean[1] (Standard Error) Unit of Measure: µmol/L	-21.73 (43.125)	95.55 (30.488)

[1]The difference between treatment groups in change from Week 18 to Week 22 in fasting sBA levels was evaluated using an analysis of covariance (ANCOVA) model with treatment group as a factor, and Week 18 sBA as a covariate.

○ Secondary Outcome Measure: change from week 18 to week 22 in pruritis as measured by ItchRO(Obs) weekly average. The ItchRO(Obs) outcome is used to measure a participant's pruritis as observed by their caregiver twice daily (once in the morning and once in the evening). Pruritis symptoms were assessed on a 5-point scale, with scores ranging from 0 (no reported symptoms) to 4 (very severe). The average of the worst daily ItchRO(Obs) was computed for each week. For randomized patients, the mean (SD) at baseline was 3.1 (0.5) and the mean (SD) at week 18 was 1.4 (0.9). Participants aged 5 years or older were able to self-report their itching severity. Participants who were administered Livmarli through week 22

maintained pruritis reduction. Participants in the placebo group returned to baseline pruritis scores by week 22.

	Livmarli (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)

CI = Confidence Interval
Results based on an analysis of covariance model with treatment groups and Week 18 average worst daily pruritis score as covariates

- Adverse Reactions: occurring in ≥ 5% of patients treated with Livmarli

LIVMARLI (N=86)		
Adverse Reaction	**Any Grade n (%)**	**Number of events per 100 person-years[1]**
Diarrhea	48 (55.8%)	41.6
Abdominal pain*	46 (53.5%)	38.6
Vomiting	35 (40.7%)	19.8
Nausea	7 (8.1%)	2.9
FSV Deficiency*	22 (25.6%)	11.1
Transaminases increased (AST, ALT)*	16 (18.6%)	6.9
Gastrointestinal Bleeding*	9 (10.4%)	3.8
Bone Fractures*	8 (9.3%)	3.3

*Terms were defined as:
FSV deficiency includes: vitamin A, D, E, or K deficiency, or INR increase
Abdominal Pain includes: abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper
Transaminase increased includes: ALT abnormal, ALT increased, AST abnormal, AST increased
Gastrointestinal Bleeding includes: hematochezia, hematemesis, gastrointestinal hemorrhage, melena
Bone Fracture includes: tibia 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

Price Per Unit (WAC):

- $46,500.00 per 30 mL bottle
- The estimated annual cost for Livmarli is $396,025 for a 17 kg patient (average patient weight in clinical trials). However, based on approved Livmarli dosing the annual cost could potentially range from $113,150 to $1,697,250 depending on patient weight.

Therapeutic Alternatives:

- Pharmacologic Treatment for ALGS
  - Treatment of ALGS is dependent on the specific symptoms of each patient, and often requires a multidisciplinary team given the multiple organs affected.
  - Pharmacologic treatment is aimed at alleviating pruritic symptoms and increasing quality of life. Vitamin supplementation is used in patients with FSV deficiency to support proper growth and development.

Medication	Annual Cost*	Notes
Ursodiol	$1,066	• First-line therapy • Improves hepatic bile flow, promotes bile acid excretion
Cholestyramine	$2,952	• First-line therapy • Binds to bile acid in intestines, promoting excretion
Rifampin	$932	• Second-line therapy • Believed to bind to bile acids and make them less pruritogenic and excretable by the kidneys

Naltrexone	$720	• Third-line therapy • Blocks mu receptors that are upregulated by cholestasis
Diphenhydramine	$86	• Adjunctive therapy • Can provide some relief in mild cases
Sertraline	$97	• Adjunctive therapy • Mechanism of action is unknown for use in pruritis, data for use mostly in adults
Pipeline Agents		
Bylvay™	$385,000	• Recently approved IBAT inhibitor • Not currently indicated for ALGS, however currently being studied for use in ALGS

*Estimated based on average weight of participant in clinical trials utilizing high end of therapeutic dose range

- Non-pharmacologic ALGS Treatment
  - Partial Biliary Diversion
    - Surgical procedure to disrupt or divert recirculation of bile acids between liver and gastrointestinal tract. This procedure has been shown to improve symptoms such as itching or xanthoma formation but does not prevent the progression of liver disease.
  - Liver Transplantation
    - Various reports indicate between 20-70% of ALGS patient require a liver transplant by age 18 due to severe pruritus or liver failure.
    - Indicated for patients with progressive hepatic dysfunction, severe portal hypertension, failure to thrive, and/or intractable pruritis.
    - One-year survival rate is 80%.

Prior Authorization Approval Criteria:

Initial Therapy:

- Participant has documented diagnosis of Alagille syndrome (Q44.7) confirmed by either:
  - Genetic testing confirming pathogenic variant of *JAG1* or *NOTCH2* **OR**
  - Presence of ≥ 3 of the following clinical features:
    - Cholestasis
    - Ophthalmologic abnormalities
    - Characteristic facial features
    - Cardiac defect
    - Skeletal abnormalities **AND**
- Prescribed by or in consultation with a hepatologist, gastroenterologist, or other specialist in the treated disease state **AND**
- Participant aged 1 year or older **AND**
- Participant is not currently pregnant **AND**
- Presence of moderate to severe pruritis as evidenced by clinically acceptable scales/tools (e.g., Whittington scale, ItchRO(Obs)) **AND**
- Participant lacks lifetime history of liver transplant or decompensated cirrhosis **AND**
- Participant history demonstrates therapeutic trial of ursodiol (60/90 days) **AND**
- Dose does not exceed 3 mL per day
- Initial approval period: 6 months

Continuation of Therapy:

- Participant demonstrates compliance to therapeutic regimen (90/120 days) **AND**
- Documented benefit of therapy as evidenced by reduction in pruritic symptoms

	Additional Provider Diagnostic/Monitoring Criteria, if desired: • Liver function tests during treatment (AST, ALT, TB, DB, sBA, INR). If abnormalities occur, consider dose reductions or treatment interruption. Persistent/recurring abnormalities should prompt a consideration to discontinue therapy. • Monitor for signs of worsening portal hypertension. Consider discontinuation of therapy if participant develops clinically significant portal hypertension. • Monitor for dehydration. Interrupt therapy if diarrhea is persistent and discontinue if diarrhea persists after treatment resumes. • Monitor for fat-soluble vitamin deficiency at baseline as well as during treatment and supplement as necessary. Discontinue if deficiencies persist despite adequate supplementation. • Monitor bile acid level at baseline and during treatment.
Implication to State Medicaid Program:	• LOE: 2032 • Livmarli is currently in Phase 3 trials for progressive familial intrahepatic cholestasis (PFIC) and biliary atresia. • Mirum Pharmaceuticals, the manufacturer of Livmarli, has another IBAT inhibitor in their pipeline – volixibat. This product is currently being studied in primary sclerosing cholangitis, intrahepatic cholestasis of pregnancy, and primary biliary cholangitis. Interim analysis is expected in 2022. • Bylvay™ is another IBAT inhibitor that was recently approved by the FDA for the indication of PFIC. Bylvay is currently in Phase 3 trials for both Alagille syndrome and biliary atresia. Livmarli will be in direct competition with Bylvay.

References:

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