PDL NEW DRUG REVIEW

Proprietary Name: Cholbam®
Common Name: cholic acid
PDL Category: GI, Bile Acid

Summary

Indications and Usage: For the treatment of bile acid synthesis disorders due to single enzyme defects (SEDs) AND for the adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption. The safety and efficacy of use on extrahepatic manifestations of bile acid synthesis disorders due to SEDs or PDs, including Zellweger spectrum disorders, have not been established.

While there is no pregnancy category provided, the risk summary indicates that no studies in pregnant women or animal reproduction studies have been performed with this product. There is a pregnancy surveillance program that monitors pregnancy outcomes in women exposed to Cholbam® during pregnancy. Women who become pregnant during Cholbam® treatment are encouraged to enroll. The safety and efficacy of use have been established in the pediatric population who are ≥3 weeks of age for both indications.

Dosage Forms: Capsules: 50mg, 250mg

Recommended Dosage: It is recommended that treatment with Cholbam® be initiated and monitored by an experienced hepatologist or pediatric gastroenterologist**.** Take 10-15mg/kg QD or in two divided doses with food. Please refer to the specific charts in the prescribing information that show the number of capsules to give daily per body weight. If not able to swallow the capsules, they can be opened and mixed with either infant/expressed breast milk or soft food such as mashed potatoes or apple puree.

Those patients with newly diagnosed or a family history of familial hypertriglyceridemia may have poor absorption of Cholbam® from the intestine and require a 10% increase in the recommended dosage to account for losses due to malabsorption. Thus, the recommended dose in those with concomitant familial hypertriglyceridemia is 11-17mg/kg QD or in two divided doses with food.

If liver function does not improve within 3 months of the start of treatment or if complete biliary obstruction develops, Cholbam® should be discontinued. In addition, discontinue treatment at any time if there are clinical or laboratory indicators of worsening liver function or cholestasis. It is recommended to monitor serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), bilirubin, and INR every month for the first 3 months, every 3 months for the next 9 months, every 6 months during the subsequent 3 years, and then annually thereafter.

Drug Interactions: It is recommended that Cholbam® be taken at least 1 hour before or 4-6 hours after an aluminum-based antacid or a bile acid binding resin (such as cholestyramine, colestipol, or colesevelam). Concomitant use of inhibitors of the bile salt efflux pump (BSEP), such as cyclosporine, should be avoided. If concomitant use is necessary, it is recommended to monitor serum transaminases and bilirubin.

Common Adverse Drug Reactions: *Note that placebo data available was not available. The % listed below is the overall incidence from two trials reported across 9 patients taking Cholbam®.* The most commonly reported adverse events included diarrhea (2%), reflux esophagitis (1%), malaise (1%), jaundice (1%), skin lesion (1%), nausea (1%), abdominal pain (1%), intestinal polyp (1%), urinary tract infection (1%), and peripheral neuropathy (1%).

There were 10 patients overall from two trials that experienced worsening serum transaminases, elevated bilirubin values, or worsening cholestasis on liver biopsy.

There were reported deaths in each trial.

Contraindications: There are none listed.

Manufacturer: Manchester Pharmaceuticals

Analysis: Cholic acid, the active ingredient of Cholbam®, is a main bile acid produced by the liver where it is synthesized from cholesterol. In bile acid synthesis disorders due to SEDs and in PDs, deficiency of primary bile acid leads to an accumulation of intermediate bile acids and cholestasis. Endogenous bile acids, such as cholic acid, enhance bile flow and provide the physiologic feedback inhibition of bile acid synthesis. Nevertheless, the exact mechanism of action of cholic acid has not been fully established.

The effectiveness of Cholbam® in patients with SEDs was assessed in a non-randomized open-label, single arm study (N=50), in an extension study of 12 new patients along with 21 who rolled-over from the first study (N=33), and a published case series of 15 patients. In studies 1 and 2, most patients were treated for an average of 310 weeks (6 years), and patient ages at the end of treatment ranged from 19 to 36 years. Response to treatment was assessed by lab criteria (ALT or AST values reduced to <50U/L or baseline levels reduced by 80%; total bilirubin reduced to ≤1mg/dl; and no evidence of cholestasis on liver biopsy) and clinical criteria (body weight ↑ by 10% or stable at >50%; and survival for >3 years on treatment or alive at end of trial 2). Cholbam® responders were defined as patients who met ≥2 lab criteria and were alive at the last follow-up; OR met ≥1 lab criteria, had increased body weight and were alive at the last follow-up.

Overall, 64% (N=28/44) were responders. In addition, it is estimated that overall 67% (N=41/62) survived greater than 3 years from trial entry. The published report of a case series included 15 patients with SEDs who were all treated with cholic acid with a median duration of treatment of 12.4 years. All patients had resolution of their pre-existing jaundice and steatorrhea following treatment, and all but one had resolution of hepatosplenomegaly. Weight and height also improved and sexual maturation progressed normal in all patients. After at least 5 years of cholic acid treatment, liver biopsies were performed in 14 patients and all showed resolution of cholestasis.

The effectiveness of Cholbam® in those with PDs was assessed in a non-randomized open-label, single arm study (N=29) over an 18 year period, in an extension study of 2 new patients along with 10 who rolled-over from the first study (N=12), and published case reports of 3 patients. Most patients in trial 1 and 2 were treated for an average of 254 weeks (4.8 weeks). Response to Cholbam® treatment and Cholbam® responders were defined as above.

Overall, 46% (N=11/24) were responders. Among the responders, 38% met the two clinical criteria plus 1-3 lab criteria and 63% met the weight criteria. Overall, 42% (N=13/31) survived >3 years from the time of trial entry. There was no evidence of improvement in survival over that seen in historical controls. One patient, who did not have cholestasis on pre-treatment liver biopsy, developed cholestasis on treatment with Cholbam® and died. In the case reports, 2 patients with Zellweger syndrome treated with oral bile acids had decreased serum transaminases. A 6 month old treated with cholic and chenodeoxycholic acid had normalization of serum transaminases and bilirubin, improvement in liver histology, reduced serum and urinary atypical bile acid intermediates, and improvement in steatorrhea and growth.

Place in Therapy: Cholbam® is indicated for the treatment of bile acid synthesis disorders due to single enzyme defects (SEDs) AND for the adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption. The safety and efficacy of use on extrahepatic symptoms of these disorders have not been established.

It is recommended that Cholbam® remain non-preferred and require clinical prior authorization to verify diagnosis and appropriate lab testings.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1] Cholbam [package insert]. San Diego, CA: Manchester Pharmaceuticals; 2015.