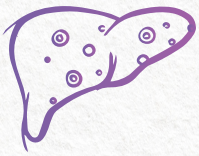
Helping patients understand and navigate long-term therapy on CHOLBAM® (cholic acid)[1]

☑ Explain to patients with SLOS, BASD, PBD-ZSD, or CTX that their body is unable to process primary bile acids properly, which can lead to serious complications, including[2-4]:

Accumulation of toxic bile acid intermediates



Progressive liver disease

Impaired absorption of fat and fat-soluble vitamins

Impaired weight gain and growth

No evaluable patients with SLOS were included in the pivotal studies. SLOS is a BASD due to a single enzyme defect.[1] The clinical studies included patients with other BASDs due to SEDs.[1]

Patients with SLOS should know that cholesterol supplementation without cholic acid therapy may be insufficient for nutrient absorption.[5*]

*While the exact reason is unknown, it is possibly because their body is unable to effectively absorb dietary cholesterol.
BASDs=bile acid synthesis disorders; CTX=cerebrotendinous xanthomatosis; PBD-ZSD=peroxisomal biogenesis disorder-Zellweger spectrum disorder; SEDs=single enzyme defects; SLOS=Smith-Lemli-Opitz Syndrome.

INDICATION

CHOLBAM® (cholic acid) is a bile acid indicated for

- Treatment of bile acid synthesis disorders due to single enzyme defects.
- Adjunctive treatment of peroxisomal disorders, including Zellweger spectrum disorders, in patients who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat-soluble vitamin absorption.

LIMITATIONS OF USE

The safety and effectiveness of CHOLBAM on extrahepatic manifestations of bile acid synthesis disorders due to single enzyme defects or peroxisomal disorders, including Zellweger spectrum disorders, have not been established.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS – Exacerbation of liver impairment

- Monitor liver function and discontinue CHOLBAM in patients who develop worsening of liver function while on treatment.
- Concurrent elevations of serum gamma glutamyltransferase (GGT) and alanine aminotransferase (ALT) may indicate CHOLBAM overdose.
- Discontinue treatment with CHOLBAM at any time if there are clinical or laboratory indicators of worsening liver function or cholestasis.

ADVERSE REACTIONS

- The most common adverse reactions (≥1%) are diarrhea, reflux esophagitis, malaise, jaundice, skin lesion, nausea, abdominal pain, intestinal polyp, urinary tract infection, and peripheral neuropathy.

Please see full Prescribing Information for CHOLBAM for additional Important Safety Information.

Cholbam®
(cholic acid) capsules

Addressing cholic acid deficiency

CHOLBAM is a prescription medicine specifically designed to help increase cholic acid levels.[1]

☑ **Ensure patients understand that CHOLBAM is a long-term therapy** for patients with SLOS,* BASD, PBD-ZSD, or CTX. Potential effects of CHOLBAM will take time to show through ongoing tests.[1]

The safety and effectiveness of CHOLBAM on extrahepatic manifestations of bile acid synthesis disorders due to single enzyme defects or peroxisomal disorders, including Zellweger spectrum disorders, have not been established.[1]

☑ Explain how CHOLBAM may help[1,5]:

Enhance bile flow and may reduce accumulation of hepatotoxic atypical bile acids†

Lower key liver function parameters

Response to CHOLBAM treatment was assessed using the following laboratory criteria: (1) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values reduced to less than 50 U/L, or baseline levels reduced by 80%; (2) total bilirubin values reduced to less than or equal to 1 mg/dL; and (3) no evidence of cholestasis on liver biopsy.[1]

Improve certain growth parameters

In a pivotal study, body weight increased by 10% or was stable at greater than the 50th percentile, among responders.*

In a 2-month pilot study of patients with SLOS, 9 of 12 patients showed an increasing trend in weight gain from baseline, though statistical significance was not reached.

Improvements in height have been reported.[5]

Increase plasma cholesterol in patients with SLOS

In 11 of 12 patients with SLOS given CHOLBAM 10 mg/kg/day and cholesterol supplementation for 2 months in an open-label pilot study. Long-term studies are needed to determine durability of effect and possible clinical benefits.[5]

*__No evaluable patients with SLOS were in the pivotal studies.__ SLOS is a BASD due to an SED. The clinical studies included patients with other BASDs due to SEDs.

