

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

<sup>P</sup>**LIVMARLI**<sup>®</sup>

Maralixibat oral solution  
solution, 9.5 mg/mL maralixibat (as maralixibat chloride), oral

Ileal bile acid transporter inhibitor

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United States of America

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## RECENT MAJOR LABEL CHANGES

None	
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## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **1 INDICATIONS**

LIVMARLI® (maralixibat oral solution) is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS).

#### **1.1 Pediatrics**

Pediatrics (12 months to 18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of LIVMARLI in these pediatric patients have been established. Therefore, Health Canada has authorized an indication for pediatric use.

Pediatrics (<12 months): The safety and efficacy of LIVMARLI in these pediatric patients have not been established.

#### **1.2 Geriatrics**

No data are available to Health Canada. Clinical studies of LIVMARLI did not include patients aged 65 years and over. Therefore, the safety and efficacy in this patient population have not been established.

### **2 CONTRAINDICATIONS**

LIVMARLI is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

### **4 DOSAGE AND ADMINISTRATION**

#### **4.1 Dosing Considerations**

Hepatic biomarkers

- Baseline values for hepatic biomarkers including serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total and direct bilirubin, and International Normalized Ratio (INR) should be established.
- Serum ALT, serum AST, total and direct bilirubin, and INR, should be monitored during treatment with LIVMARLI.
- Should increases occur in the absence of other causes or expected progression of underlying disease, dose reduction or interruption of LIVMARLI treatment may be considered. In these circumstances, should LIVMARLI be restarted, a dose of 190 mcg/kg/day should be considered, and if tolerated, further increases to 380 mcg/kg/day may be instituted with monitoring of hepatic biomarkers.
- If liver abnormalities persist beyond those expected due to underlying disease, permanent discontinuation of LIVMARLI should be considered (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, and 8.4 ADVERSE REACTIONS, Abnormal Laboratory Findings, *Hepatic Biomarkers*).

## 4.2 Recommended Dose and Dosage Adjustment

The recommended maintenance dosage of LIVMARLI is 380 mcg/kg taken once daily in the morning. LIVMARLI should be initiated at a dose of 190 mcg/kg orally once daily. If tolerated, LIVMARLI may be increased to 380 mcg/kg once daily after one week. The maximum daily dose volume for patients above 70 kg is 3 mL or 28.5 mg per day. Refer to dosing by weight guidelines presented in Table 1.

**Table 1: Individual Dose Volume by Patient Weight**

Patient Weight (kg)	Days 1-7 (190 mcg/kg once daily)		Beginning Day 8 (380 mcg/kg once daily)	
	Volume per day (mL)	Dosing dispenser size (mL)	Volume per day (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 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 or higher	1.5		3	

There are limited data currently available regarding the long-term use of maralixibat in patients with Alagille Syndrome. Because Alagille Syndrome is a rare, intractable genetic disease, long-term therapy is expected. Periodic re-assessment, including dosing recalculation as the patient grows, is required.

### Geriatrics

The safety and efficacy in patients 65 years of age and older have not been established.

### Renal impairment

Maralixibat has not been studied in patients with renal impairment or end-stage renal disease (ESRD) requiring hemodialysis. However, due to the minimal plasma concentrations and negligible renal excretion, no dose adjustment is required for these patients (see 10.3 CLINICAL PHARMACOLOGY, Pharmacokinetics).

### Hepatic impairment

Maralixibat has not been sufficiently studied in patients with liver impairment. Due to minimal absorption, no dose adjustment is required for patients with hepatic impairment. Close monitoring is, however, advised for patients with end-stage liver disease or progression to decompensation (see 10.3 CLINICAL PHARMACOLOGY, Pharmacokinetics).

### 4.3 Administration

LIVMARLI is to be administered orally via an oral syringe by a caregiver or the patient, 30 minutes before a meal in the morning.

A calibrated measuring device (0.5 mL, 1 mL or 3 mL oral dosing dispenser) will be provided by the pharmacy to measure and deliver the prescribed dose accurately.

Store LIVMARLI at 2-30°C (35.6-86°F); do not freeze (see 11 STORAGE, STABILITY AND DISPOSAL).

Discard any remaining LIVMARLI 100 days after first opening of bottle.

LIVMARLI contains propylene glycol (364.5 mg/mL) as an excipient. Store securely to limit accidental ingestion of excess doses of LIVMARLI.

### 4.4 Missed Dose

If a dose is missed, it should be taken as soon as possible within 12 hours of the time it is usually taken, with the original dosing schedule then to be resumed. If a dose is missed by more than 12 hours, the dose can be omitted and the original dosing schedule resumed.

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

LIVMARLI contains propylene glycol (364.5 mg/mL) as an excipient. Overdoses of propylene glycol may manifest with hyperosmolality, central nervous system, cardiovascular and respiratory effects.

For management of a suspected drug overdose, contact your regional poison control centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 2: Dosage Forms, Strengths, Composition and Packaging**

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Solution, 9.5 mg of maralixibat per mL, as maralixibat chloride	Edetate disodium, grape flavor, propylene glycol (364.5 mg/mL), purified water and sucralose

LIVMARLI® (maralixibat) oral solution is a clear, colorless to yellow liquid supplied in a 30 mL amber plastic bottle. Each mL contains 9.5 mg of maralixibat, equivalent to 10 mg of maralixibat chloride. The pH of the oral solution is 3.8 – 4.8.

## **7 WARNINGS AND PRECAUTIONS**

### **Gastrointestinal**

Diarrhea is a common adverse reaction when taking maralixibat, and may lead to dehydration. Patients should be monitored regularly to ensure adequate hydration during episodes of diarrhea or vomiting while taking LIVMARLI.

Patients with chronic diarrhea requiring intravenous fluid or nutritional intervention were not studied in clinical trials.

