Drug Use Research & Management Program
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New Drug Evaluation: Cholbam (cholic acid) capsule, oral

Date of Review: November 2019
Generic Name: cholic acid

End Date of Literature Search: 06/18/2019
Brand Name (Manufacturer): Cholbam™ (Retrophin, Inc.)
Dossier Received: yes

Research Questions:

1. What is the efficacy of cholic acid for treatment of bile acid synthesis disorders (BASDs) due to single enzyme defects (SEDs) or as an adjunctive treatment for peroxisomal disorders (PDs) such as Zellweger syndrome (ZS) pertaining to important outcomes such as hepatic impairment or mortality?
2. Is cholic acid safe for treatment of bile acid synthesis disorders due to SEDs or as an adjunctive treatment for PDs?
3. Are there any subgroups (i.e. age, gender, ethnicity, concomitant diabetes, disease duration or severity) that would particularly benefit or be harmed from treatment with cholic acid?

Conclusions:

- The Food and Drug Administration (FDA) approval of cholic acid was based on a phase 3, nonrandomized, open-label, single-arm compassionate use trial in 85 patients conducted over an 18-year period.[1] There is insufficient evidence from this poor quality trial to demonstrate cholic acid is effective in reducing atypical urinary bile acids patients with BASDs due to SEDs or PD.[2] Accumulation of these hepatotoxic bile acids results in hepatic impairment and injury. Among patients with SED, the percentage of patients with normalized urinary bile acid excretion increased from 2.3% at baseline to 65.1% post-treatment with cholic acid ($P<0.0001$.[2] Among patients with PDs, the percentage with normalized urinary bile acid excretion increased from 33.3% to 85.2% with cholic acid treatment ($P<0.0001$).[2]
- There were only small numbers of adverse effects reported from the manufacturer's phase 1 and phase 3 trials of cholic acid. Diarrhea was the most frequent common adverse effect (2%) in patients with either BASD or Zellweger syndrome, the most common PD.[3] Other adverse events including abdominal pain, neuropathy, esophagitis, nausea, jaundice, and skin lesions, occurred at rates of 1%.[3]
- An extension trial in 15 patients with BASDs with SED was conducted over 10 years in patients that participated in the initial efficacy trial for cholic acid.[4] All patients were alive with their native liver and normal findings on physical examination upon last follow-up.[4] Also, all patients had normal serum liver biochemistry tests, the excretion of atypical bile acid metabolites remained low or in trace amounts, and no patients reported serious adverse effects.[4] Due to the small sample size of this trial, there is insufficient evidence regarding the impact of cholic acid treatment in reducing mortality or hepatic injury in patients with BASDs or PDs.
- The safety and effectiveness of cholic acid on extrahepatic manifestations of bile acid synthesis disorders due to SEDs or PDs including Zellweger spectrum disorders have not been established.[3]

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Recommendations:

- Designate cholic acid as a non-preferred agent on the Preferred Drug List (PDL) of the Oregon Practitioner-Managed Prescription Drug Plan (PMPDP).
- Implement PA criteria for cholic acid to ensure use according to FDA-approved indications (**Appendix 2**).
- Review costs in executive session.

Background:

Biosynthesis of bile acids from cholesterol involves several complex steps catalyzed by at least 15 hepatic enzymes.[5] In bile acid synthesis, cholesterol is altered by a cascade of reactions that add hydroxyl groups, reduce and shorten the side-chain, and conjugate the terminal acid group with glycine or taurine, resulting in the two primary bile acids, chenodeoxycholic acid and cholic acid.[5] Bile acids promote the flow and excretion of bile, assist in the intestinal absorption of fat and fat-soluble vitamins, and provide feedback inhibition of bile acid synthesis. Nine inborn errors of bile acid metabolism have been identified that lead to enzyme deficiencies and impaired bile acid synthesis in humans.[1] Patients with inborn errors of bile acid metabolism cannot synthesize primary bile acids, resulting in reduced bile flow, decreased absorption of fat and fat-soluble vitamins, and accumulation of toxic intermediary cholesterol metabolites.[6] Inborn errors of bile acid metabolism are rare causes of neonatal cholestasis and liver disease in older children and adults.[7] The incidence and prevalence of BASDs are unknown.[8] These disorders have been estimated to account for as many as 1-2% of all childhood cholestatic disorders.[8] However, many cases go undiagnosed or misdiagnosed making it difficult to determine their true frequency in the general population.[8]

