

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

205750Orig1s000

OFFICE DIRECTOR MEMO

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 23, 2015

FROM: Julie Beitz, MD

SUBJECT: Addendum to March 17, 2015 Review

NDA 205750 Cholbam (cholic acid) capsules
Asklepion Pharmaceuticals, LLC
Bile Synthesis Disorders due to Single Enzyme Defects
Peroxisomal Disorders, including Zellweger spectrum disorders

Summary

The submitted studies in NDA 205750 were single arm trials in which on-treatment measurements of efficacy were compared to baseline measurements. The reference to these studies as “uncontrolled” on pp. 4 and 14 of my previous review dated March 17, 2015, should not be construed that efficacy was assessed on the basis of isolated measurements, without comparison to baseline measurements.

Product labeling will be revised to replace “uncontrolled” with “single arm” as descriptors of Trial 1 in the **Adverse Reactions** Section, **Clinical Trials Experience** subsection (6.1) and in the **Clinical Studies** Section, **Bile Acid Synthesis Disorders due to Single Enzyme Defects** subsection (14.1). Analogous changes have been made to FDA’s press release dated March 17, 2015, announcing the approval of the Cholbam NDA.

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/s/

JULIE G BEITZ
03/23/2015

MEMORANDUM

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DATE: March 17, 2015

FROM: Julie Beitz, MD

SUBJECT: Approval Action for NDA 205750 Cholbam (cholic acid) capsules
Asklepion Pharmaceuticals, LLC
Bile Synthesis Disorders due to Single Enzyme Defects
Peroxisomal Disorders, including Zellweger spectrum disorders

Summary

Cholbam (cholic acid) is a primary bile acid that has been used in patients with cholic acid deficiency states that can arise from inherited defects in enzymes involved in bile acid synthesis, including 3 β -HSD, AKR1D1, CYP27A1 or AMACR, and in peroxisomal disorders, including Zellweger spectrum disorders. In these patients, interruption of bile acid synthesis pathways leads to a deficiency of primary bile acids. Bile acid deficiency, in turn, leads to cholestasis and reduced bile flow, malabsorption of dietary fat and fat-soluble vitamins, and a lack of the physiologic down-regulation of bile acid synthesis. Thus, potentially hepatotoxic abnormal (“atypical”) bile acids specific to the enzyme defect accumulate in the liver and are detectable in serum and urine. Fat malabsorption leads to impaired growth and failure to thrive. There are no drug products approved for treatment of these disorders.

The applicant presented favorable outcomes in cholic acid-responsive patients with single enzyme defects (from submitted and published case reports), including improvement or normalization of laboratory parameters of liver function, weight gain, resolution of steatorrhea and hepatosplenomegaly, achievement of developmental milestones, sexual maturation including successful pregnancy, and prolonged survival. These outcomes are consistent with the expected actions of exogenous cholic acid in patients with cholic acid deficiency and support Cholbam’s effectiveness in this population.

The applicant also presented favorable outcomes in cholic acid-responsive patients with peroxisomal disorders, including Zellweger spectrum disorders (from submitted and published case reports), including improvement or normalization in laboratory parameters of liver function, weight gain, improvement in developmental milestones, and prolonged survival. These outcomes are consistent with the expected actions of exogenous cholic acid in patients with cholic acid deficiency, and are also consistent with the favorable outcomes observed in patients with single enzyme defects. Taken together, these findings support Cholbam’s effectiveness in this population, albeit as adjunctive therapy, as most patients with peroxisomal disorders will also receive concomitant DHA (docosahexaenoic acid) and fat-soluble vitamin supplementation.

Extrahepatic pathology can be observed in patients with certain single enzyme defects and peroxisomal disorders. For example, conversion of atypical bile acid intermediates to cholestanol in extrahepatic tissues can lead to excess deposition in various organs, including the CNS, in patients with sterol 27-hydroxylase deficiency (also known as cerebrotendinous xanthomatosis, CTX). In patients diagnosed

with neonatal adrenoleukodystrophy (NALD), peroxisomal function is impaired leading to accumulation of very long chain fatty acids in neuronal cell membranes and neurologic injury. To date, the safety and effectiveness of Cholbam on extrahepatic manifestations of bile acid synthesis disorders due to single enzyme defects or peroxisomal disorders including Zellweger spectrum disorders have not been established. This finding will be reflected as a **Limitation of Use** in the **Indications and Usage** Section of product labeling.