†The mechanism of action of cholic acid has not been fully established; however, it is known that cholic acid and its conjugates are endogenous ligands of the nuclear receptor, farnesoid X receptor (FXR). FXR regulates enzymes and transporters that are involved in bile acid synthesis and in the enterohepatic circulation to maintain bile acid homeostasis under normal physiologic conditions.[5]

Backed by >18 years of clinical data[1]

CHOLBAM has a well-characterized safety profile. There were 12 adverse reactions reported across 9 patients in the clinical trials, and the most common adverse reaction (~2%) reported was diarrhea. Other common side effects occurred in 1% of patients, including reflux esophagitis, malaise, jaundice, skin lesion, nausea, abdominal pain, intestinal polyp, urinary tract infection, and peripheral neuropathy.[1]

Review the side effects that patients may experience with CHOLBAM. Remind patients to reach out to you if they experience side effects that concern them.

Safety data are available for 3 years and 11 months of treatment. Adverse events were not collected systematically in either of these trials. Most patients received an oral dose of 10 mg/kg/day to 15 mg/kg/day of CHOLBAM.[1]

"Mallie had diarrhea for about a week that resolved."

—Dr Ferren, prescribing physician to Mallie, a real patient living with SLOS

Individual results may vary.

Watch Dr Ferren's story diagnosing SLOS and treating with CHOLBAM.

Visit cholbamhcp.com/slos/educational-videos

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

- Inhibitors of Bile Acid Transporters: Avoid concomitant use of inhibitors of the bile salt efflux pump (BSEP) such as cyclosporine. Concomitant medications that inhibit canalicular membrane bile acid transporters such as the BSEP may exacerbate accumulation of conjugated bile salts in the liver and result in clinical symptoms. If concomitant use is deemed necessary, monitoring of serum transaminases and bilirubin is recommended.

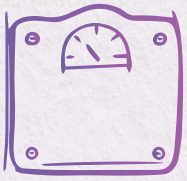
Please see full Prescribing Information for CHOLBAM for additional Important Safety Information.

Cholbam®
(cholic acid) capsules

Supporting adherence

Primary reasons for discontinuation of treatment are: vomiting, diarrhea, and inability to tolerate the taste (if unable to swallow capsules whole).[6]

☑ **Guide patients through the process of dosing and administration** to help mitigate adherence challenges and help them stay on treatment.



Weight-based daily dosing

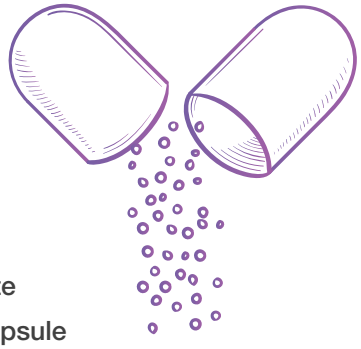
- The recommended dosage of CHOLBAM is 10 mg/kg to 15 mg/kg taken once per day, or in 2 divided doses with food, in pediatric and adult patients[1]
- For patients experiencing gastrointestinal side effects, CHOLBAM may be administered in 2 divided doses per day instead of once daily[1]
- Increase monitoring and titrate during periods of rapid growth
  - For complete dosing and administration instructions, review full Prescribing Information with patients

Please see the Prescribing Information for dose modification instructions for newly diagnosed patients or patients with a family history of familial hypertriglyceridemia, treatment monitoring guidelines, and administration instructions.[1]

For patients struggling with taste

Recommend mixing CHOLBAM with[1]:

- A small amount of infant formula or expressed breast milk
- A small amount of a favorite syrup (chocolate/maple)
- A spoonful of soft foods such as yogurt, apple sauce, or mashed potatoes, or thick drinks such as coffee creamer



Other tips:

- Drink a small amount of a favorite juice to further mask the taste
- Patients **should not sprinkle on top of food;** thoroughly mix capsule contents with a small amount of food to mask the taste

Advise patients to consult with you to discuss options before discontinuing treatment

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

- Bile Acid Binding Resins: Bile acid binding resins such as cholestyramine, colestipol, or colesevelam adsorb and reduce bile acid absorption and may reduce the efficacy of CHOLBAM. Take CHOLBAM at least 1 hour before or 4 to 6 hours (or at as great an interval as possible) after a bile acid binding resin.
- Aluminum-based Antacids: Aluminum-based antacids have been shown to adsorb bile acids *in vitro* and can reduce the bioavailability of CHOLBAM. Take CHOLBAM at least 1 hour before or 4 to 6 hours (or at as great an interval as possible) after an aluminum-based antacid.

