Helping patients understand

WHAT TO EXPECT WITH

Livmarli®
(maralixibat) oral solution

LIVMARLI is indicated for the treatment of cholestatic pruritus in patients who are 3 months of age and older with Alagille syndrome and for the treatment of cholestatic pruritus in patients who are 12 months of age and older with progressive familial intrahepatic cholestasis (PFIC).

Limitations of Use: LIVMARLI is not recommended in a subgroup of PFIC type 2 patients with specific *ABCB11* variants resulting in nonfunctional or complete absence of bile salt export pump (BSEP) protein.[1]

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

LIVMARLI is contraindicated in patients with prior or active hepatic decompensation events (eg, variceal hemorrhage, ascites, or hepatic encephalopathy).

WARNINGS AND PRECAUTIONS

Hepatotoxicity: LIVMARLI treatment is associated with a potential for drug-induced liver injury (DILI). In the PFIC trial, treatment-emergent hepatic decompensation events and elevations of liver tests or worsening of liver tests occurred. Two patients experienced DILI attributable to LIVMARLI. Two additional patients experienced DILI in the open-label extension portion of the trial. Of these 4 patients, 1 patient required liver transplant and another patient died.

In the Alagille syndrome trial, treatment-emergent elevations of liver tests or worsening of liver tests occurred.

Obtain baseline liver tests and monitor during treatment. Liver-related adverse reactions and physical signs of hepatic decompensation should also be monitored. Dose reduction or treatment interruption may be considered if abnormalities occur in the absence of other causes. For persistent or recurrent liver test abnormalities, consider treatment discontinuation. Permanently discontinue LIVMARLI if a patient experiences the following: persistent or recurrent liver test abnormalities, clinical hepatitis, or a hepatic decompensation event.

Please see Important Safety Information throughout and full Prescribing Information.

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RESULTS WITH LIVMARLI

In the ICONIC study* for once-daily LIVMARLI, **significant improvements in cholestatic pruritus from baseline were seen at the very first assessment** (Week 3), with the full effect achieved by Week 18 and maintained through 1 year (*P*<0.0001).[2,3]

84%

During the first year of treatment, **84% (n=26/31) of patients with Alagille syndrome experienced clinically meaningful† improvements in cholestatic pruritus** compared with baseline.[2]

4 YEARS

For patients who remained on LIVMARLI in the long-term part of the study (n=15), **relief from cholestatic pruritus was maintained for nearly 4 years.**[2]

WHAT PATIENTS SHOULD KNOW

- In the clinical study, most patients taking LIVMARLI saw meaningful improvements in their cholestatic pruritus (some had little to no itch)[2]
- Some patients felt better within 3 weeks[2]
- In the long-term part of the study, results lasted for nearly 4 years[2]

*The ICONIC study was a placebo-controlled, double-blind, randomized withdrawal period, Phase 2b study with a long-term, open-label extension. The study assessed efficacy and safety of treatment with LIVMARLI in patients ≥1 year old with cholestatic pruritus associated with Alagille syndrome.[2]

†Cholestatic pruritus was assessed each day, in the morning and evening, using the Itch Reported Outcome (ItchRO) scale—a validated tool designed to assess the impact of cholestatic pruritus in people with cholestatic liver disease, including Alagille syndrome. The ItchRO score is a 0–4 scale, where 0 is none, 1 is mild, 2 is moderate, 3 is severe, and 4 is very severe. Changes in ItchRO score of 1.0 or more have been shown to be clinically meaningful. ItchRO(Obs) was completed by caregivers and was the basis for the key pruritus endpoint. The patient-rated ItchRO (ItchRO[Pt]) was completed independently by participants aged 9 years or older and with caregiver assistance for participants aged 5 to 8 years.[2]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Gastrointestinal Adverse Reactions: Diarrhea and abdominal pain were reported as the most common adverse reactions. Monitor for dehydration and treat promptly. Consider reducing the dosage or interrupting LIVMARLI dosing if a patient experiences persistent diarrhea or diarrhea with bloody stool, vomiting, dehydration requiring treatment, or fever.

Please see Important Safety Information throughout and full Prescribing Information.