### **Hepatic/Biliary/Pancreatic**

In clinical trials, serum ALT elevations were observed in patients receiving maralixibat treatment. Elevations in serum bilirubin beyond those at baseline were also observed (see 8 ADVERSE REACTIONS). Their clinical significance should be carefully considered, given the underlying liver disease of the patient. Liver function tests should be monitored in patients before and during treatment with maralixibat, so that liver enzyme elevations from baseline can be identified and evaluated.

LIVMARLI has not been studied in patients with hepatic decompensation. Close monitoring is advised for patients with end-stage liver disease or decompensation.

### **Vitamin Deficiency**

Patients with Alagille syndrome may have fat-soluble vitamin (FSV) deficiency at baseline before taking LIVMARLI. Vitamin A, D and E levels should be measured before and during LIVMARLI treatment, and INR values determined to reflect vitamin K effects. If FSV deficiency is diagnosed, supplement these vitamins as appropriate.

#### **7.1 Special Populations**

##### **7.1.1 Pregnant Women**

There is no experience in clinical trials with the use of LIVMARLI in pregnant women.

In animal reproduction studies, no developmental effects were observed (see 16 NON-CLINICAL TOXICOLOGY).

##### **7.1.2 Breast-feeding**

No clinically relevant effects on breastfed children are anticipated since the systemic exposure of the breast-feeding woman to maralixibat is negligible.

##### **7.1.3 Pediatrics**

Pediatrics (12 months to 18 years): The safety and effectiveness of LIVMARLI for the treatment of cholestatic pruritus in Alagille syndrome have been established in these patients (see 1.1 INDICATIONS, Pediatrics).

Pediatrics (<12 months): The safety and efficacy of LIVMARLI in these pediatric patients have not been established (see 1.1 INDICATIONS, Pediatrics).

#### **7.1.4 Geriatrics**

The safety and effectiveness of LIVMARLI for the treatment of pruritus in Alagille syndrome in adult patients, 65 years of age and older, have not been established.

#### **7.1.5 Hepatic Impairment**

Clinical studies of LIVMARLI evaluated patients with Alagille syndrome having impaired hepatic function at baseline. However, the efficacy and safety in these patients with clinically significant portal hypertension or hepatic decompensation have not been established (see 4.3 DOSAGE AND ADMINISTRATION, Hepatic Impairment, 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, and 14.1 CLINICAL TRIALS, Alagille Syndrome).

### **8 ADVERSE REACTIONS**

#### **8.1 Adverse Reaction Overview**

The most frequently occurring adverse reactions reported in patients with Alagille syndrome 12 months of age and older (N=86) who were treated with maralixibat over a period of up to 5 years in long-term extension trials, included diarrhea (36%) and abdominal pain (35%). Across the Alagille syndrome clinical program, these adverse reactions were generally considered to be of mild to moderate severity and self-limited in nature.

Although 30.2% patients sustained serious adverse events at some time during the long-term extension studies or their parent clinical trials, most were considered related to the underlying disease of Alagille syndrome or transient medical illnesses, e.g., viral infections. Serious gastrointestinal adverse events were reported overall in 9.3%, of which, 5.8% consisted of diarrhea, abdominal pain or vomiting, while 3.5% were related to gastrointestinal bleeding.

There were 16% of patients who experienced at least one adverse event that led to study drug discontinuation. Of these, 8% experienced increased serum alanine transaminase (ALT), and 2% increased blood bilirubin, that led to study drug discontinuation, although these adverse events were not necessarily due to maralixibat exposure since almost all patients had abnormal hepatic biomarkers at baseline in these clinical trials.

#### **8.2 Clinical Trial Adverse Reactions**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the Alagille syndrome clinical development program, which includes five clinical studies comprising 86 patients, patients received doses of LIVMARLI up to 760 mcg/kg per day with a median duration of exposure of 32.3 months. Generally, the maintenance dose of maralixibat was 380 mcg/kg per day.

The ICONIC study was comprised of an initial 18-week open-label (OL) study phase, followed by a 4-week placebo-controlled randomized drug withdrawal (RDW) study phase in patients with Alagille syndrome that were 12 months of age or older. The study then continued with an OL long-term extension (LTE) phase. Doses of maralixibat were titrated to 380 mcg/kg OD, and then maintained at that level, as tolerated. In the OL LTE, some patients received 380 mcg/kg bid. Overall, mean treatment exposure to maralixibat was 2.6 years in the study.



The most common adverse events by body system were gastrointestinal in nature, with 67.7% of patients experiencing these types of adverse events in the initial 18-week open-label segment of the trial, consisting mainly of diarrhea, abdominal pain or vomiting.

Common adverse events reported during maralixibat treatment in the ICONIC trial are presented in Table 3, below, by study treatment phase.

**Table 3: Incidence of Common Adverse Events (>10%) with Maralixibat in the ICONIC Study**

Open-label Study Treatment Phase to Week 18		
	Maralixibat 380 mcg/kg/d N=31 n (%)	
Number of participants with at least 1 common AE	22 (71%)	
<b>Gastrointestinal disorders</b>		
Abdominal pain*	13 (42%)	
Diarrhea	13 (42%)	
Vomiting	11 (35%)	
<b>General disorders and administration site conditions</b>		
Pyrexia	6 (19%)	
<b>Infections and infestations</b>		
Upper respiratory tract infection	6 (19%)	
Nasopharyngitis	4 (13%)	
<b>Injury, poisoning and procedural complications</b>		
Fall	4 (13%)	
<b>Nervous system disorders</b>		
Headache	5 (16%)	
Randomised Drug Withdrawal Study Phase - Week 18 to 22		
	Maralixibat 380 mcg/kg/d (N=13) n (%)	Placebo (N=16) n (%)
Number of participants with at least 1 common AE	3 (23%)	7 (44%)
<b>General disorders and administration site conditions</b>		
Pyrexia	0	2 (13%)
<b>Infections and infestations</b>		
Upper respiratory tract infection	2 (15%)	0
Open-label Study Phase - Week >22		
	Overall Maralixibat <sup>1</sup> (N=29) n (%)	
Number of participants with at least 1 common AE	27 (93%)	
<b>Gastrointestinal disorders</b>		
Abdominal pain*	11 (38%)	
Vomiting	9 (31%)	
Diarrhea	8 (28%)	
<b>General disorders and administration site conditions</b>		
Pyrexia	14 (48%)	
<b>Infections and infestations</b>		
Nasopharyngitis	9 (31%)	
Ear infection	6 (21%)	
Gastroenteritis	5 (17%)	
Upper respiratory tract infection	4 (14%)	