Disorders of bile acid synthesis are classified as primary or secondary. Primary BASDs are caused by enzyme defects which result in insufficient production of the 2 primary bile acids and cause overproduction of hepatotoxic bile acids. BASDs are a heterogeneous group of disorders, each of which is associated with a defect of a specific enzyme that is needed in the synthesis of bile acids.[9] Bile acid disorders involving specific enzymes include:

- 3-beta-hydroxy-delta-5-C27-steroid oxidoreductase (3-beta-HSD) deficiency*
- alpha-methylacyl-CoA racemase (AMACR) deficiency
- amino acid n-acyltransferase deficiency
- bile acid CoA ligase deficiency
- cholesterol 7alpha-hydroxylase deficiency
- delta4-3-oxosteroid 5-beta-reductase (AKR1D1 mutation) deficiency*
- oxysterol 7-alpha-hydroxylase deficiency
- sterol 27-hydroxylase deficiency (cerebrotendinous xanthomatosis)
- trihydroxycholestanoic acid CoA oxidase deficiency

  **occurs more frequently than other BASDs*[9]

Secondary BASDs due to peroxisomal disorders are associated with the production of abnormal bile acids and progressive liver disease.[5] Reactions modifying and shortening the cholesterol side-chain take place in mitochondria and peroxisomes.[5] Peroxisomes are small structures within the cytoplasm of cells that catalyze catabolic and anabolic functions critical to cellular metabolism.[10] The defect in patients with PD involves failure to adequately perform the side-chain oxidation of bile acid precursors, which results in accumulation of long-chain bile acids.[5] Zellweger syndrome (ZS) is the most common PD and is generally diagnosed in infancy. During the first year of life, children with ZS will present with multi-organ dysfunction, craniofacial dysmorphism, and significant neurologic deficits.[1] Treatment of ZS includes fat-soluble vitamin supplementation, anti-epileptic drugs to treat seizures, and adrenal replacement therapy if warranted. Cholic acid replacement therapy has only been shown to help relieve signs and symptoms of hepatic disease in patients with ZS.

Diagnosis of inborn errors of metabolism should be considered in infants with conjugated hyperbilirubinemia with low serum gamma glutamyl transpeptidase (GGT) and low or normal serum bile acids measured by conventional testing methods.[7] The atypical bile acid metabolites are generally not detected by the routine or classic methods for bile acid measurement, and mass spectrometric (MS) techniques provide the most appropriate means of characterizing defects in bile acid synthesis.[7] Detection of atypical bile acids in urine and serum can be obtained using fast atom bombardment (FAB-MS), liquid secondary ionization (LSI-MS), or gas chromatography (GC-MS).[5]

The phenotype of bile acid synthetic defects is highly variable.[11] Patients present with varying degrees of hyperbilirubinemia, elevations in serum transaminases and on clinical examination, hepatosplenomegaly.[11] The mortality rate is about 50% in reported cases of SED, many of whom were diagnosed late in the course of liver disease.[12] Those who are diagnosed early may benefit from cholic acid replacement therapy. For those who have significant liver disease, liver transplantation may be the only option. Treatment of PD patients is primarily supportive care.[12]

In the past year, there have been 114 Oregon Health Plan (OHP) patients that have presented with a diagnosis of peroxisomal disorder or a disorder of bile acid and cholesterol metabolism. These disorders are funded by the Health Evidence Review Commission (HERC) on line 60 of the Prioritized List of Health Services.[13] Fourteen patients with these diagnoses are currently enrolled in Fee-For-Service (FFS) and 84 are currently enrolled in a Coordinated Care Organization (CCO), and 16 are no longer eligible for coverage. Of the 114 patients, 4 of them had a pharmacy claim for cholic acid; 3 of them were enrolled in a CCO and 1 patient is a FFS member.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Cholic acid (Cholbam™), an oral bile acid, received FDA approval in 2015 for the treatment of BASDs due to SEDs.[3] Cholic acid is also indicated as an adjunctive treatment for patients with PD, including Zellweger spectrum disorders, who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat-soluble vitamin absorption.[3] The recommended dosage is 10 to 15 mg/kg once daily or in two divided doses, in pediatric patients and adults.[3]

