CHOLBAM® (cholic acid) oral capsule

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms “experimental” and "investigational" are considered to be interchangeable.

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Description:

Cholbam® (cholic acid) is indicated for the treatment of bile acid synthesis disorders due to single enzyme defects (SED). It is also indicated as adjunctive treatment of peroxisomal disorders (PD) including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea or complications from decreased absorption of fat soluble vitamins. The safety and effectiveness of Cholbam® (cholic acid) has been established in pediatric patients 3 weeks of age and older for the treatment of bile acid synthesis disorders due to SED, and for adjunctive treatment of patients with PD including Zellweger spectrum disorders.

Cholic acid and chenodiol (chenodeoxycholic acid) are primary bile acids. Bile acids are secreted by hepatocytes and are necessary for the absorption of dietary fats and fat-soluble vitamins from the intestinal lumen; they are the major catabolic pathway for elimination of cholesterol from the body; they are essential for the biliary excretion of toxic substances; and they promote flow and excretion of bile (bile dependent bile flow). After secretion from hepatocytes, bile acids enter enterohepatic circulation where they are reabsorbed and transported to the liver and secreted once again.
CHOLBAM® (cholic acid) oral capsule (cont.)

Biosynthesis of the two primary bile acids from cholesterol involves at least 16 different enzymes, the majority of which are found in the liver. The synthetic pathway is regulated by negative feedback control that is exerted by the end products and their metabolites. The metabolites, the secondary bile acids, are produced by intestinal bacterial flora and include deoxycholic acid, lithocholic acid, and ursodeoxycholic acid.

In bile acid synthesis disorders due to SED in the biosynthetic pathway, impaired hepatocyte production of primary bile acids reduces canalicular bile acid secretion and there is a reduction in bile acid dependent bile flow. Atypical bile acid precursors accumulate in the hepatocyte that causes cellular injury. As a result there is cholestasis, malabsorption of nutrients, and ultimately liver failure that is almost always fatal in the absence of treatment. Developmental defects may be seen as well as neurologic dysfunction and neuropathy. Bile acid synthesis disorders are extremely rare diseases that affect 25-50 cases per year in the US.

PD represents a group of genetic diseases in which there is impairment in one or more peroxisomal functions. Peroxisomes (also called microbodies) are organelles found in virtually all cells. Peroxisomes contain various enzymes such as catalase, peroxidase, and other enzymes that are needed to perform essential metabolic functions such as oxidative reaction of very long chain and branched chain fatty acids. Individuals with PD have varying degrees of neurologic dysfunction and can have liver dysfunction similar to that seen with bile acid synthesis disorders, even though synthesis of primary bile acid is not completely impaired. These individuals have accumulation of defective bile acids that lead to the liver dysfunction seen in this condition and in bile acid synthesis disorder.

PD is subdivided into three subgroups: (1) peroxisome biogenesis disorders (PBD); (2) single peroxisomal enzyme deficiencies; and (3) single peroxisomal substrate transport deficiencies. PBD is further divided into 4 groups: infantile resum's disease (IRD), neonatal adrenoleukodystrophy (NALD), rhizomelic chondrodysplasia punctata type 1 (RCDP1), and Zellweger syndrome (ZWS). IRD, NALD, and ZWS are referred to the Zellweger spectrum disorders due to overlapping clinical manifestations. Of the Zellweger spectrum disorders, ZWS is the most severe and IRD the less severe disorder. ZWS occurs in 1 of 50,000 live births, 80% of whom will develop liver disease.

There are no standardized protocols or guidelines on the treatment of affected individuals with bile acid synthesis disorder with SED or PD. Many affected individuals respond to treatment by administering one of the missing primary bile acids, so called bile acid replacement therapy. This therapy involves the oral administration one of the two primary bile acids: cholic acid or chenodeoxycholic acid. Replacement of the missing bile acids has led to improvement or normalization of liver function in individuals with specific types of bile acid synthesis disorders.