Viral infection	5 (17%)
Bronchitis	3 (10%)
<b>Injury, poisoning and procedural complications</b>	
Fall	3 (10%)
<b>Nervous system disorders</b>	
Headache	5 (17%)
<b>Respiratory, thoracic and mediastinal disorders</b>	
Cough	10 (34%)
Oropharyngeal pain	5 (17%)

AE=adverse event; n=number in a given category; N=number of participants; n/a=not applicable;

\*Abdominal pain includes: abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper.

<sup>1</sup> Only adverse events occurring while participants received 380 mcg/kg/day or lower are summarized. Participants were counted only once for each System Organ Class and Preferred Term.

### 8.3 Less Common Clinical Trial Adverse Reactions

Other less common adverse reactions reported in <10% of patients in ICONIC include the following:

Gastrointestinal disorders: gastritis, nausea, gastrointestinal bleeding

Nervous system disorders: headache, lethargy

### 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

#### Clinical Trial Findings

##### *Hepatic Biomarkers*

In the ICONIC study, Alagille syndrome patients 12 months of age and older that were enrolled were severely cholestatic, as reflected by elevated mean baseline levels of serum bile acids (sBA) at 283.4 µmol/L, total bilirubin of 6.1 mg/dL, aspartate aminotransferase (AST) of 167.7 U/L, alanine transaminase (ALT) of 181.0 U/L, gamma glutamyl transferase (GGT) at 508.4 U/L, alkaline phosphatase (ALP) of 601.3 U/L, and total cholesterol of 512.1 mg/dL.

Adverse events related to elevations in serum transaminases were reported only during the open-label long-term extension study phase in 4 patients (17%) with increased ALT, of which, 2 (9%) also had increased AST. However, none of these study participants experienced a serious adverse event associated with these elevated transaminases. One adverse event in a single patient (3%) was reported with elevated bilirubin after the randomized drug withdrawal phase of the study, however, was not considered to be related to study drug by the investigator. Nevertheless, this adverse event resulted in withdrawal of study drug for this patient.

## 9 DRUG INTERACTIONS

### 9.4 Drug-Drug Interactions

Maralixibat is not a substrate of the drug transporters MDR1 (P-gp), BCRP, OATP1B1, OATP1B3, or OATP2B2; therefore, concomitant use of drug products affecting these transporters are not predicted to affect the disposition of maralixibat.

Maralixibat inhibits CYP3A4 *in vitro*, however clinically relevant effects on the pharmacokinetics of CYP3A4 substrates are unlikely.

*In vitro*, maralixibat did not induce CYP isoforms 1A2, 2B6, or 3A4, nor inhibit CYP isoforms 1A2, 2B6,

2C8, 2C9, 2C19 or 2D6 at clinically relevant concentrations.

*In vitro*, maralixibat did not inhibit the transporters MDR1 (P-gp), BCRP, OAT1, OAT3, OATP1B1, OATP1B3, PEPT1, OCT1, OCT2, OCT3, OCTN1, OCTN2, MRP2, MATE1, or MATE2-K at clinically relevant concentrations.

The drugs listed in Table 4 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

**Table 4: Established or Potential Drug-Drug Interactions**

Drug	Source of Evidence	Effect	Clinical Comment
<b>Effect of Maralixibat on Other Drugs</b>			
OATP2B1 substrates (e.g. statins)	T	Maralixibat is an OATP2B1 inhibitor based on <i>in vitro</i> studies. A decrease in the oral absorption of OATP2B1 substrates due to OATP2B1 inhibition in the GI tract cannot be ruled out. In clinical studies coadministration of 4.75 mg maralixibat (once daily in the morning) with daily doses of either simvastatin, or lovastatin in the evening, did not have a clinically relevant effect on the pharmacokinetics of these statins and their metabolites. Coadministration of 4.75 mg maralixibat did not affect pharmacokinetics of atorvastatin. However, the effect of maralixibat on the pharmacokinetics of OATP2B1 substrates at higher doses has not been evaluated in a clinical study.	Consider monitoring the drug effects of OATP2B1 substrates as needed (see 10.3 CLINICAL PHARMACOLOGY, Pharmacokinetics).

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

## 9.5 Drug-Food Interactions

Concomitant administration of a high-fat meal with a single oral dose of maralixibat decreased both the rate and extent of absorption. AUC and C<sub>max</sub> of maralixibat values in the fed state were 64.8% to 85.8% lower relative to oral administration of 30 mg in fasted conditions. These changes in systemic levels of maralixibat are not clinically relevant.

## 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

## 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

# 10 CLINICAL PHARMACOLOGY

## 10.1 Mechanism of Action

Maralixibat is an inhibitor of the ileal bile acid transporter (IBAT). It decreases the reabsorption of bile acids from the terminal ileum.

Pruritus is a common symptom in patients with Alagille syndrome and elevations in serum bile acids have been strongly linked to cholestatic pruritus. Maralixibat improves pruritus in Alagille syndrome patients likely through decreasing serum bile acids.

