

## PRIOR AUTHORIZATION POLICY

- POLICY:** Cholbam Prior Authorization Policy
- Cholbam<sup>®</sup> (cholic acid capsules – Retrophin)

**REVIEW DATE:** 06/30/2021

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### OVERVIEW

Cholbam, a bile acid, is indicated for the following uses:<sup>1</sup>

- **Bile acid synthesis disorders due to single enzyme defects (SEDs).**
- **Peroxisomal disorders (PDs), including Zellweger spectrum disorders,** as adjunctive treatment 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.<sup>1</sup> 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.

### 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.<sup>2</sup> The two primary bile acids are cholic acid and chenodeoxycholic acid (available as Chenodal<sup>®</sup> [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. Primary bile acid synthesis disorders may be caused by a defect in the gene encoding any one of these enzymes. Enrollment criteria in the pivotal studies with Cholbam were based on abnormal urinary bile acids analysis by Fast Atom Bombardment ionization – mass spectrometry (FAB-MS).<sup>1</sup> 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.<sup>3</sup> Among their many roles, peroxisomes are vital to the production of bile acids, as well as for neurologic function. Zellweger spectrum disorder is a type of PD and may be severe (Zellweger syndrome) or intermediate/milder (previously called neonatal adrenoleukodystrophy, infantile Refsum disease, or Heimler syndrome).<sup>4</sup> Enrollment criteria in the pivotal trials were based on abnormal urinary bile acids analysis by FAB-MS and a neurologic exam.<sup>1</sup> However, molecular genetic testing is now available.<sup>4</sup>

### GUIDELINES

A joint guideline by the North American and European societies for Pediatric Gastroenterology, Hepatology, and Nutrition is available (2017).<sup>5</sup> 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

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analysis; FAB-MS 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 the duration 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 patient 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) **Patient is 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.
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- B) Patient is 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 prescriber; AND  
Note: Examples of a response to initial Cholbam therapy include improvements in liver enzymes or improvement in steatorrhea.
  - 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**

Coverage of Cholbam is not recommended in the following situations:

- 1. Concomitant Use with Chenodal.** There are no efficacy data available to support concomitant use of 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**

1. Cholbam® capsules [prescribing information]. San Diego, CA: Retrophin Inc.; October 2020.
  2. Bile acid synthesis disorders. National Organization for Rare Diseases. Updated 2020. Available at: <https://rarediseases.org/rare-diseases/bile-acid-synthesis-disorders/>. Accessed on June 22, 2021.
  3. Zellweger spectrum disorders. National Organization for Rare Diseases. Updated 2020. Available at: <https://rarediseases.org/rare-diseases/zellweger-spectrum-disorders/>. Accessed on June 22, 2021.
  4. Steinberg SJ, Raymond GV, Braverman NE, et al. Zellweger Spectrum Disorder. 2003 Dec 12 [Updated 2020 Oct 29]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1448/>. Accessed on June 22, 2021.
  5. Fawaz R, Baumann U, Ekong U, et al. Guideline for the evaluation of cholestatic jaundice in infants: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutrition. 2017;64(1):154-168.
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