



Louisiana

cholic acid capsules (Cholbam™)

Policy # 00491

Original Effective Date: 11/16/2015

Current Effective Date: 11/21/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider cholic acid capsules (Cholbam™)[†] for the treatment of bile acid synthesis disorders due to single enzyme defects (SEDs) or the adjunctive treatment of peroxisomal disorders (PDs) to be **eligible for coverage**.

Singe Enzyme Defects Patient Selection Criteria

Coverage eligibility for cholic acid capsules (Cholbam) for the treatment of bile acid synthesis disorders due to single enzyme defects (SEDs) will be considered when the following criteria are met:

Initial (3 months):

- Patient has a diagnosis of a bile acid synthesis disorder due to single enzyme defects (SEDs) based on an abnormal urinary bile acid analysis as confirmed by Fast Atom Bombardment ionization-Mass Spectrometry (FAB-MS)

Continuation:

- Patient has responded to initial cholic acid capsule (Cholbam) therapy as evidenced by improvement in liver function tests (e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin levels); AND
- Patient does NOT have complete biliary obstruction

Peroxisomal Disorders Patient Selection Criteria

Coverage eligibility for cholic acid capsules (Cholbam) for the adjunctive treatment of bile acid synthesis disorders due to peroxisomal disorders (PDs) will be considered when the following criteria are met:

Initial (3 months):

- Patient has a diagnosis of a bile acid synthesis disorder due to peroxisomal disorders (PDs), including Zellweger spectrum disorders, based on an abnormal urinary bile acid analysis as confirmed by Fast Atom Bombardment ionization-Mass Spectrometry (FAB-MS); AND
- Patient has liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption (e.g., rickets)

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Continuation:

- Patient has responded to initial cholic acid capsule (Cholbam) therapy as evidenced by improvement in liver function tests (e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin levels, improvement in steatorrhea); AND
- Patient does NOT have complete biliary obstruction

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of cholic acid capsules (Cholbam) when patient selection criteria are not met to be **investigational**.*

Background/Overview

Cholbam is composed of cholic acid. Cholic acid is a primary bile acid synthesized from cholesterol in the liver. Cholbam is indicated for the treatment of bile acid disorders due to SEDs or for the adjunctive treatment of PDs in patients who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption. In bile acid synthesis disorders due to SEDs and in PDs, deficiency of primary bile acids leads to unregulated accumulation of intermediate bile acids and cholestasis. Bile acids facilitate fat digestion and absorption by forming mixed micelles, and facilitate absorption of fat-soluble vitamins in the intestine. Cholbam is dosed at 10-15 mg/kg once daily or in two divided doses in pediatric patients and adults. The recommended dose for those with concomitant familial hypertriglyceridemia is 11-17 mg/kg once daily or in two divided doses. The package insert recommends discontinuing Cholbam therapy if liver function does not improve within 3 months of starting treatment, if complete biliary obstruction develops, or if there are persistent clinical or laboratory indicators of worsening liver function or cholestasis.

Bile Acid Synthesis Disorders

The bile acid synthesis pathway is supported by 16 different enzymes. Disease causing mutations have been found in 9 out of the 16 enzymes and are categorized as SEDs. The single enzyme defect can compromise the production of primary bile acids, which are essential for promoting the bile flow. The two principal bile acids synthesized by the liver are cholic acid and chenodeoxycholic acid. Common SEDs include 3 β -hydroxy-C27-steroid oxidoreductase deficiency (3 β -HSD gene defect), Δ 4-3-oxosteroid 5 β -reductase deficiency (aldo-keto reductase 1D1 [AKR1D1] gene), 27-hydroxylase deficiency (cerebrotendinous xanthomatosis [CTX]), and alpha-methylacyl-CoA racemase deficiency (AMACR gene). Most patients in the pivotal trial had the 3 β -HSD gene defect.

Peroxisomal Disorders

PDs occur due to gene mutations in 12 genes (which are essential to the formation of peroxisomes). Peroxisomes are subcellular organelles that are present in all cells except erythrocytes. Peroxisomes host catabolic and anabolic pathways that are essential to normal cellular catabolism. This group of disorders

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also includes a spectrum of disorders: Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease. Patients with Zellweger spectrum disorders present with other clinical issues such as feeding problems in infants, weak muscle tone, hearing and vision loss, and seizures. Cholbam is indicated only for the adjunctive treatment of liver disease symptoms such as steatorrhea.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Cholbam was approved in 2015, and is indicated for the treatment of bile acid disorders due to SEDs as well as for the adjunctive treatment of PDs, including Zellweger spectrum disorders, in patients who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The effectiveness of Cholbam in patients with SEDs was assessed in a non-randomized open label, single arm trial (50 patients), an extension trial (33 patients), and a published case series (15 patients). Enrollment in the trials was based on abnormal urinary bile acid by FAB-MS analysis. Response to Cholbam treatment was assessed by meeting various predetermined combinations of the following: AST/ALT reduction, total bilirubin values, and absence of cholestasis. Response was also assessed by clinical criteria relating to body weight increases and survival timeframes. Overall, 28 of 44 patients (64%) were considered responders.

The effectiveness of Cholbam in patients with PDs (including Zellweger spectrum disorders) was assessed in patients in the same clinical trials as those with SEDs as well as additional patient case reports. Enrollment in the trials was based on abnormal urinary bile acid by FAB-MS analysis. Cholbam treatment was assessed by meeting various predetermined combinations of the following: AST/ALT reduction, total bilirubin values, and absence of cholestasis. Response was also assessed by clinical criteria relating to body weight increases and survival timeframes. Overall, 11 of 24 patients (46%) were considered responders.

References

1. Cholbam [package insert]. San Diego, CA: Retrophin Inc, March 2015.
2. Cholbam. Express Scripts Prior Authorization Program Document. May 2015.
3. Cholbam (cholic acid capsules). Bile-acid synthesis disorders. Available at: <http://www.cholbam.com/bile-acid-deficiency-disorder-b-a-d-d/single-enzyme-defects/>. Accessed on April 8, 2015.
4. Heubi JE, Setchell KDR, Bove KE. Inborn errors of bile acid metabolism. *Semin Liver Dis.* 2007;27:282-294.
5. Genetics Home Reference. Zellweger Spectrum. Reviewed April 2010. Available at: <http://ghr.nlm.nih.gov/condition/zellweger-spectrum>. Accessed on April 3, 2015.

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10/29/2015 Medical Policy Committee review

11/16/2015 Medical Policy Implementation Committee approval. New policy.

11/03/2016 Medical Policy Committee review

11/16/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

11/02/2017 Medical Policy Committee review

11/15/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

11/08/2018 Medical Policy Committee review

11/21/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 11/2019

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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