Clinical Considerations for CHOLBAM Replacement Therapy

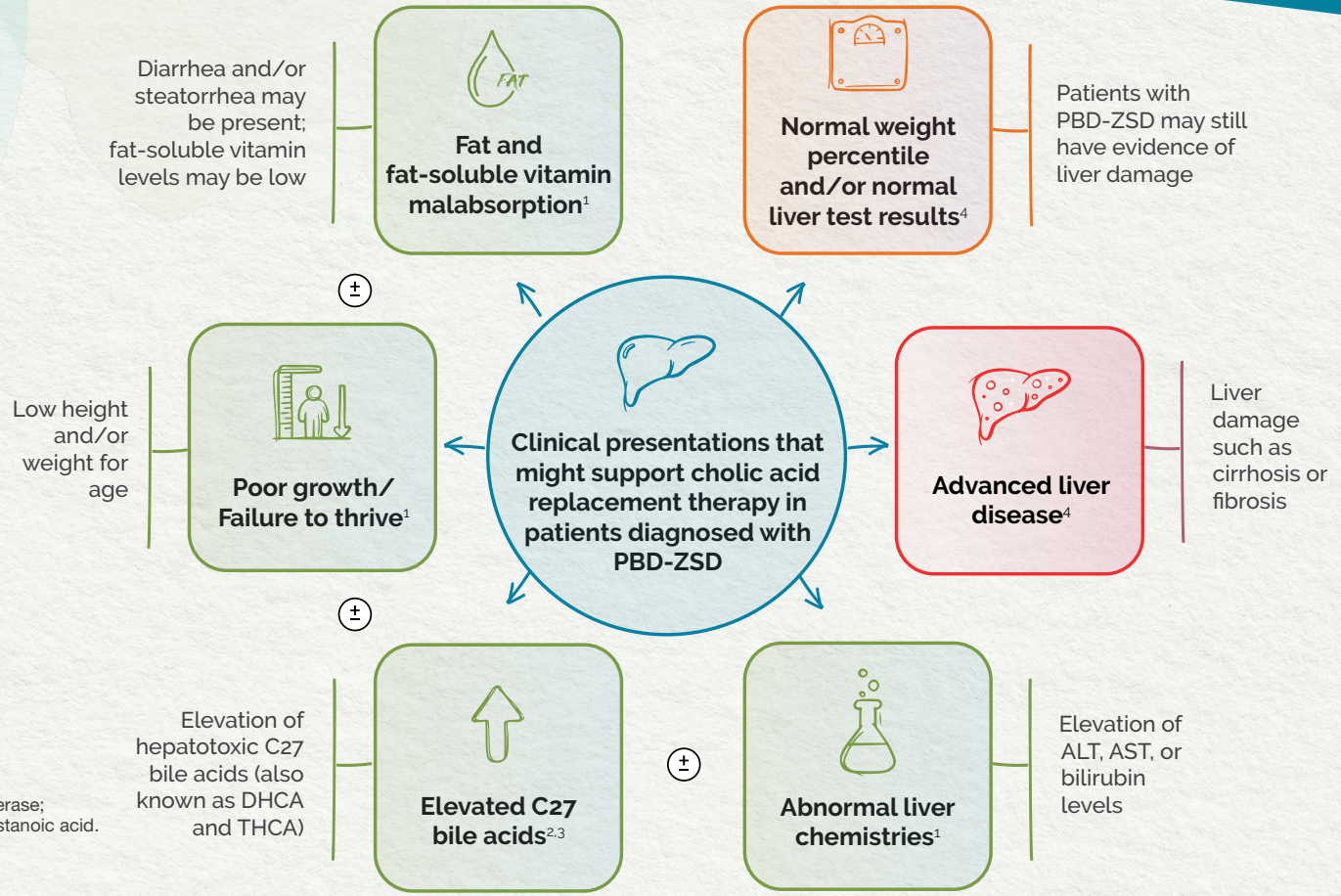
For individuals diagnosed with peroxisomal biogenesis disorder–Zellweger spectrum disorder (PBD-ZSD)[1]

± Patients may have one or a combination of presentations.

Consider cholic acid replacement therapy

Consult with an experienced gastroenterologist, hepatologist, or medical geneticist to discuss appropriateness of cholic acid therapy

Cholic acid replacement therapy is not recommended in patients with advanced liver disease



ALT=alanine aminotransferase; AST=aspartate aminotransferase; DHCA=dihydroxycholestanoic acid; THCA=trihydroxycholestanoic acid.

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.

Please see additional Important Safety Information for CHOLBAM on the next page and full Prescribing Information.

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(cholic acid) capsules

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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.

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.
- 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.

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 additional Important Safety Information for CHOLBAM on the previous page and full Prescribing Information.

References: 1. CHOLBAM® (cholic acid) capsules. Prescribing information. Mirum Pharmaceuticals, Inc. **2.** Braverman NE, Raymond GV, Rizzo WB, et al. Peroxisome biogenesis disorders in the Zellweger spectrum: an overview of current diagnosis, clinical manifestations, and treatment guidelines. *Mol Genet Metab*. 2016;117(3):313-321. doi:10.1016/j.ymgme.2015.12.009 **3.** Zeynelabidin S, Klouwer FCC, Meijers JCM, et al. Coagulopathy in Zellweger spectrum disorders: a role for vitamin K. *J Inherit Metab Dis*. 2018;41(2):249-255. doi:10.1007/s10545-017-0113-8 **4.** Klouwer FCC, Koot BGP, Berendse K, et al. The cholic acid extension study in Zellweger spectrum disorders: results and implications for therapy. *J Inherit Metab Dis*. 2019;42:303–312. doi.org/10.1002/jimd.12042

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