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HOW LIVMARLI WORKS

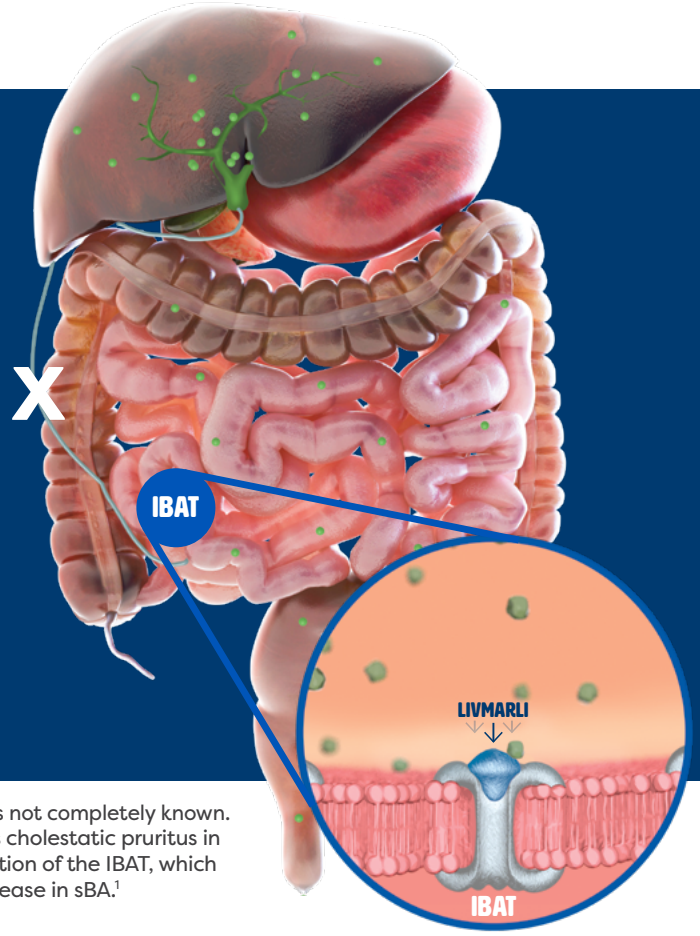
Bile acid buildup in Alagille syndrome

In Alagille syndrome, narrow, malformed, or a reduced number of bile ducts results in a persistent state of cholestasis,* or inhibition of bile flow from the liver.[4,5] As a result, bile acids spill over into the bloodstream, resulting in increased serum bile acid (sBA) levels systemically.[6,7]

LIVMARLI BATTLES BILE ACID BUILDUP

LIVMARLI is an ileal bile acid transporter (IBAT) inhibitor designed to **decrease the bile acid pool in the body.**[1,2,8]

LIVMARLI interrupts recirculation of bile acids to the liver and increases their fecal excretion to reduce bile acid levels in the body (as measured by sBA), with minimal systemic absorption.[1,2,8†]



*The pathophysiology of cholestatic pruritus in Alagille syndrome is not completely known.
†Although the complete mechanism by which LIVMARLI improves cholestatic pruritus in patients with Alagille syndrome is unknown, it may involve inhibition of the IBAT, which results in decreased reuptake of bile salts, as observed by a decrease in sBA.[1]

WHAT PATIENTS SHOULD KNOW

- Patients with Alagille syndrome have levels of bile acids in the body that are higher than usual[2,6,7]
- These high bile acid levels can cause cholestatic pruritus[2,6,7]
- LIVMARLI works to reduce bile acid levels by increasing the amount of bile acids eliminated from the body in feces[2,6,7]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Fat-Soluble Vitamin (FSV) Deficiency: Patients can have FSV deficiency (vitamins A, D, E, and K) at baseline, and LIVMARLI may adversely affect absorption of FSVs. Treatment-emergent bone fracture events have been observed more frequently with patients treated with LIVMARLI compared with patients treated with placebo. If bone fractures or bleeding occur, consider interrupting LIVMARLI and supplement with FSVs. LIVMARLI can be restarted once FSV deficiency is corrected and maintained at corrected levels.