The lower rates of response and survival observed in patients with peroxisomal disorders (relative to patients with single enzyme defects) may reflect complications related to extrahepatic manifestations of disease and/or more severe biochemical abnormalities (e.g., absence of peroxisomes vs. a defect in a single enzyme) which can negatively impact the patient's overall clinical course, growth trajectory and prospect for survival. In a mouse model of Zellweger syndrome, bile acid feeding reduced the number of cholestatic deposits in bile ducts and alleviated cholangitis, but exacerbated the degree of hepatic steatosis, and mitochondrial and cellular damage in the peroxisome-deficient livers of these animals. The clinical significance of these findings remains unclear.

A postmarketing observational study will be required to assess the long-term safety of cholic acid treatment in patients with bile acid synthesis disorders due to single enzyme defects and peroxisomal disorders. In addition, to ensure that the potential risks of cholic acid treatment are reasonably managed in the postmarket setting, product labeling will contain the following statements:

- **Dosage and Administration, Treatment Monitoring:**
 - Treatment with Cholbam should be initiated and monitored by an experienced hepatologist or pediatric gastroenterologist.
 - Discontinue treatment with Cholbam if liver function does not improve within 3 months of the start of treatment.
- **Warnings and Precautions, Exacerbation of Liver Impairment:**
 - Monitor liver function and discontinue Cholbam if liver function worsens while on treatment.

I conclude that the benefits of exogenous cholic acid treatment outweigh the potential risks for patients with bile acid synthesis disorders due to single enzyme defects and peroxisomal disorders, including Zellweger spectrum disorders. This memo documents my recommendation for approval of NDA 205750 for Cholbam (cholic acid) capsules: 1) for the treatment of bile acid synthesis disorders due to single enzyme defects, and 2) for adjunctive treatment of peroxisomal disorders, including Zellweger spectrum disorders, in patients who exhibit manifestations of liver disease, steatorrhea or complications from decreased fat-soluble vitamin absorption.

Dosing

The recommended dosage for oral Cholbam is 10-15 mg/kg administered daily either as a single dose or as two divided doses. Two capsule strengths are available: 50 mg and 250 mg. Cholbam can be taken with food.

Hepatic function should be monitored every month for the first 3 months, every 3 months for the next 9 months, every 6 months during the subsequent three years and annually thereafter. More frequent

monitoring should be undertaken during periods of rapid growth, concomitant disease, and pregnancy. The lowest dose of Cholbam that effectively maintains hepatic function should be chosen.

Treatment with Cholbam should be discontinued if hepatic function does not improve within 3 months of the start of treatment, or at any time if there are persistent clinical or laboratory indicators of worsening hepatic function or cholestasis. Concurrent elevations of serum GGT and ALT may indicate Cholbam overdose.

Regulatory History

Over 12,000 patients world-wide with idiopathic liver disease have been screened at Cincinnati Children's Hospital Medical Center (CCHMC) by evaluation of serum and urinary bile acid profiles using FAB-MS (fast atom bombardment – mass spectrometry) analysis. Between 1987 and 2013, approximately 250 cases of bile acid synthesis disorders were identified. Since January 1992, patients with these disorders have received oral cholic acid, either under the direct care of Drs. James Heubi and Kenneth Setchell at CCHMC or under the care of physicians in their home country.

In June 1994, Drs. James Heubi and Kenneth Setchell submitted IND 45,470 providing for oral cholic acid treatment in patients with bile acid synthesis disorders due to single enzyme defects (Study CAC-91-10-10). Patients with a variety of enzyme defects were treated, including those diagnosed with 3 β -HSD, AKR1D1, sterol 27-hydroxylase (CTX), and AMACR deficiency.