Cholic acid was approved under the FDA accelerated approval regulations, requiring further adequate and controlled clinical trials to verify the clinical benefit.[9] The FDA approval of cholic acid was based on a phase 3, nonrandomized, open-label, single-arm compassionate use trial in 85 patients (64% with SED and 36% with PD) over an 18-year period.[1] The primary efficacy variables were changes from baseline to post-treatment (mean duration of treatment was 145 weeks) in atypical urinary bile acids, liver chemistries (serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), and height and weight percentiles.[2] Additional efficacy variables included changes in serum bilirubin and liver histology.[2]

Enrollment in the trial was based on abnormal urinary bile acid levels by FAB-MS analysis.[2] Using a scoring system based on signal/noise ratio for the major ions, the FAB-MS at baseline and post-treatment were assessed as normal (score 0) or as showing slight (score 1), significant (score 2), or marked (score 3) increases in the levels of atypical bile acids.[2] This semi-quantitative assessment was validated for 3-beta-HSD deficiency and shown to correlate well with quantitative excretion as measured by a targeted tandem MS method.[2] Laboratory assessment of serum AST, serum ALT, and serum bilirubin (total and direct) were performed at baseline and at regular intervals during treatment.[2] A value of 50 IU/L was selected as the upper limit of normal (ULN) for AST and ALT.[2] Percutaneous liver biopsies were performed at baseline (if no historical sample was available) and between 1 and 10 months after treatment initiation.[2] In

patients with ZS, a liver biopsy was performed if there was no contraindication to biopsy that increased the risk of the procedure.[2] Liver biopsies were not required for patients enrolled in the trial. Disease progression was defined as increase of serum bile acids, transaminases, and bilirubin; or cholestasis on liver biopsy.[9]

In the original study protocol, a combination of ursodeoxycholic acid (UDCA) and cholic acid was stipulated as study medication.[2] However, after analysis of urinary bile acids suggested that UDCA could interfere with the intestinal absorption of cholic acid, UDCA was removed as study medication and patients were administered cholic acid as monotherapy.[2] Forty patients received 15 mg/kg cholic acid once daily, and 39 patients had cholic acid in combination with UDCA.[9]

The analysis of the primary outcome was evaluated using a worst-to-best analysis (comparing the least favorable outcome before intervention with the best favorable outcome after intervention) of changes in urinary bile acids.[2] Among patients with SED, the percentage with normal FAB-MS scores (indicating normalized urinary bile acid excretion) increased from 2.3% at baseline to 65.1% post-treatment; the percentage with marked abnormalities decreased from 72.1% to 14.0% post-treatment (P<0.0001).[2] Among patients with ZS, the percentage with normal FAB-MS scores increased from 33.3% to 85.2% with cholic acid treatment (P<0.0001).[2]

For patients with SED and PD, there was a marked increase in the number of patients with normal serum ALT and AST values over the mean treatment period of 145 weeks.[2] In the SED population, only 18.4% had a baseline AST < 50 IU/L, but post-treatment AST values were normal in 85% of the SED population (change: 66.6%, P<0.0001).[2] In the PD population, 7.4% had a baseline AST < 50 IU/L, and post-treatment AST values were normal in 15.4% of the PD population (improvement for 8% of patients, P=0.0073).[2] Treatment with cholic acid improved weight percentiles in patients with SED and those with PD (**Table 3**). The changes in weight percentiles were statistically and clinically significant (P=0.006 and P=0.014) for patients with SED and PD, respectively.[2] Pre- and post-treatment liver biopsies were available for analysis in 4 patients. With the exception of bridging fibrosis and unspecified fibrosis, all histopathologic features were less prominent in post-treatment biopsies than in pretreatment biopsies.[2] Refer to **Table 3** for more details about this study.

