BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

CHOLBAM® (cholic acid) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Cholbam (cholic acid) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Pediatrician, Hepatologist, Gastroenterologist, Metabolic Specialist, or Pediatric Gastroenterologist

2. Individual is 3 weeks of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Bile Acid Synthesis Disorder due to **ANY** of the following Single Enzyme Defects (SED):
        i. Delta 4-3 oxosteroid 5-beta-reductase, also known as aldoketoreductase (AKR1D1) deficiency

ii. Alpha-methylacyl-CoA racemase (AMACR) deficiency
iii. 3-beta-hydroxy-delta-5-C27-steroid oxidoreductase (3β-HSD) deficiency
iv. Cerebrotendinous xanthomatosis (CTX) due to sterol 27-hydroxylase (CYP27A1) deficiency
v. Smith-Lemli-Opitz

b. As adjunctive therapy of Peroxisomal Disorder (PD) in a patient who exhibits manifestations of liver disease (e.g., jaundice, enlarged liver, abnormal liver enzyme tests), steatorrhea, or complications from decreased fat-soluble vitamin absorption due to **ANY** of the following:
i. Neonatal adrenoleukodystrophy
ii. Refsum disease (phytanoyl CoA hydroxylase deficiency), a single enzyme deficiency
iii. Infantile Refsum disease, a biogenesis disorder
iv. Zellweger syndrome
v. Peroxisomal disorder, type unknown
vi. Generalized peroxisomal disorder

4. Individual has completed **ALL** the following **baseline tests** before initiation of treatment and will have continued monitoring of the individual as clinically appropriate:
a. Serum aspartate aminotransferase (AST)
b. Alanine aminotransferase (ALT)
c. Gamma glutamyltransferase (GGT)
d. Alkaline phosphatase
e. Bilirubin
f. INR

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

Initial approval duration: 3 months
Cholbam **will not be renewed with** demonstration of worsening defined as **ANY** of the following:
Liver function did not improve within 3 months of starting treatment
Complete biliary obstruction developed
There is persistent clinical or laboratory indicators of worsening liver function or cholestasis

➢ **Criteria for continuation of coverage (renewal request):** Cholbam (cholic acid) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Pediatrician, Hepatologist, Gastroenterologist, Metabolic Specialist, or Pediatric Gastroenterologist

2. Individual has documentation of positive clinical response to therapy defined as **TWO** of the following:
a. ALT or AST decreased to < 50 U/L **or** reduced by at least 80% over baseline
b. Total bilirubin decreased to ≤ 1 mg/dL
c. No evidence of cholestasis
d. Body weight increased by at least 10% **or** is stable

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant adverse drug effect that may exclude continued use such as:
   a. Worsening of liver impairment
   b. Complete biliary obstruction
   c. Persistent clinical or laboratory indicators of worsening liver function or cholestasis

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

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. The safety and effectiveness of Cholbam® (cholic acid) on extrahepatic manifestations of bile acid synthesis disorders due to SED or PD including Zellweger spectrum disorders have not been established.

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.

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.

PHARMACY COVERAGE GUIDELINE

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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 as the Zellweger spectrum disorders due to overlapping clinical manifestations. Of the Zellweger spectrum disorders, ZWS is the most severe and IRD the least 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.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

PHARMACY COVERAGE GUIDELINE

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

Peroxisome Biogenesis Disorders (PBD)	Single peroxisomal enzyme deficiency
Zellweger syndrome (ZWS) – also known as cerebrohepatorenal syndrome	X-linked adrenoleukodystrophy (X-ALD)
Neonatal Adrenoleukodystrophy (NALD)	Refsum disease (phytanoyl CoA hydroxylase deficiency)
Infantile Refsum disease (IRD)	Acyl CoA oxidase deficiency (pseudo-NALD)
Rhizomelic chondrodysplasia punctata type 1 (RCDP1)	D-bifunctional protein deficiency (DBP deficiency)
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.	Rhizomelic chondrodysplasia punctata type 2 (RCDP2; dihydroxy-acetone phosphate acyltransferase deficiency)
	Rhizomelic chondrodysplasia punctata type 3 (RCDP3; alkyldihydroxyacetone phosphate synthase deficiency)
	Peroxisomal sterol carrier protein-X deficiency (SCPx deficiency)
	Acatalasemia (catalase deficiency)
	Hyperoxaluria type 1 (alanine glyoxylate aminotransferase deficiency)

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Resources:

Cholbam (cholic acid) product information, revised by Manchester Pharmaceuticals, LLC. 03-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 09, 2025.

Wanders RJA, Braverman N. Peroxisomal disorders. In: UpToDate, Firth HV, Kremen J (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2025. Topic last updated September 24, 2024. Accessed July 10, 2025.

Sutton VR. Inborn errors of metabolism: Classification. In: UpToDate, Kaplan SL, Kremen J (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2025. Topic last updated October 26, 2023. Accessed July 10, 2025.

Sutton VR. Inborn errors of metabolism: Epidemiology, pathogenesis, and clinical features. In: UpToDate, Kaplan SL, Kremen J (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2025. Topic last updated October 26, 2023. Accessed July 10, 2025.