## 10.2 Pharmacodynamics

In Trial 304, pediatric patients with Alagille syndrome were administered open-label treatment with LIVMARLI (maralixibat) 380 mcg/kg once daily for 13 weeks after an initial 5-week dose-escalation period (see 14 CLINICAL TRIALS). At baseline, serum bile acids were highly variable among patients ranging from 20 to 749  $\mu\text{mol/L}$  and mean (SD) serum bile acid level was 283 (210.6)  $\mu\text{mol/L}$ . Serum bile acid levels decreased from baseline in the majority of patients and the reduction in serum bile acids was generally maintained for the treatment period.

## 10.3 Pharmacokinetics

Due to the low systemic absorption of maralixibat, pharmacokinetic parameters cannot be reliably calculated at the recommended dose. Concentrations of maralixibat in the pediatric Alagille syndrome patients were below the limit of quantification (0.25 ng/mL) in the majority of plasma samples. In Trial 304, the highest concentration of maralixibat in pediatric Alagille syndrome patients following treatment with LIVMARLI 380 mcg/kg once daily was 5.93 ng/mL.

Following single oral administration of maralixibat in healthy adults at doses ranging from 1 mg to 500 mg, plasma concentrations of maralixibat were below the limit of quantification (0.25 ng/mL) at doses less than 20 mg and PK parameters could not be reliably estimated.

### Absorption

Maralixibat is minimally absorbed and plasma concentrations are often below the limit of quantification (0.25 ng/mL) after single or multiple administrations at recommended doses. When detectable, plasma drug levels peak on average 0.75 hr after dosing ( $T_{\text{max}}$ ). Following a single oral administration of maralixibat 30, 45, and 100 mg liquid formulation under fasted condition,  $AUC_{\text{last}}$  and  $C_{\text{max}}$  increased in a dose-dependent manner. No accumulation of maralixibat was observed following repeated oral administration of maralixibat in healthy adults at doses up to 100 mg once daily.

### Distribution

Maralixibat shows high binding (91%) to human plasma proteins *in vitro*.

## Metabolism

No maralixibat metabolites have been detected in plasma. Three minor metabolites, accounting for <3% of maralixibat-associated fecal radioactivity in total, were identified following oral administration of [<sup>14</sup>C]maralixibat.

## Elimination

Following a single oral dose of 30 mg maralixibat in healthy adults, the mean half-life ( $t_{1/2}$ ) was 1.6 hours.

Fecal excretion was found to be the major route of elimination. Following a single oral dose of 5 mg [<sup>14</sup>C]-maralixibat, 73% of the dose was excreted in the feces with 0.066% excreted in the urine. 94% of the fecal excretion was as unchanged maralixibat.

## Special Populations and Conditions

### Hepatic Insufficiency:

The pharmacokinetics of maralixibat have not been systematically investigated in patients with decompensated liver disease or cirrhosis.

**Renal Insufficiency:** The pharmacokinetics of maralixibat were not studied in patients with impaired renal function, including those with end-stage renal disease (ESRD) or those on hemodialysis.

## 11 STORAGE, STABILITY AND DISPOSAL

Store bottle at 2-30°C (35.6-86°F); do not freeze. Store in the original package to protect from light. Discard any remaining LIVMARLI 100 days after first opening of bottle. Always store with cap on the bottle.

## 12 SPECIAL HANDLING INSTRUCTIONS

Oral syringes may be rinsed with water, air dried and reused for 100 days.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

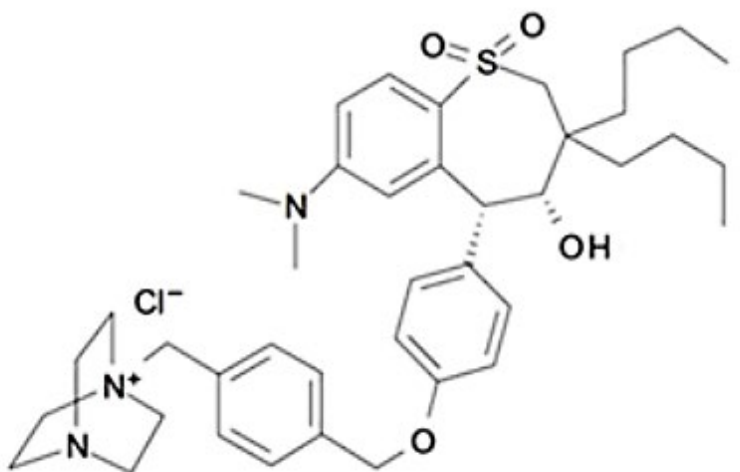
#### Drug Substance

Proper/Common name: Maralixibat chloride

Chemical name: 1-[[4-[[4-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy)methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride.

Molecular formula and molecular mass:  $C_{40}H_{56}ClN_3O_4S$  710.42 daltons

Structural formula:



Physicochemical properties: Maralixibat (as maralixibat chloride) is a white to light yellow solid, highly water soluble

## 14 CLINICAL TRIALS

### 14.1 Clinical Trials by Indication

#### Alagille Syndrome

**Table 5: Summary of Patient Demographics for Clinical Trial in Alagille Syndrome**

Study #	Study Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Sex
The ICONIC Study - Trial 304 - (NCT02160782)	Randomized, double-blind, placebo-controlled drug-withdrawal trial	Maralixibat 380 mcg/kg once daily for 43 weeks after an initial 5-week dose-escalation period orally administered	31	5.4 years (1-15)	M: 19 (61.3%) F: 12 (38.7%)

The efficacy of LIVMARLI was assessed in patients with Alagille syndrome that were 12 months of age or older in the ICONIC trial, which consisted of an 18-week open-label treatment period followed by a 4-week, double-blind, placebo-controlled randomized drug-withdrawal period followed by a subsequent 26-week open-label treatment period, and finally, a long-term open-label extension period.

