Drug Monograph

Drug/Drug Class: **Cholbam™ (cholic acid) capsule / Bile Acid Salts**

Prepared for: MO HealthNet
Prepared by: Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Cholbam™ is available in capsules containing 50 mg and 250 mg of cholic acid respectively. Manufactured by: Patheon France SA, 38300 Bourgoin-Jallieu, France Manufactured for: Manchester Pharmaceuticals, Inc., San Diego, CA 92130
Summary of Findings:	Cholbam™ demonstrated efficacy in a nonrandomized, open-label, uncontrolled trial that included 50 patients with bile acid synthesis disorders due to single enzyme defects and 29 patients with peroxisomal disorders including Zellweger spectrum disorders, which was then followed by an extension trial. Patients were followed for more than 18 years. Response was evident in 64% of patients with bile acid synthesis disorders and 46% of patients with peroxisomal disorders, with survival for more than 3 years in 67% and 42%, respectively.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Non-Preferred Agent

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[2]

Cholic acid capsules are indicated for patients who have bile acid synthesis disorders caused by single enzyme defects, or who have peroxisomal disorders. Peroxisomes are cellular organelles that aid in metabolism and help produce bile acids, cholesterol, and plasmalogens. Peroxisomal disorders include so-called Zellweger spectrum disorders such as Zellweger syndrome, characterized by abnormal facial features, an enlarged liver, and nerve damage in infants.

With both sets of rare congenital disorders, individuals lack enzymes needed to synthesize cholic acid, a primary bile acid, according to the FDA. A lack of cholic acid results in reduced bile flow, accumulation of potentially toxic bile-acid intermediates in the liver, and malabsorption of fats and fat-soluble vitamins in food.

Dosage Form(s) [1]

Cholbam™ is available in capsules containing 50 mg and 250 mg of cholic acid respectively.

Manufacturer [1]

Manufactured by: Patheon France SA, 38300 Bourgoin-Jallieu, France
Manufactured for: Manchester Pharmaceuticals, Inc., San Diego, CA 92130

Indication(s) [1]

Cholbam™ is indicated for the treatment of bile acid synthesis disorders due to single enzyme defects and for the adjunctive treatment of peroxisomal disorders, including Zellweger spectrum disorders, in patients with liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption.

Clinical Efficacy [1] (mechanism of action/pharmacology, comparative efficacy)

Cholbam™ is a bile acid replacement therapy that corrects deficiencies due to defective biosynthesis or intestinal malabsorption. Cholbam™ and its conjugates are ligands of the farnesoid X receptor (FXR), which regulates enzymes and transporters that are important in bile acid synthesis and homeostasis in the enterohepatic circulation.

Pharmacokinetics:

Cholbam™ capsules undergo the same metabolic pathway as endogenous cholic acid, which enters the bile acid pool and undergoes enterohepatic circulation.

Bile Acid Synthesis Disorders

Cholbam was effective in 64% of patients with bile acid synthesis disorders due to single enzyme defects in a long-term, uncontrolled, open-label study.

STUDY DESIGN	Nonrandomized, open-label, uncontrolled trial (n=50), followed by an extension that included 21 previous patients plus 12 new patients (n=33).
INCLUSION CRITERIA	Patients with bile acid synthesis disorders due to single enzyme defects and abnormal urinary bile acid.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were treated with Cholbam 10 to 15 mg/kg/day over an 18- year period. The average age was 4 years at the start of treatment (range, 3 weeks to 36 years) and the average length of treatment was 6 years.
RESULTS	Of 44 evaluable patients, 64% responded to Cholbam treatment. Response was determined by a combination of lab values (AST/ALT reduction, total bilirubin level of 1 mg/dL or less, no cholestasis on liver biopsy) and clinical outcomes (increased body weight, survival > 3 years). Pre- and post-treatment liver biopsies (n=6) generally revealed improvements in inflammation and giant cell formation, and no progression of fibrosis. Survival for > 3 years was reported in 67% (41 of 62) of subjects, and 13 of the surviving subjects lived 10 to 24 years on treatment.
SAFETY	Not specified.