The major limitations of the study include: nonrandomized, single arm trial design, many protocol deviations which were identified by the clinical inspection team, and the responder analyses which contained 3 biomarker components (bile acids, transaminases).[9] Documentation of adherence to treatment, concomitant medications, and response to treatment were incomplete during this trial.[9] The choice of a worst-to-best analysis is considered not an acceptable statistical method in biomedical studies due to the risk of a Type 1 error occurring (i.e. detecting an effect that was not present).[14] In addition, the study population was small, narratives of patients who died during the study were incomplete, and clinical laboratory data were missing for some patients.[9] Some subjects had exposure to multiple types of primary bile acids with different dosing regimens.[9] Finally, rates of lost-to-follow-up were high (11/50, 22% of SED patients and 6/29, 21%).[9]

An extension trial in 15 patients with 2 specific bile acid deficiencies (3-beta-HSD (n=13) and AKR1D1 (n=2) mutations) was conducted over 10 years in patients that participated in the initial efficacy trial for cholic acid.[4] The 2 mutations included in this trial have been identified as the most frequent inborn errors of bile acid metabolism.[4] The follow-up evaluations were performed every year and included: 1) physical examination at least once a year; 2) blood liver biochemistry tests including alpha-fetoprotein and total serum bile acids; 3) abdominal ultrasonography; 4) urine bile acid analyses by gas chromatography/mass spectrometry (GC-MS).[4] Bile acid analyses in urine samples were performed and predominant specific atypical bile acids were determined in urine and expressed as a percentage of total urinary bile acids.[4] Liver biopsy specimens were analyzed by the same pathologist and compared to previous biopsies.[4]

The median age at last follow-up and the median time of follow-up with treatment were 24.3 years (range: 15.3–37.2) and 21.4 years (range: 14.6–24.1), respectively.[4] All patients were alive with their native liver, with normal findings on physical examination upon last follow-up visit.[4] Also, all patients had normal serum liver biochemistry tests and the excretion of the atypical metabolites of bile acids remained low or traces in amount, signing a good metabolic control of the primary bile acid synthesis defects.[4] Most patients had normal liver ultrasonography and 4 patients had minor ultrasonographic liver abnormalities.[4] In all patients, serum alpha-fetoprotein (AFP) level was persistently normal and none of the patients developed hepatocellular carcinoma. Alpha-fetoprotein is a glycoprotein that is produced by a variety of tumors including hepatocellular carcinoma and hepatoblastoma. Most studies report elevated AFP concentrations in approximately 70% of patients with hepatocellular carcinoma.

Clinical Safety:

There were only small numbers of adverse effects reported from the 18-year study of cholic acid. Diarrhea was the most frequent common adverse effect (2%) in both the BASD and ZS populations.[9] A summary of common adverse events observed during case reports and clinical trials is presented in **Table 1.**[4] In the extension trial no serious adverse events were observed over 10 years and five women treated at therapeutic doses had given birth to 10 healthy newborns.[4]

Table 1: Common adverse reactions with cholic acid observed in clinical trials[3]

Adverse Reactions	Overall Incidence (n=140)
Diarrhea	3 (2%)
Reflux Esophagitis	1 (1%)
Malaise	1 (1%)
Jaundice	1 (1%)
Skin Lesion	1 (1%)
Nausea	1 (1%)
Abdominal Pain	1 (1%)
Intestinal Polyp	1 (1%)
Urinary Tract Infection	1 (1%)
Peripheral Neuropathy	1 (1%)

The manufacturer recommends discontinuation of cholic acid if liver function does not improve within 3 months of starting treatment, if complete biliary obstruction develops, or if there are persistent clinical or laboratory indicators of worsening liver function or cholestasis.[3] Continued monitoring of liver function is recommended and patients may consider restarting a lower dose when parameters return to baseline.[3]

Look-alike / Sound-alike Error Risk Potential: None identified

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Mortality
2) Hepatic Impairment
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Disease progression was defined as increase of serum bile acids, transaminases, and bilirubin; or cholestasis on liver biopsy