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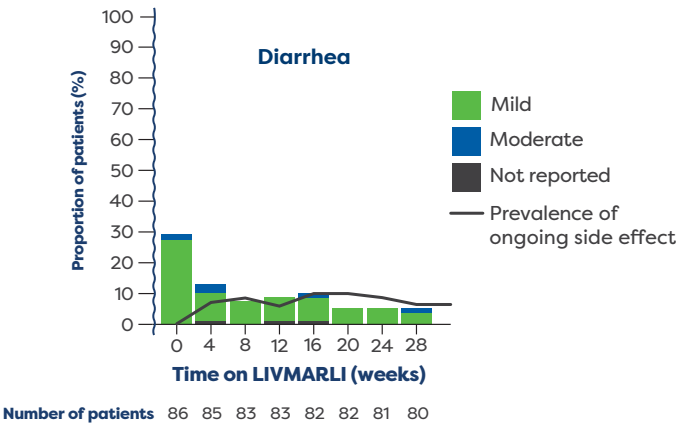
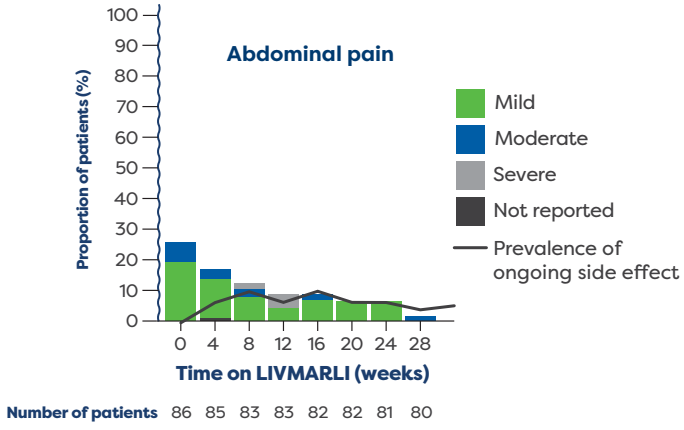
POSSIBLE SIDE EFFECTS

Safety and tolerability were evaluated in the Alagille syndrome clinical development program, which included 5 clinical studies comprising 86 patients. The most common adverse reactions were diarrhea, abdominal pain, and vomiting. **Most gastrointestinal (GI) events were mild and transient, and the majority resolved in <1 week.**[1,9]

GI side effects over time[9]





Five patients experienced treatment interruptions or dose reductions due to diarrhea, abdominal pain, or vomiting.[1,9] **No patients discontinued due to diarrhea, abdominal pain, or vomiting.**[10] In the ICONIC study, **there were no discontinuations of LIVMARLI due to ineffectiveness.**[2]

Other common side effects included fat-soluble vitamin (FSV) deficiency, liver test abnormalities, and bone fractures.[1]

Patients with Alagille syndrome can have FSV deficiency (vitamins A, D, E, and/or K) at baseline.[1]
- LIVMARLI may affect absorption of FSV[1]

WHAT PATIENTS SHOULD KNOW

- **LIVMARLI is backed by more than 5 years of safety data. No meaningful changes in ALT or AST were observed over 7 years of treatment**[9,11]
- **Side effects like diarrhea and stomach pain may occur as the body adjusts to LIVMARLI. In clinical studies, most GI side effects were mild and temporary, lasting less than 1 week**[9]
- **In the clinical studies, no one stopped taking LIVMARLI due to diarrhea, stomach pain, or vomiting**[9,10]
- **A small number of patients—around 3 in 10—experienced FSV deficiency in the ICONIC study. Though LIVMARLI may affect FSV, patients with Alagille syndrome can have FSV deficiency at the start of treatment and are often supplemented with FSV**[1]

ALT=alanine transaminase; AST=aspartate aminotransferase.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Risk of Propylene Glycol Toxicity (Pediatric Patients Less Than 5 Years of Age):
Total daily intake of propylene glycol should be considered for managing the risk of propylene glycol toxicity. Monitor patients for signs of propylene glycol toxicity. Discontinue LIVMARLI if toxicity is suspected.

 Please see Important Safety Information throughout and full Prescribing Information.

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RESULTS WITH LIVMARLI

In the MARCH-PFIC study—the largest Phase 3 study conducted in children with PFIC*†—LIVMARLI was shown to provide **statistically significant improvements in cholestatic pruritus‡ vs placebo** at 6 months. **Improvements were seen as early as Week 2.**[1,12,13]

64%

During the first 6 months of treatment, **64% of patients in the All-PFIC cohort experienced clinically meaningful improvements§ in cholestatic pruritus** vs 29% of patients treated with placebo (*P*=0.0064).[12]

2 YEARS

For patients who remained on LIVMARLI during the long-term part of the study (n=13), **relief from cholestatic pruritus was maintained through 2 years** (*P*<0.001).[14]

WHAT PATIENTS SHOULD KNOW

- **In the clinical study, many patients taking LIVMARLI saw meaningful improvements in their cholestatic pruritus (some had little to no itch)**[12]
- **Some patients felt better within 2 weeks**[12]
- **In the long-term part of the study, results lasted through 2 years**[14]

BSEP=bile salt export pump; FIC1=familial intrahepatic cholestasis associated protein 1; TJP2=tight junction protein 2.