In addition, patients with a variety of peroxisomal disorders received oral cholic acid treatment under Study CAC-92-8-19, including those diagnosed with Zellweger syndrome, neonatal adrenoleukodystrophy (NALD) and infantile Refsum disease (IRD). There was no final visit planned for these studies as treatment was expected to be life-long. For regulatory reporting purposes, the data collection cut-off date for these studies was specified as December 31, 2009.

On July 18, 2003, Cholbam was granted Orphan designation for “treatment of inborn errors of cholesterol and bile acid synthesis and metabolism”. On May 6, 2007, ownership of the IND was transferred to Asklepiion Pharmaceuticals, LLC (hereafter referred to as Asklepiion). In anticipation of future commercialization of the product, Asklepiion contracted to produce a new capsule formulation under GMPs that would replace earlier formulations produced by the CCHMC Pharmacy.

In accordance with advice provided by FDA that an *in vivo* bioequivalence study would be needed to compare the pharmacokinetic profiles of the clinical formulations and the to-be-marketed (TBM) formulation of cholic acid, Asklepiion contracted with Frontage Clinical Services, Inc., to conduct Study CAC-003-01 in healthy male volunteers. This was a Phase I single center study conducted to compare the CCHMC Pharmacy formulation used in Study CAC-91-10-10 to an oral solution and to the TBM formulation. Form 483 was issued following OSI’s inspection conducted May 12 to 20, 2014. Inspectors found that the study site was in violation of 21 CFR (b) (4)

Nevertheless, OSI has recommended that data generated by Frontage for Study CAC-003-01 not be accepted for Agency review.

In 2010, bridging Study CAC-001-01 was conducted in 16 patients with single enzyme defects (15 previously enrolled in Study CAC-91-10-10 and one treatment naive patient diagnosed with 3 β -HSD) to assess the short-term impact on efficacy and safety of switching from the CCHMC capsule formulation to

the TBM formulation of cholic acid. This study provided evidence of therapeutic equivalence of the two formulations.

Study CAC-002-01 was initiated on January 1, 2010 as a continuation study to allow patients to receive treatment with the TBM formulation. This study enrolled 45 patients: 1) 21 patients with single enzyme defects previously treated with the CCHMC formulation on Study CAC-91-10-10, 2) 10 patients with peroxisomal disorders previously treated on Study CAC-92-8-19, and 3) 14 additional treatment naïve patients (12 with single enzyme defects and 2 with peroxisomal disorders). This study is currently ongoing and is expected to close following US marketing approval of Cholbam.

An application for marketing authorization for cholic acid FGK capsules (tradename Kolbam, (b) (4) Cholbam) was submitted by the FGK Representative Service GmbH to EMA on February 29, 2012. Although the conduct of Study CAC-91-10-10 and Study CAC-92-8-19 was subject to IRB approval, these studies were not conducted according to currently applied GCP guidelines. During the course of EMA's review (b) (4), Asklepiion conducted extensive re-monitoring of study data (including patient charts, screening logs, adverse events, laboratory findings, and study medications) with the result that additional patients could be included in analyses of efficacy and safety. In January 2014, the CHMP adopted a positive opinion for granting a Marketing Authorization under exceptional circumstances to cholic acid FGK for the treatment of patients diagnosed with sterol 27-hydroxylase (CTX), AMACR and CYP7A1 deficiencies based on the results of Study CAC-91-10-10 and interim data from Study CAC-002-01, supported by literature reports. The product has been marketed since April 2014.

In Europe, Laboratoires CTRS' cholic acid capsules (tradename Orphacol) received marketing authorization in September 2013 for the treatment of patients diagnosed with 3 β -HSD and AKR1D1 deficiencies based on safety and efficacy information obtained from literature reports.

On November 21, 2013, NDA 205750 was submitted and granted a priority review. The applicant sought approval for bile acid synthesis disorders due to single enzyme defects and peroxisomal disorders, including Zellweger spectrum disorders. The review clock was extended three months due to major amendments received on January 24, 2014 and February 14, 2014 containing requested information on measurement of urinary atypical bile acid intermediates. On March 21, 2014, interim safety data from Study CAC-002-01 were submitted with the 120-day safety update, with a data cut-off date of November 30, 2013. On January 7, 2015, interim efficacy data from Study CAC-002-01 were submitted, with a data cut-off date of September 30, 2012.