Table 2. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Bile acid replacement therapy
Oral Bioavailability	Extensively absorbed by passive diffusion along the length of the gastrointestinal tract
Distribution and Protein Binding	N/A
Elimination	Bile as conjugated cholic acid Fecal as unabsorbed cholic acid
Half-Life	N/A
Metabolism	Liver: primary via conjugation

Abbreviations: NA=Not Available

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimen/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Heubi et al.[2] CAC-91-10-10 Phase 3, OL, single arm trial	1. Cholic acid 10 to 15mg/kg po once or divided twice daily Conducted over 18 years. Average duration of treatment was 145 weeks (approximately 12 years).	Demographics: 1. Mean age at diagnosis: 2 yrs 2. Mean age at start of treatment: 3 yrs 3. Gender: Male 59% 4. Disorder type: SED 64% PD 36% Key Inclusion Criteria: A. SED Population: 1. Cholestasis at baseline must meet ≥ 2 of abnormal biomarkers: -ALT/AST > 50 U/L -Total bilirubin > 1 mg/dL, or direct bilirubin > 0.3 mg/dL -Evidence of cholestasis on liver biopsy	ITT: N=85 SED: 54 PD: 31 mITT: (received at least one dose of cholic acid) n=79 SED: 50 PD: 29 Attrition: 1. SED: 7 (13%) 2. PD: 14 (45%)	Primary Endpoint: Percentage of patients with change in normal bile acid metabolites from baseline to post-treatment assessed by urine FAB-MS. a. SED Population: Baseline: 2.3% Post-treatment: 65.1% Change: 62.8% b. PD Population Baseline: 33.3% Post-treatment: 85.2% Change: 51.9% P< 0.0001 for both populations Secondary Endpoint: 1. Percentage of patients with improved liver chemistry from baseline to post-treatment. A. Baseline AST < 50 IU/L SED Population Baseline: 18.4% Post-treatment: 85%	NA NA NA	AE: n=38 (48%) SAE: n=16 (20%) AE leading to drug discontinuation: n=4 (5%) Death n=21 (27%) p-value and 95% CI NR for all	NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Nonrandomized, open label trial design Performance Bias: High. This was an open-label, single-arm study. Detection Bias: High. This study was not blinded. Attrition Bias: High. High drop out in the PD population due to death. Reporting Bias: High. Numerous protocol violations. Use of worst-to-best analysis (comparing the least favorable outcome before intervention with the best favorable outcome after intervention) may overestimate treatment outcomes. Other Bias: Unclear. Sponsored by Retrophin, manufacturer of cholic acid **Applicability**: Patient: Applies to patients with BASDs due to SEDs and PD. Intervention: Cholic acid administered concurrently with another bile acid (ursodeoxycholic acid) in 46% of the patients. Comparator: No comparator used due to ethics of not treating patients with BASDs.

		-Urinary FAB-MS score > 2 B. PD Population: 1. Neurologic evaluation 2. Serum long-chain fatty acids positive 3. Urinary FAB-MS analysis positive for atypical bile acids <u>Key Exclusion Criteria</u>: None were defined for this trial		Change: 66.6% P<0.0001 PD Population Baseline: 7.4% Post-treatment: 15.4% Change: 8% P=0.0073 B. Baseline ALT < 50 IU/L SED Population Baseline: 22.5% Post-treatment: 87.5% Change: 65% P<0.0001 PD Population Baseline: 18.5% Post-treatment: 51.9% Change: 33.4% P=0.0003 2. Change in weight from baseline to post-treatment (absolute percentile rank) SED Population Baseline: 31.1% Post-treatment: 54.9% Change: 23.8% P = 0.006 PD Population Baseline: 8.3% Post-treatment: 25.6% Change: 17.3% P = 0.014	NA NA NA NA NA			<u>Outcomes</u>: Biomarkers used to assess efficacy. <u>Setting</u>: Primarily one site in the United States (Cincinnati Children's Hospital) and additional sites on Canada