*The MARCH-PFIC study was a 26-week, Phase 3, randomized, placebo-controlled study that assessed efficacy and safety of treatment with LIVMARLI in patients ≥12 months to <18 years old with cholestatic pruritus in PFIC. The study populations for MARCH-PFIC included a BSEP cohort, an All-PFIC cohort, and a Full cohort. The study included PFIC types that had not previously been studied. The full study cohort included 8 patients with prior surgery to treat PFIC. Surgery participants had the following PFIC types: non-truncated BSEP (LIVMARLI: 3, placebo: 0); FIC1 (LIVMARLI: 2, placebo: 2); and TJP2 (LIVMARLI: 0; placebo: 1).[12]

†Limitations of Use: LIVMARLI is not recommended in a subgroup of PFIC type 2 patients with specific *ABCB11* variants resulting in nonfunctional or complete absence of BSEP protein.[1]

‡The primary efficacy endpoint for MARCH-PFIC was the mean change in the average morning Itch Reported Outcome (Observer) (ItchRO[Obs]) severity score between baseline and the last 12 weeks of treatment (Weeks 15 to 26) in the BSEP cohort, as reported by caregivers.[12]

§Cholestatic pruritus was assessed each day, in the morning and evening, using the ItchRO scale—a validated tool designed to assess the impact of cholestatic pruritus in people with cholestatic liver disease, including PFIC. The ItchRO score is a 0–4 scale, where 0 is none, 1 is mild, 2 is moderate, 3 is severe, and 4 is very severe. Changes in ItchRO score of 1.0 or more have been shown to be clinically meaningful.[1,12]

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

Alagille syndrome: The most common adverse reactions are diarrhea, abdominal pain, vomiting, FSV deficiency, liver test abnormalities, and bone fractures.

PFIC: The most common adverse reactions are diarrhea, FSV deficiency, abdominal pain, liver test abnormalities, hematochezia, and bone fractures.

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HOW LIVMARLI WORKS

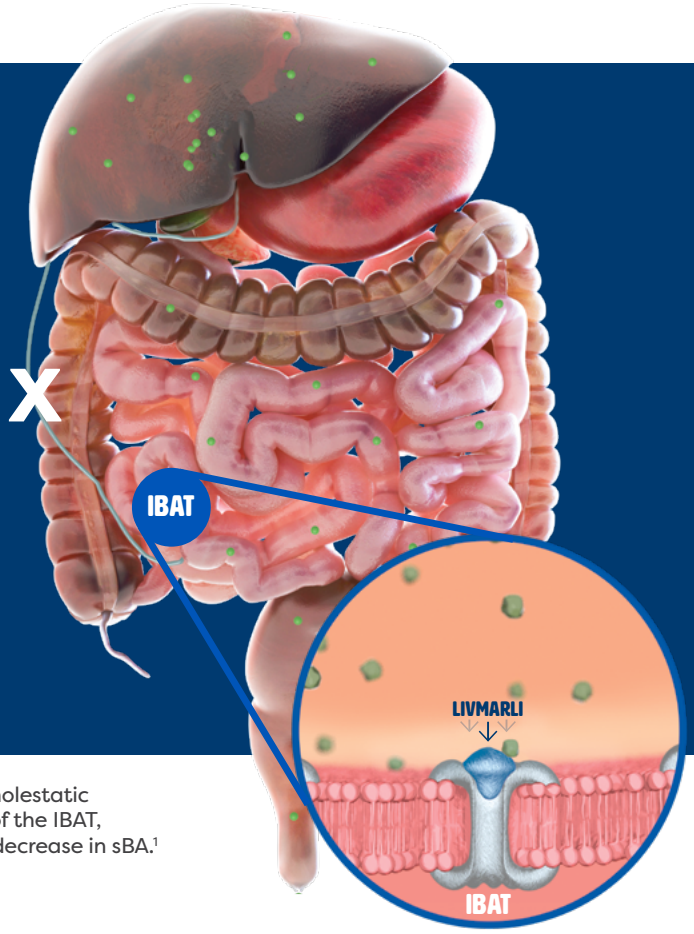
Bile acid buildup in PFIC

Across all PFIC subtypes, there is an inhibition of bile flow between the liver and small intestine, resulting in a persistent state of cholestasis.[4,15] Mutations in hepatocellular transport genes cause functional deficiencies that disrupt the ability for bile acids to be transported out of hepatocytes. This results in increased serum bile acid (sBA) levels systemically.[16-19]

