PRIOR AUTHORIZATION POLICY

POLICY: Cholbam® (cholic acid capsules – Retrophin)

DATE REVIEWED: 06/03/2020

OVERVIEW

Cholbam, a bile acid, is indicated for the treatment of bile acid synthesis disorders due to single enzyme defects (SEDs).[1] It is also 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. The effects of Cholbam on extrahepatic manifestations (e.g., neurologic symptoms) of bile acid synthesis disorders due to SEDs or PDs have not been established.

The prescribing information states that treatment with Cholbam should be discontinued if liver function does not improve within 3 months of the start of treatment or if complete biliary obstruction develops.[1]

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-C_{27}-steroid oxidoreductase deficiency (3β-HSD gene defect).[5] Other common defects include Δ^4-3-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 Fast Atom Bombardment ionization – mass spectrometry (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]

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GUIDELINES

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.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Cholbam. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cholbam as well as the monitoring required for efficacy, approval requires Cholbam to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 1 year in duration unless otherwise noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cholbam is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Bile Acid Synthesis Disorders Due to Single Enzyme Defects (SEDs).** Approve for the duration noted if the patient meets one of the following conditions (A or B):
   - **A)** Initial Therapy: Approve for 3 months if the patients meets both of the following criteria (i and ii):
     - **i.** Patient has a diagnosis of SED based on at least one of the following criteria (a or b):
       - **a)** An abnormal urinary bile acid as confirmed by Fast Atom Bombardment ionization – Mass Spectrometry (FAB-MS) analysis; OR
       - **b)** Molecular genetic testing consistent with the diagnosis; AND
     - **ii.** Cholbam is prescribed by or in consultation with a hepatologist, metabolic specialist, or a gastroenterologist.
   - **B)** Patients Currently Receiving Cholbam: Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient has responded to initial Cholbam therapy with an improvement in liver function tests (e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin levels); AND
     - **ii.** Patient does not have complete biliary obstruction; AND
     - **iii.** Cholbam is prescribed by or in consultation with a hepatologist, metabolic specialist, or a gastroenterologist.

2. **Bile Acid Synthesis Disorders Due to Peroxisomal Disorders (PDs), Including Zellweger Spectrum Disorders.** Approve for the duration noted if the patient meets one of the following conditions (A or B):
   - **A)** Initial Therapy: Approve for 3 months if the patient meets the following criteria (i, ii, and iii):

i. Patient has peroxisomal disorders with at least one of the following criteria (a or b):
  a) An abnormal urinary bile acid analysis by Fast Atom Bombardment ionization – Mass Spectrometry (FAB-MS); OR
  b) Molecular genetic testing consistent with the diagnosis; AND
ii. Patient has liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption (e.g., rickets); AND
iii. Cholbam is prescribed by or in consultation with a hepatologist, metabolic specialist, or a gastroenterologist.

B) Patients Currently Receiving Cholbam: Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
i. Patient has responded to initial Cholbam therapy as per the prescribing physician (e.g., improvements in liver enzymes, improvement in steatorrhea); AND
ii. Patient does not have complete biliary obstruction; AND
iii. Cholbam is prescribed by or in consultation with a hepatologist, metabolic specialist, or a gastroenterologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cholbam has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Combination Therapy with Chenodal.** There are no efficacy data available to support use of combination therapy with Cholbam and Chenodal.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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