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 binds bile salts with high affinity, with chenodeoxycholic acid the most potent activator of FXR. FXR regulates enzymes and transporters that are involved in bile acid synthesis and transport, lipid and carbohydrate metabolism and in the enterohepatic circulation to maintain bile acid homeostasis under normal physiologic conditions.

Chenodal™ (chenodiol or chenodeoxycholic acid) was previously used off-label for bile acid synthesis disorders; however, it was found to be hepatotoxic in animals. Its use is contraindicated in patients with known hepatocyte dysfunction or bile ductal abnormalities. Ursodeoxycholic acid (Urso forte, Urso 250, Ursodiol, Actigall®) has a sufficient track record of safety, but it is no longer considered a treatment option for bile acid synthesis disorders and peroxisomal disorders due to lack of benefit. The safety and effectiveness of Cholbam® (cholic acid) on
CHOLBAM® (cholic acid) oral capsule (cont.)

extrahepatic manifestations of bile acid synthesis disorders due to SED or PD including Zellweger spectrum disorders have not been established.

Definitions:

<table>
<thead>
<tr>
<th>Bile acid synthesis disorders: single enzyme defects</th>
<th>Other names</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-beta-hydroxy-delta-5-C27-steroid oxidoreductase (3β-HSD) deficiency</td>
<td>Congenital bile acid synthesis defect type 1</td>
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<tr>
<td></td>
<td>3-beta-hydroxy-delta-5-C27-steroid dehydrogenase</td>
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<tr>
<td>Aldoketoreductase (AKR1D1 or SRD5B1) deficiency</td>
<td>Congenital bile acid synthesis defect type 2</td>
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<td>Delta-4-3-oxosteroid 5-beta-reductase deficiency</td>
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<td>Oxysterol 7-alpha-hydroxylase (CYP7B1) deficiency</td>
<td>Congenital bile acid synthesis defect type 3</td>
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<td>Alpha-methylacyl-CoA racemase (AMACR) deficiency</td>
<td>Congenital bile acid synthesis defect type 4</td>
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<td>2- methylacyl-CoA racemase</td>
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<tr>
<td>Amino acid n-acyltransferase (BAAT) deficiency</td>
<td>Bile acid-CoA amino acid N-acyltransferase</td>
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<td>Bile acid CoA ligase (SLC27A5) deficiency</td>
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<tr>
<td>Cholesterol 7-alpha-hydroxylase (CYP7A1) deficiency</td>
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<tr>
<td>Sterol 27-hydroxylase (CYP27A1) deficiency</td>
<td>Cerebrotendinous xanthomatosis; CTX</td>
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<tr>
<td>Trihydroxycholestanolic acid CoA oxidase deficiency</td>
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Peroxisome Biogenesis Disorders (PBD)

Zellweger syndrome (ZWS) – also known as cerebrohepatorenal syndrome

Neonatal Adrenoleukodystrophy (NALD)

Infantile Refsum disease (IRD)

Rhizomelic chondrodysplasia punctata type 1 (RCDP1)

Note: The first three disorders (ZWS, NALD, and IRD) are thought to represent a clinical continuum, referred to as Zellweger spectrum disorder, with ZWS being the most severe, IRD the mildest and NALD intermediate in severity.

Single peroxisomal enzyme deficiency

X-linked adrenoleukodystrophy (X-ALD)

Refsum disease (phytanoyl CoA hydroxylase deficiency)

Acyl CoA oxidase deficiency (pseudo-NALD)

D-bifunctional protein deficiency (DBP deficiency)

Rhizomelic chondrodysplasia punctata type 2 (RCDP2; dihydroxy-acetone phosphate acyltransferase deficiency)

Peroxisomal sterol carrier protein-X deficiency (SCPX deficiency)

Acatalasemia (catalase deficiency)

Hyperoxaluria type 1 (alanine glyoxylate aminotransferase deficiency)
CHOLBAM® (cholic acid) oral capsule (cont.)