LIVMARLI BATTLES BILE ACID BUILDUP

LIVMARLI is an ileal bile acid transporter (IBAT) inhibitor **designed to decrease the bile acid pool in the body.**[1,2,8]

LIVMARLI interrupts recirculation of bile acids to the liver and increases their fecal excretion to reduce bile acid levels in the body (as measured by sBA), with minimal systemic absorption.[1,2,8*]



*Although the complete mechanism by which LIVMARLI improves cholestatic pruritus in patients with PFIC is unknown, it may involve inhibition of the IBAT, which results in decreased reuptake of bile salts, as observed by a decrease in sBA.[1]

WHAT PATIENTS SHOULD KNOW

- Patients with PFIC have levels of bile acids in the body that are higher than usual[2,6,7]
- These high bile acid levels can cause cholestatic pruritus[2,6,7]
- LIVMARLI works to reduce bile acid levels by increasing the amount of bile acids eliminated from the body in feces[2,6,7]

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

Administer bile acid binding resins at least 4 hours before or 4 hours after administration of LIVMARLI. A decrease in the absorption of OATP2B1 substrates (eg, statins) due to OATP2B1 inhibition by LIVMARLI in the GI tract cannot be ruled out. Consider monitoring the drug effects of OATP2B1 substrates as needed.

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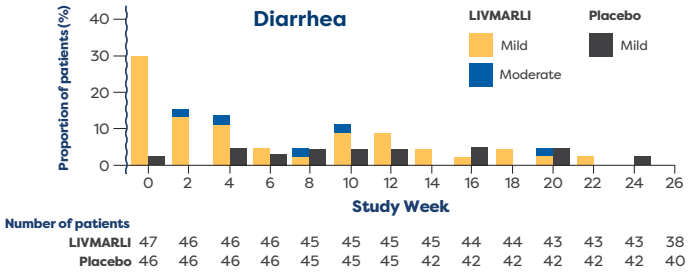
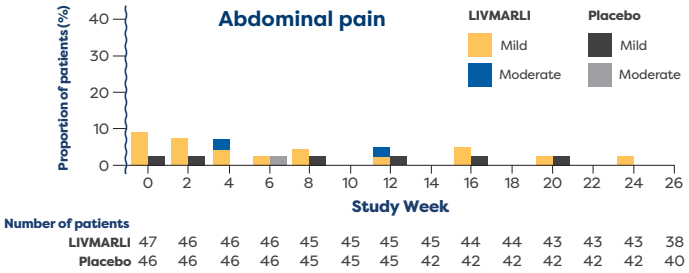
POSSIBLE SIDE EFFECTS

The most common adverse reactions seen with LIVMARLI in the MARCH-PFIC study were gastrointestinal (GI) (diarrhea and abdominal pain*) and were generally mild and transient, resolving within 5.5 days.[1,20]

GI side effects over time[20]





Other common adverse reactions included transaminases increased (ALT or AST), hematochezia or rectal hemorrhage, and bone fractures.[1†]

Treatment with LIVMARLI is associated with a potential for drug-induced liver injury (DILI).[1]

- Two patients experienced DILI attributable to LIVMARLI. One patient received 570 mcg/kg twice daily and the second patient required dose interruption and reduction[1]

Patients with PFIC can have fat-soluble vitamin (FSV) deficiency (vitamins A, D, E, and/or K) at baseline.[1]

- LIVMARLI may affect absorption of FSV[1]

WHAT PATIENTS SHOULD KNOW

- **Side effects may occur as the body adjusts to LIVMARLI. In the clinical study, the most common side effects were GI related (diarrhea and abdominal pain). Most cases were mild and temporary, lasting 5.5 days on average**[1,20]
- **FSV deficiency is common in patients with PFIC. LIVMARLI may affect absorption of FSV; however, in the clinical study, FSV deficiency occurred more often in the placebo group than in the LIVMARLI group**[1]

ALT=alanine transaminase; AST=aspartate aminotransferase.