The uncontrolled design of the submitted studies and incomplete data collection, especially of earlier Studies CAC-91-10-10 and CAC-92-8-19, limited the assessment of efficacy and adverse events. In its interim report for Study CAC-002-01, Asklepiion reported that since November 2010 it has performed auditing and monitoring programs as well as onsite training to enhance the quality of data collection over previous efforts which did not meet GCP guidelines.

Three Center-level briefings were held during the course of this review (September 11, 2014, November 3, 2014 and December 9, 2014) to discuss the efficacy and safety of cholic acid treatment in patients with disorders of bile acid synthesis, and the approvability of the two indications sought. An FDA advisory committee was not convened as outside expertise was not deemed necessary. Action on the application was delayed past the PDUFA goal date of October 21, 2014, so that safety and efficacy information from continuation Study CAC-002-01 could be reviewed and described in product labeling.

Description

Cholbam (cholic acid) capsules contain 50 mg or 250 mg of cholic acid as the active ingredient in size 2 Swedish orange or size 0 white opaque gelatin capsules, respectively.

Cholic acid is a new molecular entity. Sufficient information regarding raw materials, manufacturing process and controls, and stability has been submitted to ensure that the drug substance and drug product have been adequately characterized.

Nonclinical Findings

Carcinogenicity, genetic toxicology, and nonclinical fertility studies have not been performed with cholic acid.

The *PEX2*^{-/-} mouse model of Zellweger syndrome offers the opportunity to characterize biochemically the progression of hepatic disease and the effects of bile acid feeding.¹ Feeding with a combination of cholic acid and ursodeoxycholic acid normalized C₂₄ bile acid concentrations in bile to that of untreated control animals. Although growth was only mildly improved, there was near complete normalization of stool fat content, resolution of steatorrhea, and improved survival. Bile acid feeding reduced the number of cholestatic deposits in bile ducts and alleviated cholangitis, but exacerbated the degree of hepatic steatosis and mitochondrial and cellular damage in the peroxisome-deficient livers of these animals.

Total hepatic lipids analysis found a 1.75-fold increase in untreated *PEX2*^{-/-} mouse livers compared with control animals, and an additional 2-fold increase in bile acid-fed mutants. *PEX2*^{-/-} mouse livers demonstrated mitochondrial abnormalities which persisted with bile acid feeding. The efficacy of bile acid feeding in these animals is limited by changes in bile acid transporter (BSEP) expression that limit hepatic excretion of bile acids, persistent canalicular damage, and limits to bile acid conjugation capacity. There can be increased mitochondrial autophagy and hepatocellular necrosis. Compared to mice deficient in the peroxisomal enzyme, α -methylacyl-CoA racemase (AMACR), which have a similar degree of accumulation of C₂₇-bile acid intermediates and have C₂₇ conjugation defects, *PEX2*^{-/-} mice have more widespread peroxisomal defects that can produce more severe biochemical disturbances and increase the potential for greater toxicity to bile acid feeding.

Clinical Pharmacology²

I. Regulation of Bile Acid Synthesis and Bile Flow

1. General Overview

Cholic acid, one of two primary bile acids, is synthesized *de novo* in the liver from cholesterol; the rate limiting enzyme involved is CYP7A1 (cholesterol 7- α hydroxylase). In the liver, cholic acid is conjugated with glycine and/or taurine and actively secreted into bile by transporters localized in the canalicular

¹ Keane MH, Overmars H, Wikander TM, Ferdinandusse S, Duran M, Wanders RJA, Faust PL. Bile acid treatment alters hepatic disease and bile acid transport in peroxisome-deficient *PEX2* Zellweger mice. *Hepatology* 2007; 45:982-997.

² Information in this section was prepared for the Center-level briefing dated December 9, 2014.

membrane, notably BSEP (bile salt export pump), and then released into the small intestine. The canalicular secretion of bile acids via BSEP is the rate-limiting step in enterohepatic circulation.

In the intestine, bile acids modulate the release of pancreatic secretions and gastrointestinal peptides, and activate enzymes required for the absorption of fat-soluble vitamins. The detergent effects of bile acids also assist in the solubilization of cholesterol and dietary fats in the intestine.