Please see full Prescribing Information for CHOLBAM for additional Important Safety Information.

Cholbam®
(cholic acid) capsules

Tracking progress

Encourage patients to stay consistent with therapy by:

- ☑ **Inquiring and addressing** potential adherence concerns.
- ☑ **Advising** that it will take time for CHOLBAM to work in their body.[1]
- ☑ **Reminding** them that CHOLBAM is a lifelong treatment that helps replace a bile acid (cholic acid) that their body cannot make on its own.[1]
- ☑ **Scheduling** ongoing appointments to track progress and monitor their bodies' response to treatment, including liver function tests, toxic bile acid intermediates, cholesterol levels, and growth in height and weight.[1]

mirum access PLUS Navigating Together

Mirum Access Plus is committed to helping your patients with access, financial, and emotional support.

For complete information, tools, and resources, **visit CHOLBAMhcp.com**.

Subject to program terms and conditions.

IMPORTANT SAFETY INFORMATION (cont'd)

PREGNANCY

No studies in pregnant women or animal reproduction studies have been conducted with CHOLBAM.

LACTATION

Endogenous cholic acid is present in human milk. Clinical lactation studies have not been conducted to assess the presence of CHOLBAM in human milk, the effects of CHOLBAM on the breastfed infant, or the effects of CHOLBAM on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CHOLBAM and any potential adverse effects on the breastfed infant from CHOLBAM or from the underlying maternal condition.

GERIATRIC USE

It is not known if elderly patients respond differently from younger patients.

HEPATIC IMPAIRMENT

- Discontinue treatment with CHOLBAM if liver function does not improve within 3 months of the start of treatment.
- Discontinue treatment with CHOLBAM at any time if there are clinical or laboratory indicators of worsening liver function or cholestasis. Continue to monitor laboratory parameters of liver function and consider restarting at a lower dose when the parameters return to baseline.

OVERDOSAGE

Concurrent elevations of serum GGT and serum ALT may indicate CHOLBAM overdose. In the event of overdose, the patient should be monitored and treated symptomatically. Continue to monitor laboratory parameters of liver function and consider restarting at a lower dose when the parameters return to baseline.

Please see full Prescribing Information for CHOLBAM for additional Important Safety Information.

References: 1. CHOLBAM® (cholic acid) capsules. Prescribing Information. Mirum Pharmaceuticals, Inc. **2.** Heubi JE, Bove KE, Setchell KDR. Oral cholic acid is efficacious and well tolerated in patients with bile acid synthesis and Zellweger spectrum disorders. *J Pediatr Gastroenterol Nutr*. 2017;65(3):321-326. doi:10.1097/MPG.0000000000001657 **3.** DeBarber AE, Eroglu Y, Merkens LS, Pappu AS, Steiner RD. Smith-Lemli-Opitz syndrome. *Expert Rev Mol Med*. 2011;13:e24. doi:10.1017/S146239941100189X **4.** Berendse K, Klouwer FCC, Koot BGP, et al. Cholic acid therapy in Zellweger spectrum disorders. *J Inherit Metab Dis*. 2016;39(6):859-868. doi:10.1007/s10545-016-9962-9 **5.** Elias ER, Orth LE, Li A, Xu L, Jones SM, Rizzo WB. Cholic acid increases plasma cholesterol in Smith-Lemli-Opitz syndrome: a pilot study. *Mol Genet Metab Rep*. 2023;38:101030. doi:10.1016/j.ymgmr.2023.10103 **6.** Data on file. REF-02532. Mirum Pharmaceuticals, Inc.

mirum | Cholbam® (cholic acid) capsules