<u>Abbreviations</u>: ALT= alanine transaminase; AST=aspartate transaminase; ARR = absolute risk reduction; BASD = bile acid synthesis disorder; CI = confidence interval; FAB-MS= Fast Atom Bombardment ionization–Mass Spectrometry; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR =not reported; OL = open-label; PD=peroxisomal disorder; PO = oral; PP = per protocol; SED=single enzyme defect; yrs = years

References:

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Appendix 1: Prescribing Information Highlights

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, for oral use
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------
CHOLBAM is a bile acid indicated for:

- Treatment of bile acid synthesis disorders due to single enzyme defects (SEDs). (1.1)
- 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 (1.2)

Limitation of use:
The safety and effectiveness of CHOLBAM on extrahepatic manifestations of bile acid synthesis disorders due to SEDs or PDs including Zellweger spectrum disorders have not been established. (1.3).

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage is 10 to 15 mg/kg once daily or in two divided doses, in pediatric patients and adults. See prescribing information for weight-based dosing tables. (2.1)
- The recommended dosage in patients with concomitant familial hypertriglyceridemia is 11 to 17 mg/kg once daily or in two divided doses and is adjusted based on clinical response (2.1)
- Monitor AST, ALT, GGT, alkaline phosphatase, bilirubin and INR every month for the first 3 months, every 3 months for the next 9 months, every 6 months during the next three years and annually thereafter. Administer the lowest dose that effectively maintains liver function (2.2)
- Discontinue CHOLBAM if liver function does not improve within 3 months of starting treatment, if complete biliary obstruction develops, or if there are persistent clinical or laboratory indicators of worsening liver function or cholestasis; continue to monitor liver function and consider restarting a lower dose when parameters return to baseline. (2.2, 5.1, 8.6)

Administration Instructions:

- Take with food. (2.3)
- Do not crush or chew the capsules. For patients unable to swallow the capsules, the capsules can be opened and the contents mixed with drink/food (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 50 mg, 250 mg (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
Exacerbation of Liver Impairment: Monitor liver function and discontinue CHOLBAM if liver function worsens while on treatment (5.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥1%) are diarrhea, reflux esophagitis, malaise, jaundice, skin lesion, nausea, abdominal pain, intestinal polyp , urinary tract infection, and peripheral neuropathy. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Asklepion Pharmaceuticals LLC at 1-844-CHOLBAM or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Bile Salt Efflux Pump (BSEP) Inhibitors (e.g., cyclosporine): Avoid concomitant use; if concomitant use is necessary, monitor serum transaminases and bilirubin (7.1)
- Bile Acid Resins and Aluminum-Based Antacids: 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 or aluminum-based antacids. (2.3, 7.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: March 2015

Cholic Acid (Cholbam™)

Goal(s):

- To ensure appropriate use of cholic acid in patients with bile acid synthesis disorders (BASDs) due to a single enzyme defects (SEDs) or as an adjunct to patients with peroxisomal disorders (PD), including Zellweger spectrum disorders, who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat-soluble vitamin absorption.

Length of Authorization:

- Up to 12 months

Requires PA:

- Cholic acid

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 5
5. Is cholic acid prescribed by a hepatologist or pediatric gastroenterologist?	**Yes:** Go to # 6	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
6. Has baseline hepatic function been assessed? *The manufacturer recommends providers to monitor AST, ALT, GGT, alkaline phosphatase, bilirubin, and international normalized ratio (INR) every month for the first 3 months of therapy, every 3 months for the next 9 months, every 6 months during the next 3 years and annually thereafter.[1]	**Yes:** Approve for 6 months. Document baseline hepatic function values (AST,ALT, Alk Phos, bilirubin) and date obtained:_____	**No:** Pass to RPh. Deny; medical appropriateness

	Renewal Criteria	
1. Has the patient's condition stabilized or improved as assessed by the prescribing provider?	**Yes:** Approve for 12 months. Document most recent hepatic function values and date obtained:_____	**No**: Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 11/19 (DM)
Implementation: TBD

1. Cholbam (cholic acid) capsules [Full Prescribing Information]. San Diego, CA: Retrophin, Inc. March 2015.