Thirty-one pediatric patients with Alagille syndrome having cholestasis and pruritus were enrolled, with 90.3% of patients receiving at least one background medication at a stable dose to treat pruritus at study entry. All patients had a 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 study treatment 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 (n=13) or receive matching placebo (n=16) during the 4-week drug withdrawal study period from Weeks 19-22. All 29 patients completed this randomized, blinded drug withdrawal period. Subsequently, patients received open-label LIVMARLI for up to an additional 266 weeks.

All patients had cholestatic liver disease at study entry. The baseline mean serum values of hepatic biomarkers observed in 29 patients were sBA 280 mcmol/L, AST 158 U/L, ALT 179 U/L, GGT 498 U/L, and total bilirubin 5.6 mg/dL. Given the young age of most study patients, a single-item observer-reported outcome was used as the primary instrument to measure patients' pruritus symptoms as observed by their caregiver twice daily, i.e., once in the morning and once in the evening. This Itch Reported Outcome Instrument (ItchRO[Obs]) assessed pruritus symptoms on a 5-point ordinal response scale, with scores ranging from 0 (none observed) to 4 (very severe). Patients were included in the study having an average of the worst daily pruritus score greater than 2.0 (moderate) for each week in the 2 weeks prior to baseline. For randomized patients, the mean baseline weekly average morning ItchRO(Obs) severity score in the overall population was 2.9.

Key efficacy results of the ICONIC trial are presented below, in Table 6. Statistical analyses of secondary endpoints were not adjusted for multiplicity. Therefore, statistical findings are considered nominal.

**Table 6: Results of the ICONIC Trial during the Randomized Drug Withdrawal Study Phase**

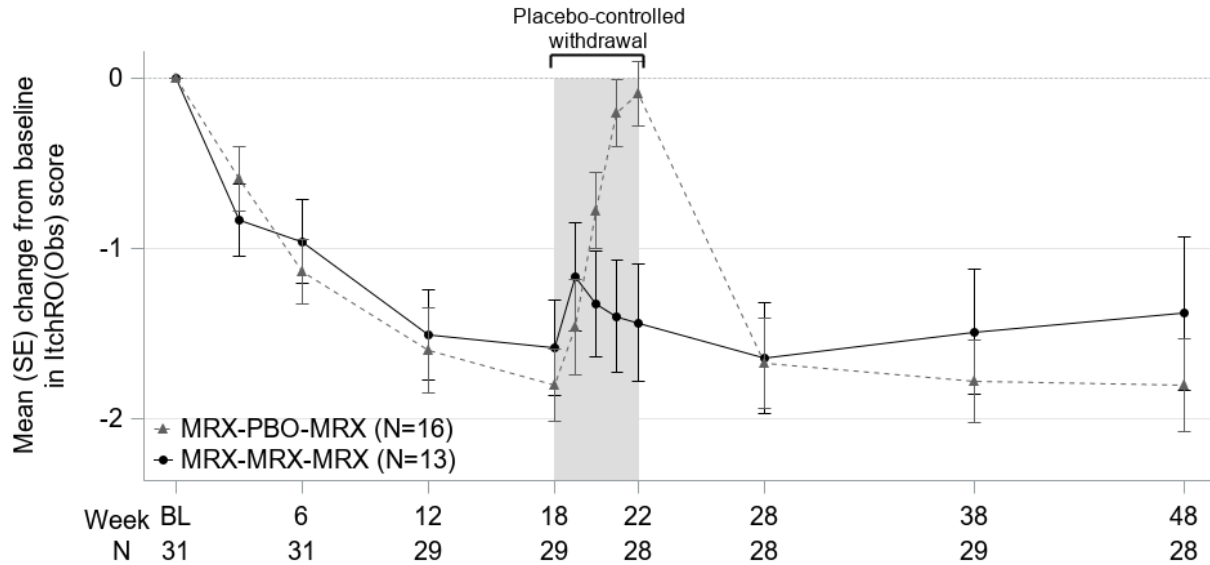
Key Efficacy Endpoints	LIVMARLI	Placebo	Mean Difference
<b>Serum bile acid (µmol/L)</b>	(N =13)	(N=16)	
Week 22, LS Mean (95% CI)	186.5 (115.4, 257.5)	277.4 (213.4, 341.4)	
Change from Week 18 to Week 22, LS Mean (95% CI)	-18.7 (-91.2, 53.7)	95.2 (30.1, 160.3)	-114.0 (-212.7, -15.2)
<b>Pruritus (ItchRO[Obs])*</b>	(N=12)	(N=16)	
Week 22, LS Mean (95% CI)	1.4 (0.9, 1.9)	2.8 (2.4, 3.3)	
Change from Week 18 to Week 22, LS Mean (95% CI)	0.2 (-0.3, 0.7)	1.7 (1.3, 2.1)	-1.5 (-2.1, -0.8)

\* weekly average morning ItchRO (Obs) severity score ; CI = confidence interval; LS = least squares; N = number of patients

At the end of the initial 18-week open-label study phase, the change in the mean (95% CI) weekly average morning ItchRO(Obs) severity score from baseline in the intent-to-treat (ITT) population was -1.70 (-2.05, -1.36), with maralixibat treatment. In general, patients administered LIVMARLI for 22 weeks maintained pruritus reduction whereas those in the placebo group who were withdrawn from LIVMARLI after Week 18 returned to baseline pruritus scores by Week 22. At Week 48, during the second open-label phase of the trial when all participants were again administered maralixibat, an improvement was observed in the mean (95% CI) weekly average morning ItchRO(Obs) severity score at -1.62 (-2.12, -1.12) from baseline. Overall, a decrease from baseline in mean weekly average morning ItchRO(Obs) severity scores was observed in the ITT population with maralixibat treatment at each evaluable analysis visit during the entire observation period up to Week 240, demonstrating consistent and sustained improvement in pruritus, see Figure 1, below. These observer-rated pruritus scores were further supported by similar results for patient-rated pruritus scores in study participants 5 years of age and older who were able to self-report their itching severity.