*Abdominal pain includes abdominal pain, abdominal pain upper, and abdominal distension.
†Transaminases increased included hypertransaminasaemia, ALT abnormal, ALT increased, AST abnormal, AST increased, transaminases increased, and hepatic enzyme increased; bone fracture included upper limb fracture, lower limb fracture, radius fracture, ulna fracture, femur fracture, and foot fracture.

IMPORTANT SAFETY INFORMATION (cont'd)

DOSING INFORMATION

In patients with Alagille syndrome, LIVMARLI is taken once daily, 30 minutes before a meal in the morning. In patients with PFIC, LIVMARLI is taken twice daily, 30 minutes before a meal. The provided oral dosing dispenser must be used to accurately measure the dose. Any remaining LIVMARLI should be discarded 100 days after first opening the bottle.

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GETTING YOUR PATIENTS STARTED WITH LIVMARLI

STEP 1

COMPLETE THE MIRUM ACCESS PLUS PATIENT ENROLLMENT FORM

Ensure patients are enrolled in Mirum Access Plus by downloading and completing the **Patient Enrollment Form** and faxing it to **1-855-282-4884**. Consenting patients will sign the second page of the form.

STEP 2

THE MIRUM ACCESS PLUS TEAM WILL CONNECT WITH YOUR PATIENTS TO:

- **Assist with insurance coverage**
- **Discuss financial support** options and eligibility; **eligible patients may pay as little as $10 out of pocket per fill for LIVMARLI***†

Mirum Access Plus offers ongoing support and education for patients and caregivers. Patients can contact Mirum Access Plus at 1-855-MRM-4YOU (1-855-676-4968) Monday through Friday, 8:00 AM to 8:00 PM ET.

STEP 3

ONCE APPROVED, LIVMARLI WILL BE SHIPPED DIRECTLY TO YOUR PATIENT

CONTINUED SUPPORT

Mirum Access Plus will check in throughout patients' treatment to help them make the most of the available resources. The Mirum Access Plus team can support adherence if patients are consented by introducing and discussing tools to track cholestatic pruritus and encouraging communication between patients and their doctors.

Patients can read the FDA-approved patient labeling **(Patient Information and Instructions for Use)** for more information about weight-based dosing with LIVMARLI.

*Data from 1/1/2022 to 12/31/2023.
†Patients enrolled in the Mirum Patient Assistance Program are included in those paying $10 or less per fill.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

LIVMARLI is contraindicated in patients with prior or active hepatic decompensation events (eg, variceal hemorrhage, ascites, or hepatic encephalopathy).

Please see Important Safety Information throughout and full Prescribing Information.