Peroxisomal Disorders

Cholbam was effective in 46% of patients with peroxisomal disorders, including Zellweger spectrum disorders, in a long-term, uncontrolled, open-label study.

STUDY DESIGN	Nonrandomized, open-label, uncontrolled trial (n=29), followed by an extension that included 10 previous patients plus 2 new patients (n=12).
INCLUSION CRITERIA	Patients with peroxisomal disorders and an abnormal urinary bile acid.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were treated with Cholbam 10 to 15 mg/kg/day over an 18- year period, with most patients also receiving docosahexaenoic acid (DHA) and vitamins A, D, E, and K. Eighty percent of patients were younger than 2 years at the start of treatment (range, 3 weeks to 10 years) and the

	average length of treatment was 4.8 years.
RESULTS	Of 24 evaluable patients, 46% responded to Cholbam treatment. Response was determined by a combination of lab values (AST/ALT reduction, total bilirubin level of 1 mg/dL or less, no cholestasis on liver biopsy) and clinical outcomes (increased body weight, survival > 3 years). Pre- and post-treatment biopsies (n=9) were generally unchanged. Survival for > 3 years was reported in 42% (13 of 31) of subjects, and 8 of the surviving subjects lived 10 to 17 years on treatment. This was not found to be an improvement compared with historical controls.
SAFETY	Not specified.

Contraindications [(1)]

- None

Warnings and Precautions [(1)]

- Newly diagnosed or family history of familial hypertriglyceridemia associated with poor cholic acid absorption; dose adjustment recommended.
- Worsening liver function (eg, elevated bilirubin, worsening serum transaminases or cholestasis) has been reported; monitoring recommended; discontinue use if occurs.
- Concurrent elevations of serum gamma glutamyltransferase (GGT) and ALT may indicate overdose.
- Avoid concomitant cyclosporine and other inhibitors of the bile salt efflux pump.

Adverse Effects [(1)]

The most common adverse event in clinical trials was diarrhea (2%).

Drug Interactions [(1)]

- Aluminum-based antacids
- Bile acid binding resins: cholestyramine, colestipol, colesevelam
- Bile salt efflux pump inhibitors: cyclosporine

Dosage and Administration [(1)]

The recommended dose in children (3 weeks and older) and adults is 10 to 15 mg/kg orally with food once daily or in 2 divided doses; adjust based on clinical response. Concomitant familial hypertriglyceridemia: 11 to 17 mg/kg/day. Take capsules at least 1 hour before or 4 to 6 hours after a bile acid binding resin or aluminum-based antacid.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST*/ DOSE
Cholic Acid	Cholbam	Manchester	50 mg capsules	1 capsule daily	$275.83
			250 mg capsules	1 capsule daily	$830

* Wholesale Acquisition Cost

Conclusion

Cholbam™ is a once daily bile acid replacement therapy that is indicated for bile acid synthesis disorders caused by a single enzyme defect, and as an adjunct for treating peroxisomal disorders (including Zellweger spectrum disorders) when liver disease manifestations, steatorrhea, or complications due to decreased absorption of fat soluble vitamins are present. Safety and efficacy for treating extrahepatic symptoms of these disorders have not been established. Cholbam™ demonstrated efficacy in a nonrandomized, open-label, uncontrolled trial that included 50 patients with bile acid synthesis disorders due to single enzyme defects and 29 patients with peroxisomal disorders, including Zellweger spectrum disorders, which was followed by an extension trial. Patients were followed for more than 18 years. Response was evident in 64% of patients with bile acid synthesis disorders and 46% of patients with peroxisomal disorders, with survival for > 3 years in 67% and 42%, respectively. The most common adverse effect during the trial was diarrhea.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List as non-preferred

References

1. Product Information: Cholbam™, cholic acid capsules. Asklepion Pharmaceuticals LLC, Baltimore, MD, 03/2015.
2. Lowes, Robert. Cholbam Approved for Rare Metabolic Disorders. Retrieved 8/31/2015 from: http://www.medscape.com/viewarticle/841664

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