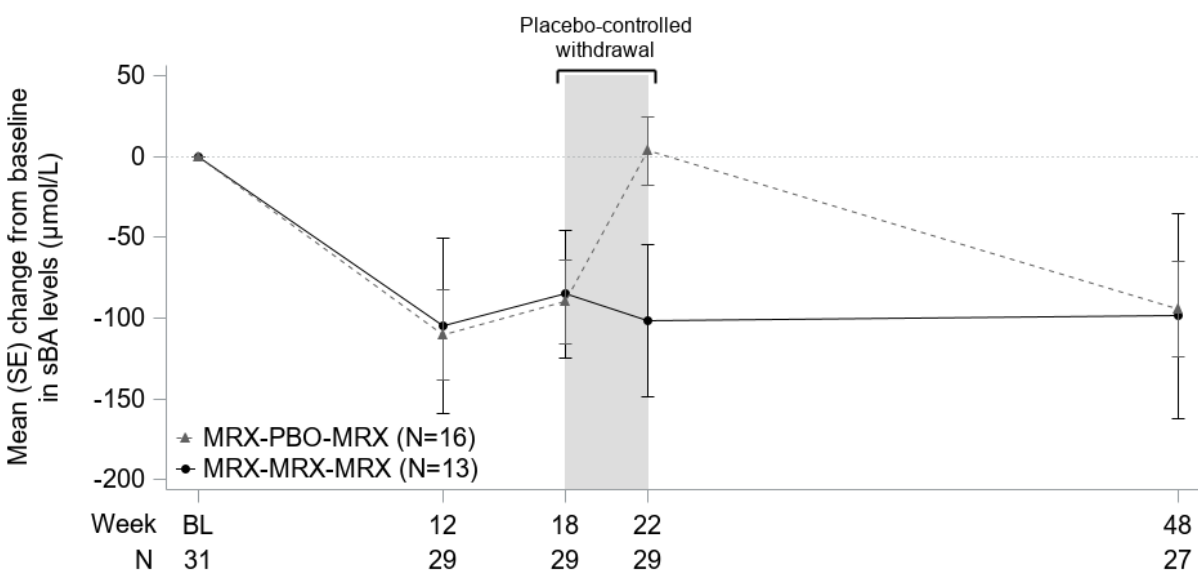
**Figure 1: Weekly Average Morning ItchRO(Obs) Severity Score Change from Baseline by Randomized Treatment Group Over Time, through Week 48, All Patients**



MRX = maralixibat; PBO = placebo; SE = standard error; BL = baseline

A mean (95% CI) reduction in sBA from baseline of -88 (-133, -42) and -96 (-162, -31)  $\mu\text{mol/L}$  was observed at Week 18 and Week 48, respectively, when study patients were administered maralixibat. At the end of the 4-week placebo-controlled period, a difference between maralixibat and placebo in least squares mean (95% CI) change in sBA of -114 (-213, -15)  $\mu\text{mol/L}$  was demonstrated from Week 18 to Week 22, in favour of maralixibat treatment. When the placebo group once again resumed treatment with maralixibat following the randomized drug withdrawal study period, sBA returned to levels previously observed with maralixibat treatment, see Figure 2, below.

**Figure 2: Mean ( $\pm$  SE) Change from Baseline sBA, through to Week 48, All Patients with Alagille Syndrome**



MRX = maralixibat; PBO = placebo; SE = standard error; BL = baseline

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

**General Toxicology:** The most significant toxicological effect observed in rodents is the reversible prolongation of coagulation times. Prolongation of coagulation times was observed primarily in male rats and was reversible. Emesis was the primary toxicity observed in the dog at doses above 200 mg/kg.

These toxicological findings occur at high doses, with large safety margins to therapeutic doses in humans.

**Carcinogenicity:** No drug-related tumors were observed following oral administration of maralixibat chloride to TgRasH2 mice at doses of up to 25 (males) or 75 (females) mg/kg/day for 26 weeks.

**Mutagenesis:** Maralixibat chloride was negative in in vitro (bacterial reverse mutation, chromosomal aberration in mammalian cells) and in vivo (mouse bone marrow micronucleus) assays.

**Reproductive and Developmental Toxicology:** No effects on fertility were observed in female rats treated orally with up to 2000 mg/kg/day or in male rats treated orally with up to 750 mg/kg/day. No effects on embryo-fetal development were observed in pregnant rats treated orally with up to 1000 mg/kg/day (approximately 3300 to 12000 times the maximum recommended dose based on AUC [area under the plasma concentration-time curve]) or in pregnant rabbits treated orally with up to 250 mg/kg/day (approximately 1200 to 4700 times the maximum recommended dose based on AUC)

during the period of organogenesis. No effects on postnatal development were observed in a pre- and postnatal development study, in which female rats were treated orally with up to 750 mg/kg/day during organogenesis through lactation. Maternal systemic exposure to maralixibat at the maximum dose tested was approximately 2500 to 9400 times the maximum recommended dose based on AUC.

**Juvenile Toxicity:** No clear adverse effects were seen in juvenile rats administered maralixibat at doses of 50, 100 and 250 mg/kg/day for 14 days (Post Natal Day [PND] 7 to 21) in both males and females. or for 43 days (PND 21 through PND 63) at doses of 50, 100 and 200 mg/kg/day in the males and 250, 500 and 1,000 mg/kg/day in the females.

## **PATIENT MEDICATION INFORMATION**

### **READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

#### **LIVMARLI®**

#### **Maralixibat oral solution**

Read this carefully before you start taking LIVMARLI and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about LIVMARLI.

