

Pharmacotherapy for Bile Acid Synthesis Disorders

Policy # 00491

Original Effective Date: 11/16/2015

Current Effective Date: 07/01/2026

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.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

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.*

cholic acid capsules (Cholbam™)

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**.**

Single 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.

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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)

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**.*

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.*

chenodiol tablets (Ctexli™)

Based on review of available data, the Company may consider chenodiol tablets (Ctexli™)[‡] for the treatment of cerebrotendinous xanthomatosis (CTX) to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for chenodiol tablets (Ctexli) for the treatment of cerebrotendinous xanthomatosis (CTX) will be considered when the following criteria are met:

- Patient has a diagnosis of cerebrotendinous xanthomatosis (CTX); AND
- Documentation has been provided to confirm the diagnosis of cerebrotendinous xanthomatosis (CTX) verified through genetic testing demonstrating pathogenic variants in the *CYP27A1* gene; AND
- Patient is 18 years of age or older.

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Based on review of available data, the Company considers the use of chenodiol tablets (Ctexli) 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 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.

Ctexli, a bile acid, is indicated for the treatment of cerebrotendinous xanthomatosis (CTX) in adults. Ctexli acts by replacing deficient levels of the endogenous bile acid chenodeoxycholic acid (chenodiol). The recommended dose of Ctexli is 250 mg taken orally three times a day.

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Cerebrotendinous xanthomatosis (CTX)

CTX is an ultra-rare, autosomal recessive metabolic disorder caused by a mutation in the *CYP27A1* gene resulting in a deficiency of the enzyme (sterol 27-hydroxylase) that is key for the body to break down fats. Due to reduced bile acid production in the liver, patients with CTX have increased serum cholestanol (a cholesterol metabolite) and elevated urinary bile alcohols (23S-pentol). These substances accumulate in various places in the body (e.g., brain, liver, skin and tendons) leading to damage to various organs and tissues. Around 300 cases have been reported globally; however, it is thought that CTX may be substantially underdiagnosed due to the variable clinical presentation. If left untreated, patients with CTX have a life expectancy into the fifth and sixth decades. However, with treatment, particularly before neurologic symptoms, patients with CTX are expected to have an average lifespan.

There is no other FDA-approved treatment for CTX. Chenodal^{®†} (chenodiol tablets), which contains the same active ingredient as Ctexli (at the same tablet strength), is FDA-approved for the treatment of gallstones; however, it has been used off-label for CTX treatment. Consequently, it received a medically necessary determination by the FDA for this condition. Due to this designation, the manufacturer was unable to market Chenodal for CTX. Chenodiol is addressed in current treatment recommendations by a CTX expert consensus panel (2021). All panelists agreed treatment with chenodiol is necessary to improve/stabilize prognosis in the majority of patients. Additionally, initiating treatment upon diagnosis was essential, regardless of age or the presence of symptoms. It was agreed that chenodiol is a lifelong treatment that serves to reverse the pathophysiologic processes in CTX and is the most effective option for treating the underlying biochemical abnormalities.

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.

Ctexli was approved in February 2025 for treatment of cerebrotendinous xanthomatosis (CTX) in adults.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to 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.

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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.

The efficacy of Ctexli was evaluated in one randomized withdrawal, double-blind, placebo-controlled, crossover, multicenter, Phase III pivotal study called RESTORE [n = 13] that involved patients with a confirmed diagnosis of CTX. The study consisted of two open-label treatment periods (including an initial run-in phase) where all patients received Ctexli and two double-blind, randomized withdrawal treatment periods. The median patient age was 42 years (range 16 to 55 years). The primary efficacy endpoint was the mean change in the urinary bile alcohol, 23S-pentol, from baseline to the end of each double-blind treatment period, Day 29 and Day 113. Withdrawal of Ctexli after the open-label treatment periods resulted in significant increases in each CTX biomarker evaluated. These included a significant 20-fold increase in the urine 23S-pentol biomarker ($p < 0.0001$). A significant proportion of patients receiving placebo (61.5%) during the trial required blinded rescue medication with Ctexli during the double-blind treatment periods ($p = 0.0006$).

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/>.
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>.
6. Ctexli [package insert]. Mirium Pharmaceuticals, Inc. Foster City, CA. Updated February 2025.
7. Ctexli Drug Evaluation. Express Scripts. Updated March 2025.
8. Stelten B, Dotti M., Verrips A, et al. Expert opinion on diagnosing, treating and managing patients with cerebrotendinous xanthomatosis (CTX): a modified Delphi study. *Orphanet J Rare Dis* 16, 353 (2021). Available at: <https://doi.org/10.1186/s13023-021-01980-5>.

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Policy History

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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.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/04/2021	Medical Policy Committee review
11/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2022	Medical Policy Committee review
11/09/2022	Medical Policy Implementation Committee approval. No change to coverage.
11/02/2023	Medical Policy Committee review
11/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/07/2024	Medical Policy Committee review
11/13/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2025	Medical Policy Committee review.
06/11/2025	Medical Policy Implementation Committee approval. Added new product, Ctexli, to the policy with relevant criteria and background information. Title changed from “cholic acid capsules (Cholbam™)” to “Pharmacotherapy for Bile Acid Synthesis Disorders”.
06/04/2026	Medical Policy Committee review.
06/10/2026	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2027

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***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 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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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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NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.