HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CHOLBAM safely and effectively. See full prescribing information for CHOLBAM.

CHOLBAM (cholic acid) capsules
50 mg, 250 mg, 500 mg
FULL PRESCRIBING INFORMATION
1 INDICATIONS AND USES
1.1 Bile Acid Synthesis Disorders due to Single Enzyme Defects
CHOLBAM is indicated for the treatment of bile acid synthesis disorders due to single enzyme defects (SEDs) (see Clinical Trials (14.1).)

1.2 Porphyria Cutanea Tarda
Zellweger Spectrum Disorders
CHOLBAM is indicated for the treatment of Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, cholestasis or complications from decreased bilirubinuria (see Clinical Trials (14.2).

1.3 Limitations of Use
The safety and effectiveness of CHOLBAM on struvite crystallization of bile acids and its role of primary or secondary disease have not been established.

2 DOSAGE AND ADMINISTRATION
2.1 Dosage Regimen
CHOLBAM is indicated for single enzyme disorders due to single enzyme defects or Zellweger spectrum disorders.

CHOLBAM is initiated with a starting dose of 10 mg/kg/day and is adjusted based on clinical response. The starting dose should be adjusted to achieve a therapeutic response (Table 1).

2.2 Treatment Monitoring
The development of symptomatic cholelithiasis requiring cholecystectomy has been evidenced with CHOLBAM. The incidence and presentation of these complications is highly variable. Monitor for increased pain or tenderness of the gallbladder or jaundice.

2.3 Administration Instructions
The capsule contents will remain as fine granules in the milk or food, and will not adhere to the contents mix with drink or food (2.3)

3 DRUG INTERACTIONS
Drug interactions with CHOLBAM mainly relate to agents capable of interrupting the enterohepatic circulation of bile acids.

3.1 Bile Acid Resins and Aluminum-Based Antacids
CHOLBAM should be administered at least 1 hour before or 2 hours after administration of bile acid resins and aluminum-based antacids.

3.2 Bile Salt Efflux Pump (BSEP) Inhibitors
Avoid concomitant use. If CHOLBAM must be used concurrently with a BSEP inhibitor, the dose of the BSEP inhibitor should be reduced. If a more rapid action is desired, switching to ursodeoxycholic acid is recommended (2.2).

3.3 Other Drugs
Clinical trials have been conducted under relatively weight-maintaining conditions; adverse reactions noted in clinical trials of this drug cannot be directly compared to rates in the clinical trials for other drugs. See Table 2 to achieve a recommended dosage of 10 mg/kg/day

4 ADVERSE REACTIONS

4.1 Clinical Gastrointestinal

4.2 Laboratory Values

4.3 Other Adverse Events

4.4 Allergic Reactions

4.5 Other Events

5 WARNINGS AND PRECAUTIONS
5.1 Impaired Liver Function

5.2 Toxicity with Overdose

5.3 Development of Struvite Calculi

5.4 Precipitation or Precipitate Formation

5.5 Cardiovascular Risk

5.6 Pregnancy

5.7 Lactation

5.8 Pediatric Use

6 USE IN SPECIFIC POPULATIONS
6.1 Geriatric Use

6.2 Renal Impairment

6.3 Pediatric Use

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on CHOLBAM

7.2 Use in Specific Populations

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

8.2 Lactation

8.3 Pediatric Use

9 PATIENT COUNSELING INFORMATION

10 DOSAGE FORMS AND STRENGTHS

50 mg, 250 mg, 500 mg

11 CONTRAINDICATIONS

12 WARNINGS AND PRECAUTIONS

13 ADVERSE REACTIONS

14 CLINICAL STUDIES

15 DRUG INTERACTIONS

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17 USE IN SPECIFIC POPULATIONS

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66 USE IN SPECIFIC POPULATIONS
Enzymes and transporters that are involved in bile acid synthesis and in the enterohepatic circulation mainly in conjugated forms. Endogenous bile acids including cholic acid enhance bile flow and provide the physiologic substrates for the synthesis of new bile acids in the intestine.

Zellweger spectrum disorders, deficiency of primary bile acids leads to unregulated cholesterol and taurocholate transport into bile, which is then excreted into the environment. Normal bile acid and cholesterol synthesis and excretion are maintained due to liver lipoholism.

In the intestine, cholesterol is conjugated with glycine or taurine by bile salt-CoA synthetase and bile acid-CoA and are secreted into the bile. Conjugated bile acid is mostly reabsorbed in the bile mainly by apical sodium-dependent bile acid transporter present back to the liver by transporters including sodium/bile acid cotransporter and organic anion transport protein and another enters into the liver from the intestine. Conjugated bile acids are reabsorbed in the colon because they do not bind to cholesterol and are deconjugated in the colon resulting in the bile acids being reabsorbed in the colon rather than the rectum.

The majority of patients (80%, 25/31) were less than 2 years of age at the start of treatment. Patient ages at the end of treatment ranged from 19 to 36 years. The median age at the end of treatment was 14 years (range of 10 to 24 years on treatment). Thirteen of 31 patients, or 42%, of patients survived greater than 3 years from trial entry. Thirteen of these 13 patients, or 32%, were "long-term" survivors (range of 10 to 17 years on treatment).

Among responsive patients with PDs, 38% of the responders met the two clinical criteria: (1) ALT or AST values reduced to less than 50 U/L, or baseline levels reduced by 80%; (2) met at least one laboratory criterion, had increased body weight and were alive at the last follow-up.

The majority of patients (90%, 27/30) were less than 2 years of age at the start of treatment (range 2 to 10 years). The majority of patients were treated for an average of 254 weeks (6 years). Sufficient data were available to assess baseline liver function and effects of CHOLBAM treatment. A responder analysis was performed to determine the response to treatment with CHOLBAM.

In Trial 1, 26 patients were treated with at least one dose of CHOLBAM. All patients in Trial 1 and 21 patients in Trial 2 were enrolled at the beginning of the study. In both trials, patients were treated with CHOLBAM capsules, provided adequate data on baseline liver function and effects of CHOLBAM treatment. A responder analysis was performed to determine the response to treatment with CHOLBAM.

Efficacy data were obtained from published case reports of 3 patients. Enroll criteria in Trial 1 and 2 were based on abnormal urinary bile acid analysis by Fast Atom Bombardment - Mass Spectrometry (FAB-MS) analysis.

Most patients received concomitant DHA (docosahexaenoic acid) and Vitamins A, D, E and K. Documenting adherence to treatment, concomitant medications and response to treatment was incompleteness in Trial 1. All other patients improved in all four criteria set of the study. Direct and indirect bile acid synthesis disorders due to single enzyme defects are diagnosed when urinary bile acid analysis show enrichment of the bile acids with cholic and chenodeoxycholic acids.

In Trial 1 treated 2 new patients along with 10 patients who rolled-over from Trial 1 (n=12 total). Efficacy data were available from Trial 2 for 21 months of treatment.

To 1024 untreated patients were treated with at least one dose of CHOLBAM. The median age at the end of treatment was 14 years (range of 10 to 24 years on treatment).

"long-term" survivors (range of 10 to 17 years on treatment).

A published report of a case series described 15 patients with SEDs; thirteen were diagnosed and treated with oral bile acid therapy showed enrichment of the bile with cholic acid.