#### **What is LIVMARLI used for?**

LIVMARLI is used to treat cholestatic pruritus (itch caused by liver problems) in patients who have Alagille syndrome.

#### **How does LIVMARLI work?**

Excess bile acids in the body can cause itching. LIVMARLI contains maralixibat which helps remove excess bile acids from the body. This helps reduce itching.

#### **What are the ingredients in LIVMARLI?**

Medicinal ingredients: Maralixibat (as maralixibat chloride)

Non-medicinal ingredients: Edetate disodium, grape flavor, propylene glycol, purified water, and sucralose.

#### **LIVMARLI comes in the following dosage forms:**

Oral solution, 9.5 mg/mL

#### **Do not use LIVMARLI if:**

- You are allergic to maralixibat, or to any of the ingredients in LIVMARLI, or the container.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LIVMARLI. Talk about any health conditions or problems you may have, including if you:**

- Have low levels of Vitamins A, D, E or K
- Have liver problems
- Are pregnant or plan to become pregnant; or are breastfeeding or plan to breastfeed
- Are giving LIVMARLI to a child younger than 12 months of age

#### **Other warnings you should know about:**

##### **Stomach/Digestive Problems:**

- LIVMARLI can cause diarrhea, stomach pain and vomiting. Diarrhea and vomiting may lead to dehydration.
- Talk to your healthcare professional if your diarrhea gets worse while taking LIVMARLI. Your healthcare professional will check your hydration levels.
- If you get diarrhea, drink plenty of liquids so you do not become dehydrated.

See the “**Serious side effects and what to do about them**” table, below, for more information on these and other serious side effects.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural health products or alternative medicines.**

**The following may interact with LIVMARLI:**

- Medicines called statins, used to treat cholesterol levels.

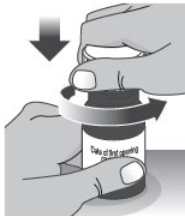
**How to take LIVMARLI:**

- Talk to your healthcare professional about how to measure your prescribed dose.
- Use only the oral dosing syringes provided by your healthcare professional to measure the correct dose.
- Take LIVMARLI exactly as your healthcare professional tells you to.
- Take LIVMARLI by mouth, 1 time each day in the morning, 30 minutes before a meal.
- See the Instructions for Use below on how to take or give the dose.

**Instructions for Use:**

**Step 1: Draw dose**

- 1.1** To open the bottle, remove the child-resistant cap by pushing down firmly while turning left (anti-clockwise) (see Figure A). Do not throw away the child-resistant cap as you will need to put it back when you have taken out the dose you need.



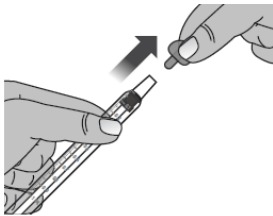
**Figure A**

- 1.2** Make sure you use the correct oral syringe size for your prescribed dose, provided by your healthcare professional.
- If using a new oral syringe, remove it from the wrapper (see Figure B). Throw away the wrapper.
  - If using a used oral syringe, make sure it has been cleaned and is dry (see 2.4 for instructions for cleaning).



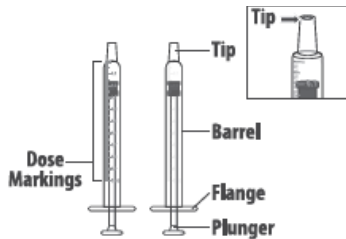
**Figure B**

- If there is a cap on the oral syringe, remove it and throw it away (see Figure C).



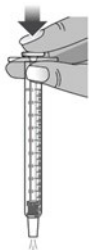
**Figure C**

The syringe has dose markings on the barrel. One end of the syringe has a tip that is used to insert into the medicine bottle. The other end of the syringe has a flange and a plunger, used to push the medicine out of the syringe (see Figure D).



**Figure D**

- 1.3** Push the plunger down fully to remove air from the syringe (see Figure E).



**Figure E**

- 1.4 Make sure that the cap is removed from the bottle and insert the tip of the syringe into the upright bottle. The tip of the syringe should fit snugly into the hole of the bottle (see Figure F).

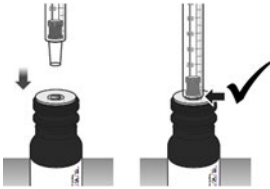


Figure F

- 1.5 With the syringe in place, turn the bottle upside down (see Figure G).

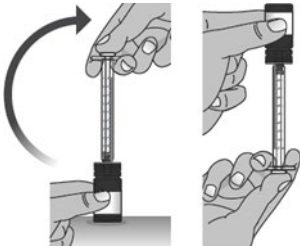


Figure G

- 1.6 To withdraw a dose from the bottle, slowly pull back on the plunger until the plunger lines up with the marking on the barrel of the syringe that matches the prescribed dose (see Figure H). There are two kinds of plungers that you might receive with the syringe: a flat tip plunger or a pointy tip plunger (see Figure I.a and I.b). See Figure I on how to align the plunger with your prescribed dose.

- For a flat tip plunger, the flat end of the plunger should be aligned with the marking on the barrel that matches the prescribed dose (Figure I.a.).
- For a clear pointy tip plunger, make sure that the flat, wide part of the plunger below the tip is lined up with the correct marking (Figure I.b.).

