BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 7/16/15
LAST REVIEW DATE: 8/15/19
LAST CRITERIA REVISION DATE: 8/15/19
ARCHIVE DATE:

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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.

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.

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.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **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. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Cholbam (cholic acid) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in pediatric liver disorders or is in consultation with a Hepatologist or Pediatric Gastroenterologist

  2. Individual is 3 weeks of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     - Bile Acid Synthesis Disorder due to **ANY** of the following single enzyme defects:
       a. Delta4-3 oxosteroid 5-beta-reductase, also known as aldoketoreductase (AKR1D1) deficiency
       b. Alpha-methylacyl-CoA racemase (AMACR) deficiency
       c. 3-beta-hydroxy-delta-5-C27-steroid oxidoreductase (3β-HSD) deficiency
       d. Cerebrotendinous xanthomatosis (CTX) due to sterol 27-hydroxylase (CYP27A1) deficiency

     - 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:
       - Neonatal adrenoleukodystrophy
       - Refsum disease (phytanoyl CoA hydroxylase deficiency), a single enzyme deficiency
       - Infantile Refsum disease, a biogenesis disorder
       - Zellweger syndrome
       - Peroxisomal disorder, type unknown
       - Generalized peroxisomal disorder

  4. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     - AST, ALT, GGT, alkaline phosphatase, bilirubin, and INR

  Initial approval duration: 3 months

- **Criteria for continuation of coverage (renewal request):** Cholbam (cholic acid) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in pediatric liver disorders or is in consultation with a Hepatologist or Pediatric Gastroenterologist

  2. Individual's condition response while on therapy is **ONE** of the following:
     - Cholbam **will be renewed** with demonstration of response, defined as:

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- Achieved and maintains **ALL** of the following:
  - ALT or AST decreased to < 50 U/L **or** reduced by at least 80% over baseline
  - Total bilirubin decreased ≤ 1 mg/dL
  - Body weight increased by at least 10% **or** is stable
- Cholbam **will not be renewed** with demonstration of worsening, defined as:
  - 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

3. Individual has been adherent with the medication

4. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use
   - Significant adverse effect such as:
     - Worsening of liver impairment

5. There are no significant interacting drugs

Renewal duration: 12 months

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.

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.

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

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Definitions:

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)
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)

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Resources:

Cholbam® (cholic acid). Package Insert. Reference ID 3720341. Revised by manufacturer March 2015. Accessed 04-07-2015, 07-19-17, 07-07-18, 07-09-19

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UpToDate: Inborn errors of metabolism: Classification. Current through June 2019.

UpToDate: Inborn errors of metabolism: Epidemiology, pathogenesis, and clinical features. Current through June 2019.

UpToDate: Causes of cholestasis in neonates and young infants. Current through June 2019.

UpToDate: Peroxisomal disorders. Current through June 2019.