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References: 1. LIVMARLI® (maralixibat) oral solution. Prescribing Information. Mirum Pharmaceuticals, Inc. **2.** Gonzales E, Hardikar W, Stormon M, et al. Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study. *Lancet.* 2021;398(10311):1581-1592. doi:10.1016/S0140-6736(21)01256-3 **3.** Gonzales E, Sturm E, Stormon M, et al. Durability of treatment effect with long-term maralixibat in children with Alagille syndrome: 4-year safety and efficacy. Presented at: American Association for the Study of Liver Diseases Annual Meeting: The Liver Meeting; November 8-12, 2019; Boston, MA **4.** Kamath BM, Stein P, Houwen RHJ, Verkade HJ. Potential of ileal bile acid transporter inhibition as a therapeutic target in Alagille syndrome and progressive familial intrahepatic cholestasis. *Liver Int.* 2020;40(8):1812-1822. doi:10.1111/liv.14553 **5.** Alagille syndrome. MedlinePlus. Updated December 1, 2014. Accessed January 3, 2025. https://medlineplus.gov/genetics/condition/alagille-syndrome **6.** Jesina D. Alagille syndrome: an overview. *Neonatal Netw.* 2017;36(6):343-347. doi:10.1891/0730-0832.36.6.343 **7.** Jones EA, Bergasa NV. The pruritus of cholestasis: from bile acids to opiate agonists. *Hepatology.* 1990;11(5):884-887. doi:10.1002/hep.1840110526l0 **8.** Martin P, Apostol G, Smith W, Jennings L, Vig P. Dose-dependent fecal bile acid excretion with apical sodium-dependent bile acid transporter inhibitors maralixibat and volixibat in a dose-ranging phase 1 study in overweight and obese adults. Poster presented at: American Association for the Study of Liver Diseases: The Liver Meeting; November 8-12, 2019; Boston, MA. **9.** Kamath BM, Raman RK, Garner W, Tucker E, Vig P, Gonzales E. Gastrointestinal tolerability of maralixibat in patients with Alagille syndrome: an integrated analysis of short- and long-term treatment. Poster presented at: The 6th World Congress of Pediatric Gastroenterology, Hepatology and Nutrition; June 2-5, 2021; Vienna, Austria. **10.** Data on file. REF-00180. Mirum Pharmaceuticals, Inc. **11.** Murray KF, Kamath BM, Gonzales E, et al. Clinical benefits of maralixibat for patients with Alagille syndrome are durable through 7 years of treatment: data from the MERGE study. Poster presented at: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Annual Meeting; November 6-9, 2024; Hollywood, Florida. **12.** Miethke AG, Moukarzel A, Porta G, et al. Maralixibat in progressive familial intrahepatic cholestasis (MARCH-PFIC): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Gastroenterol Hepatol.* 2024;9(7):620-631. doi:10.1016/s2468-1253(24)00080-3 **13.** Data on file. REF-01126. Mirum Pharmaceuticals, Inc. **14.** Miethke A, Moukarzel A, Porta G, et al. Long-term maintenance of response and improved liver health with maralixibat in patients with progressive familial intrahepatic cholestasis (PFIC): 2-year data from the MARCH-ON study. Presented at: American Association for the Study of Liver Diseases (AASLD) The Liver Meeting: November 10-14, 2023; Boston, MA. **15.** Felzen A, Verkade HJ. The spectrum of progressive familial intrahepatic cholestasis diseases: update on pathophysiology and emerging treatments. *Eur J Med Genet.* 2021;64(11):104317. doi:10.1016/j.ejmg.2021.104317 **16.** Jacquemin E. Progressive familial intrahepatic cholestasis. *Clin Res Hepatol Gastroenterol.* 2012;36(suppl 1):S26-S35. doi:10.1016/S2210-7401(12)70018-9 **17.** Srivastava A. Progressive familial intrahepatic cholestasis. *J Clin Exp Hepatol.* 2014;4(1):25-36. doi:10.1016/j.jceh.2013.10.005 **18.** Amer S, Hajira A. A comprehensive review of progressive familial intrahepatic cholestasis (PFIC): genetic disorders of hepatocanalicular transporters. *Gastroenterol Res.* 2014;7(2):39-43. doi:10.14740/gr609e **19.** Henkel SAF, Squires JH, Ayers M, Ganoza A, Mckiernan P, Squires JE. Expanding etiology of progressive familial intrahepatic cholestasis. *World J Hepatol.* 2019;11(5):450-463. doi:10.4254/wjh.v11.i5.450 **20.** Gonzalez-Peralta R, Miethke A, Moukarzel A, et al. Analysis of safety in maralixibat-treated participants with progressive familial intrahepatic cholestasis: data from the MARCH-PFIC trial. Poster presented at: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Annual Meeting; October 4-7, 2023; San Diego, CA.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Hepatotoxicity: LIVMARLI treatment is associated with a potential for drug-induced liver injury (DILI). In the PFIC trial, treatment-emergent hepatic decompensation events and elevations of liver tests or worsening of liver tests occurred. Two patients experienced DILI attributable to LIVMARLI. Two additional patients experienced DILI in the open-label extension portion of the trial. Of these 4 patients, 1 patient required liver transplant and another patient died.

In the Alagille syndrome trial, treatment-emergent elevations of liver tests or worsening of liver tests occurred.

Obtain baseline liver tests and monitor during treatment. Liver-related adverse reactions and physical signs of hepatic decompensation should also be monitored. Dose reduction or treatment interruption may be considered if abnormalities occur in the absence of other causes. For persistent or recurrent liver test abnormalities, consider treatment discontinuation. Permanently discontinue LIVMARLI if a patient experiences the following: persistent or recurrent liver test abnormalities, clinical hepatitis, or a hepatic decompensation event.

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