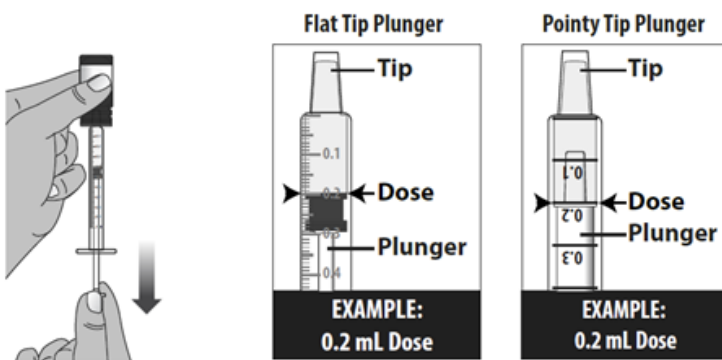
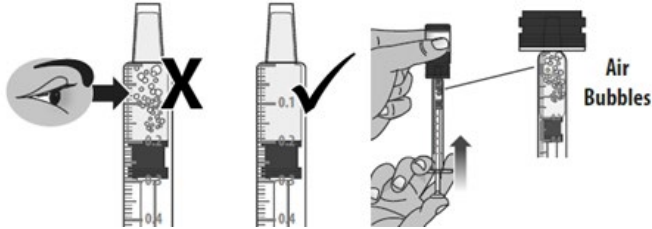


Figure H

Figure I.a.

Figure I.b.

- 1.7** Check the syringe for air bubbles. If you see any air bubbles:
- Push the air bubbles back into the bottle by pushing the plunger (see Figure J)
  - When there are no more air bubbles, re-draw the prescribed dose following the instructions in Step 1.6.



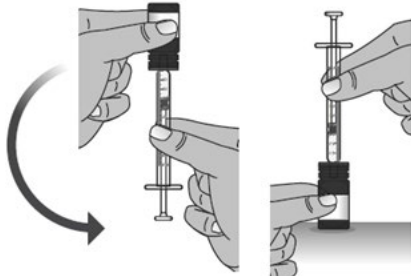
**Figure J.a.**

Check for air bubbles

**Figure J.b.**

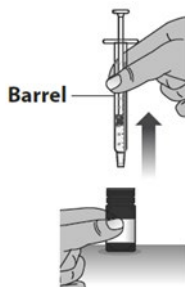
Push plunger into syringe to remove air bubbles

- 1.8** When you have taken up the correct dose with no air bubbles, leave the syringe in the bottle and turn the bottle right side up (see Figure K).



**Figure K**

- 1.9** Carefully remove the syringe from the bottle (see Figure L), by holding the bottle firmly in one hand and holding the syringe by the barrel in the other hand.
- Do not push the syringe plunger during this step.



**Figure L**

## Step 2: Give the dose

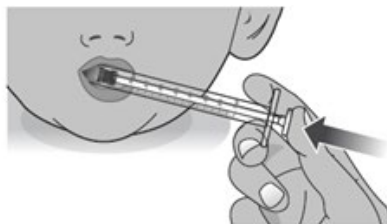
**Note:** You or your child should stay upright while taking the dose and for a few minutes after.



- 2.1** Insert the tip of the oral syringe against the inside of the cheek (see Figure M). Slowly press the plunger all the way down to fully and gently squirt the oral solution into the mouth (see Figure N).

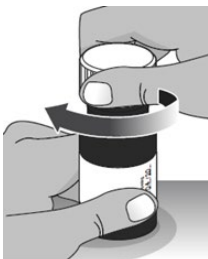


**Figure M**



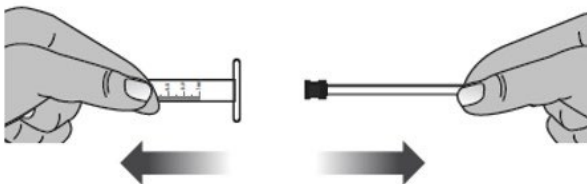
**Figure N**

- 2.2** Make sure you/the child swallow(s) the dose. If you are not sure if the entire dose was swallowed, do not give another dose. Wait until it is time for the next dose.
- 2.3** **To close the bottle,** screw the child-resistant cap back on the bottle by turning to the right (clockwise) (see Figure O).



**Figure O**

- 2.4** Remove the plunger from the barrel of the syringe (see Figure P). Wash it with water after each use. Allow the plunger to air dry before using again.



**Figure P**

- The oral syringes may be rinsed with water, air dried and reused for 100 days.

**Usual dose:**

- The dose of LIVMARLI is based on your weight. Your healthcare professional will decide the best dose for you. They will tell you how much to take and which oral syringe size to use.

- Your healthcare professional may change your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if you experience serious side effects.
- Do not change your dose or stop taking LIVMARLI without talking to your healthcare professional.

**Overdose:**

If you think you, or a person you are caring for, have taken too much LIVMARLI, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

If you miss a dose of LIVMARLI and it is:

- 12 hours or less from the time you usually take LIVMARLI: **take the missed dose as soon as possible.** Then take your next dose at the usual time.
- More than 12 hours from the time you usually take LIVMARLI: **do not take the missed dose.** Take your next dose at the usual time.

**What are possible side effects from using LIVMARLI?**

These are not all the possible side effects you may have when taking LIVMARLI. If you experience any side effects not listed here, tell your healthcare professional.

- Stomach pain
- Diarrhea
- Vomiting
- Nausea

LIVMARLI may cause abnormal blood test results. Your healthcare professional will do blood tests before and during your treatment. These will tell your healthcare professional how LIVMARLI is affecting your liver health and hydration levels.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>VERY COMMON</b>			
<b>Stomach and Digestive Problems:</b> stomach pain, vomiting, diarrhea.	X		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

### Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### Storage:

- Store LIVMARLI 2-30°C. Do not freeze.
- Store bottle in the original package in order to protect from light.
- Always store LIVMARLI with the cap on the bottle.
- Throw away any left-over LIVMARLI, 100 days after first opening the bottle.
- Keep out of reach and sight of children.

### If you want more information about LIVMARLI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>), the manufacturer's website ([www.mirumpharma.com](http://www.mirumpharma.com)), or by calling 1-833-548-6754.

This leaflet was prepared by Mirum Pharmaceuticals, Inc.

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