Cholic Acid

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**INSTRUCTIONS FOR USE**

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**Medical Necessity Criteria**

Cholic acid (Cholbam®) is considered medically necessary when EITHER of the following criteria are met:

I. Bile acid synthesis disorders due to single enzyme defects (SEDs) and BOTH of the following:
   - Diagnosis confirmed by at least ONE of the following:
     - An abnormal urinary bile acid consistent with a bile acid synthesis disorder as confirmed by Fast Atom Bombardment ionization – Mass Spectrometry (FAB-MS) analysis
     - Molecular genetic testing consistent with the diagnosis (for example, biallelic pathogenic variants in ABCD3, AKR1D1, AMACR, HSD3B7, CYP27A1, or CYP7B)
   - Prescribed by or in consultation with a hepatologist, metabolic specialist, or a gastroenterologist

II. Bile acid synthesis disorders due to peroxisomal disorders (PDs), including Zellweger spectrum disorders and ALL of the following:
   - Individual has peroxisomal disorders with at least one of the following criteria:
     - An abnormal urinary bile acid analysis consistent with a Zellweger spectrum disorder per by Fast Atom Bombardment ionization – Mass Spectrometry (FAB-MS) (for example, increased concentrations of C27 bile acid intermediates trihydroxycholestanoic acid (THCA) and dihydroxycholestanolic acid (DHCA))
     - Molecular genetic testing consistent with the diagnosis (for example, biallelic pathogenic variants in one of the PEX genes)
• Patient has liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption (for example, rickets)
• Cholbam is prescribed by or in consultation with a hepatologist, metabolic specialist, or a gastroenterologist

Initial authorization is up to 3 months.

Cholic acid (Cholbam®) is considered medically necessary for continued use when the following are met:

For bile acid synthesis disorders due to single enzyme defects (SEDs), ALL of the following criteria are met:
• Individual has responded to initial Cholbam therapy with an improvement in liver function tests (for example, aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin levels)
• Individual does not have complete biliary obstruction
• Cholbam is prescribed by or in consultation with a hepatologist, metabolic specialist, or a gastroenterologist.

For bile acid synthesis disorders due to peroxisomal disorders (PDs), Including Zellweger spectrum disorders, ALL of the following criteria are met:
• Individual has responded to initial Cholbam therapy as per the prescribing physician (for example, improvements in liver enzymes, improvement in steatorrhea)
• Individual does not have complete biliary obstruction
• Cholbam is prescribed by or in consultation with a hepatologist, metabolic specialist, or a gastroenterologist.

Reauthorization is up to 12 months

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy as applicable.

Cholic acid (Cholbam) is considered experimental, investigational or unproven for any other use including the following:
• Extrahepatic manifestations of bile acid synthesis disorders due to single enzyme defects or peroxisomal disorders, including Zellweger spectrum disorders.
• Combination therapy with Chenodal

Note: Receipt of sample product does not satisfy any criteria requirements for coverage

FDA Approved Indications

FDA Approved Indication

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)

Peroxisomal Disorders Including Zellweger Spectrum Disorders
Cholbam is indicated for 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

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.
Recommended Dosing

FDA Recommended Dosing
The recommended dosage of Cholbam is 10 to 15 mg/kg administered orally once daily, or in two divided doses, in pediatric patients and in adults.

Drug Availability
Cholbam is available in 50 mg and 250 mg capsules, in bottles of 90.

Background

Disease Overview
Bile Acid Synthesis Disorders
Bile acids are found in the liver and have several biological roles, including promotion of bile flow and intestinal absorption of fat and fat soluble vitamins.2,3 The two primary bile acids are cholic acid and chenodeoxycholic acid (available as Chenodal® [chenodiol tablets]). Bile acids are formed from cholesterol; inadequate bile acid production leads to accumulation of cholesterol in the body, as well as other intermediary metabolites. This can result in damage to various organ systems. Severe cases may progress to cirrhosis and liver failure. Progressive neurologic disease may also occur, even in the absence of liver disease. There are at least 17 known enzymes involved in bile acid synthesis.3 Primary bile acid synthesis disorders may be caused by a defect in the gene encoding any one of these enzymes, and therefore these conditions are also termed SEDs.2,3 The estimated incidence of bile acid synthesis disorders due to SEDs is 1 to 9 per one million live births.4 The most common of all of the bile acid SEDs is 3β-hydroxy-C27-steroid oxidoreductase deficiency (3β-HSD gene defect).5 Other common defects include Δ4-3-oxosteroid 5β-reductase deficiency (aldo-keto reductase 1D1 [AKR1D1] gene), 27-hydroxylase deficiency (cerebrotendinous xanthomatosis [CTX]), and alpha-methylacyl-CoA racemase deficiency (AMACR gene). Cholbam is indicated for all SEDs, though the majority of patients in the pivotal study for Cholbam had 3β-HSD defect.1 Chenodal has been used for CTX though it is not labeled for this condition.6 Bile acid synthesis disorders may be diagnosed with either genetic testing or urine bile acid profile by FAB-MS.10 FAB-MS was used for diagnosis in the pivotal trial; gene sequencing was not available when the trial was conducted.11 However, gene sequencing is now available for many of the affected enzymes.

Peroxisomal Disorders (PDs)
PDs occur due to genetic mutations which are essential to the proper formation of peroxisomes.7 Peroxisomes are found throughout the body but are most numerous in the kidneys and liver.7,8 Among their many roles, peroxisomes are vital to the production of bile acids, as well as plasmalogens, which are important for neurologic function.8 Peroxisomal disorders are estimated to affect approximately 1 in 50,000 live births.4 Zellweger spectrum disorder is a type of PD and includes Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease. Zellweger syndrome is the most severe form in the spectrum, followed by NALD, and infantile Refsum disease is the least severe form. Cholbam is indicated only for adjunctive treatment of liver disease symptoms such as steatorrhea. Patients with Zellweger spectrum disorders present with other primary clinical issues such as feeding problems in infants, weak muscle tone, hearing and vision loss, and seizures. Liver involvement with Zellweger spectrum disorders may be diagnosed by genetic testing or by bile acid profile testing with mass spectrometry.12 FAB-MS was used for diagnosis in the pivotal trial; gene sequencing was not available when the trial was conducted.11 However, gene sequencing is now available for many of the affected enzymes.

Professional Societies/Organizations
North American and European societies for Pediatric Gastroenterology, Hepatology, and Nutrition
A joint guideline by the North American and European societies for Pediatric Gastroenterology, Hepatology, and Nutrition is available (2017).9 The guideline, which briefly addresses evaluation of cholestatic jaundice in infants, provides recommendations for diagnosis of bile acid synthesis disorders. It is possible to perform rapid diagnosis of potential inborn errors in bile acid synthesis from urinary bile acid analysis; fast atom bombardment mass spectrometry of urine is recommended. The guideline also notes that molecular techniques identify the specific mutations in genes encoding enzymes responsible for bile acid synthesis.
Off Label Uses

Experimental, Investigational, Unproven Uses
There are no efficacy data available to support use of combination therapy with Cholbam and Chenodal.

References