Drug related events:

Ineffective / failure
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

Allergic reaction / hypersensitivity – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

Intolerance – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

Contraindication
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

Non-adherence
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

Precertification:
CHOLBAM® (cholic acid) oral capsule (cont.)

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.

Information about medications that require precertification is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy).

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Cholbam (cholic acid) requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to [Pharmacyprecert@azblue.com](mailto:Pharmacyprecert@azblue.com). Incomplete forms will be returned.

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Cholbam (cholic acid) is considered medically necessary with medical record documentation of ALL of the following:

  1. Individual is 3 weeks of age or older with a diagnosis of ONE of the following:
     - Bile acid synthesis disorder due to single enzyme defect due to of ANY of the following single enzyme defects:
       - Aldoketoreductase (AKR1D1) deficiency
       - Alpha-methylacyl-CoA racemase (AMACR) deficiency
       - 3-beta-hydroxy-delta-5-C27-steroid oxidoreductase (3β-HSD) deficiency
       - Cerebroside xanthomatosis (CTX) deficiency due to sterol 27-hydroxylase (CYP27A1) deficiency

     OR

     - Adjunctive treatment of peroxisomal disorder, who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption in an individual with ANY of the following:
       - Neonatal adrenoleukodystrophy
       - Refsum disease: EITHER
         - Infantile Refsum disease, a biogenesis disorder
         - Refsum disease (phytanoyl CoA hydroxylase deficiency), a single enzyme deficiency
       - Zellweger syndrome
       - Peroxisomal disorder, type unknown
       - Generalized peroxisomal disorder
2. Request is from a provider that is experienced or a specialist in ONE of the following:
   - Hepatology
   - Pediatric gastroenterology

3. Attestation that Cholbam® (cholic acid) will be discontinued with ANY of the following:
   - Liver function does not improve within 3 months of start of treatment
   - Complete biliary obstruction develops

Cholbam (cholic acid) for all other indications not previously listed is considered experimental or investigational based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:

- Familial hypertriglyceridemia without concomitant diagnosis of bile acid synthesis disorder due to single enzyme defects or peroxisomal disorder
- Hypercholesterolemia and other lipid disorders
- Gallstones dissolution or prevention and other Gallbladder disorders
- Nutritional disorders of decreased dietary fats and fat-soluble vitamins not due to bile acid synthesis disorder or peroxisomal disorder
- Congenital adrenal hyperplasia

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**History:**

<table>
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<tr>
<th>Pharmacy and Therapeutics review</th>
<th>Date: 07-21-2016</th>
<th>Activity: Approved</th>
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<tr>
<td>Director Pharmacy Mgmt. review</td>
<td>06-25-2016</td>
<td>Added “without concomitant diagnosis of bile acid synthesis disorder due to single enzyme defects or peroxisomal disorder” to Familial hypertriglyceridemia in experimental or investigational section.</td>
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<th>Date: 07-16-2015</th>
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<td>Director Pharmacy Mgmt. review</td>
<td>05-26-2015</td>
<td>Development</td>
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**Criteria Revisions:**

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<th>Criteria:</th>
<th>Revisions:</th>
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**Resources:**
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Herebian D, Mayatepek E.: Inborn errors of bile acid metabolism and their diagnostic confirmation by means of mass spectrometry. J Ped Scie 2011;3(1)e68


FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
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<tbody>
<tr>
<td>Cholbam® (cholic acid) is a bile acid indicated for:</td>
<td>• 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.</td>
</tr>
<tr>
<td>• Treatment of bile acid synthesis disorders due to single enzyme defects (SEDs).</td>
<td>• 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</td>
</tr>
<tr>
<td>• 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</td>
<td>• 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</td>
</tr>
<tr>
<td>Limitation of use: The safety and effectiveness of Cholbam® (cholic acid) on extrahepatic manifestations of bile acid synthesis disorders due to SEDs or PDs including Zellweger spectrum disorders have not been established.</td>
<td>• Discontinue Cholbam® (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; continue to monitor liver function and consider restarting a lower dose when parameters return to baseline.</td>
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