Effective Date 1/15/2024
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Coverage Policy Number IP0289

Cholic Acid

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for cholic acid (**Cholbam**®) capsules.

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

Medical Necessity Criteria

Cholic acid (Cholbam) capsules are considered medically necessary when the following are met:

1. **Bile Acid Synthesis Disorders Due to Single Enzyme Defects (SEDs).** Individual meets **BOTH** of the following criteria:
    A. Diagnosis confirmed by at least **ONE** of the following:
        i. An abnormal urinary bile acid consistent with a bile acid synthesis disorder as confirmed by Fast Atom Bombardment ionization – Mass Spectrometry analysis.
        ii. Molecular genetic testing consistent with the diagnosis (for example, biallelic pathogenic variants in *ABCD3, AKR1D1, AMACR, HSD3B7, CYP27A1, CYP7B*).

B. Medication 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.** Individual meets **ALL** of the following criteria:
   A. Diagnosis confirmed by at least **ONE** of the following:
      i. An abnormal urinary bile acid analysis consistent with a peroxisomal disorder as confirmed by Fast Atom Bombardment ionization – Mass Spectrometry (for example, increased concentrations of C27 bile acid intermediates trihydroxycholestanoic acid and dihydroxycholestanoic acid.
      ii. Molecular genetic testing consistent with the diagnosis (for example, biallelic pathogenic variants in one of the *PEX* genes).
   B. Has liver disease, steatorrhea, or complications from deceased fat soluble vitamin absorption (for example, rickets).
   C. Medication is prescribed by, or in consultation with, hepatologist, metabolic specialist, or a gastroenterologist.

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.

Reauthorization Criteria

Continuation of cholic acid (Cholbam) capsules are considered medically necessary for ALL covered diagnoses for continued use when the above medical neccesity criteria are met and **BOTH** of the following:

1. There is documentation of beneficial response (for example, improvement in liver function tests or improvements in steatorrhea.

2. Individual does not have complete biliary obstruction.

Authorization Duration

Initial approval duration is up to 3 months.
Reauthorization approval duration is up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

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

Background

OVERVIEW
Cholbam, a bile acid, is indicated for the following uses:[1]

- **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.[1] 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.[2] 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. 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).[1] However, gene sequencing is now available for many of the affected enzymes.

Peroxisomal Disorders (PDs)
PDs occur due to genetic mutations to genes that are essential to the proper formation of peroxisomes.[3] 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).[4] Enrollment criteria in the pivotal trials were based on abnormal urinary bile acids analysis by FAB-MS and a neurologic exam.[1] However, molecular genetic testing is now available.[4]

GUIDELINES
A joint guideline by the North American and European Societies for Pediatric Gastroenterology, Hepatology, and Nutrition is available (2017).[5] The guideline, which briefly addresses evaluation of cholestatic jaundice in infants, provides recommendations for diagnosis of bile acid synthesis disorders. While it is possible to perform rapid diagnosis of potential inborn errors in bile acid synthesis from urinary bile acid 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.

References

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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 July 11, 2023.
3. Zellweger spectrum disorders. National Organization for Rare Diseases. Updated 2020. Available at: https://rarediseases.org/rare-diseases/zellweger-spectrum-disorders/. Accessed on July 11, 2023.
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. Updated October 29, 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1448/. Accessed on July 11, 2023.
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.