Intraluminal bile acids are absorbed in the ileum, returned to the liver via the portal circulation and taken up by hepatocytes via transporters localized in the sinusoidal membrane, notably NCTP (Na⁺/taurocholate cotransporting polypeptide) and OATP (organic anion transport protein), thus forming an enterohepatic circuit. See schematic below from Wanders and Ferdinandusse (2012).³

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Under normal conditions, the levels of bile acids in the liver are kept low in order to prevent deleterious effects of bile acid intermediates on hepatocellular processes. The expression of CYP7A1 and BSEP is coordinately regulated by multiple transactivation pathways, notably the bile acid/farnesoid X receptor (FXR) signaling pathway. Bile acids, acting as FXR agonists, strongly **repress CYP7A1 expression** through

³ Wanders RJA and Ferdinandusse S. Peroxisomes, peroxisomal diseases, and the hepatotoxicity induced by peroxisomal metabolites. *Current Drug Metabolism* 2012; 13:1401-1411.

a negative feedback circuit involving SHP and LHR1⁴, whereas bile acids markedly **induce BSEP expression** by activating FXR. Such coordinated feedback and feed-forward regulation of CYP7A1 and BSEP by bile acids prevent excessive accumulation of toxic bile acid intermediates in hepatocytes and promote excretion of bile acids into the bile thereby stimulating bile flow.⁵

An alternate mechanism by which bile acids down-regulate their own synthesis involves the intestinal enterocyte. Here, binding of bile acids to FXR leads to the production of fibroblast growth factor 15 (FGF15). FGF15 is transported to the liver via the circulation; intracellular signaling pathways triggered in the liver give rise to **inhibition of CYP7A1 gene transcription**.

Expression of the sinusoidal transporter, NTCP, is down-regulated by bile acid intermediates thereby decreasing uptake of bile acids by hepatocytes.

2. Bile Acid Synthesis Pathways

In the “classical” pathway, bile acid synthesis begins with the conversion of cholesterol to 7 α -hydroxycholesterol by cholesterol 7 α -hydroxylase or CYP7A1. This microsomal cytochrome P450 enzyme is localized exclusively in the liver and its expression is highly regulated. The classical pathway accounts for 90% of total bile acid synthesis.⁶

The next step in bile acid synthesis is catalyzed by the microsomal 3 β -HSD (3 β -hydroxy- Δ^5 -C₂₇-steroid oxidoreductase) which can only handle 7 α -hydroxylated intermediates. At this point, any intermediates acted upon by sterol 12 α -hydroxylase or CYP8B1, another microsomal cytochrome P450, are destined to become cholic acid, otherwise they will go on to form chenodeoxycholic acid.

After a series of additional enzymatic reactions, mitochondrial sterol 27-hydroxylase or CYP27A1 catalyzes the formation of the R isomers of the C₂₇-bile acid intermediates, THCA and DHCA.⁷ The R isomers are transported into the peroxisome and converted to their respective S isomers by α -methylacyl-CoA racemase (AMACR), a peroxisomal enzyme; the S isomers are then subjected to beta-oxidation in the peroxisome.

The final step in bile acid synthesis involves conjugation with an amino acid (taurine or glycine) catalyzed by BAAT (bile acyl-CoA: amino acid *N*-acyltransferase). BAAT is localized in peroxisomes and the cytosol. Thus, peroxisomal BAAT is responsible for conjugation of newly synthesized primary bile acids in the peroxisome, whereas cytosolic BAAT is involved in the re-conjugation of the recycled bile acids that were de-conjugated in the intestine. Conjugated bile acids are more hydrophilic and less cytotoxic than their unconjugated forms. Under normal conditions, unconjugated bile acids make up only a small proportion of bile acids in bile.

⁴ The “classical” negative feedback cascade involves bile acids binding to FXR which in turn activates transcription of *SHP* (short heterodimeric partner). *SHP* then inhibits transcription of *LRH1*, the gene coding for the liver receptor homologue 1. *LRH1* normally transactivates CYP7A1.

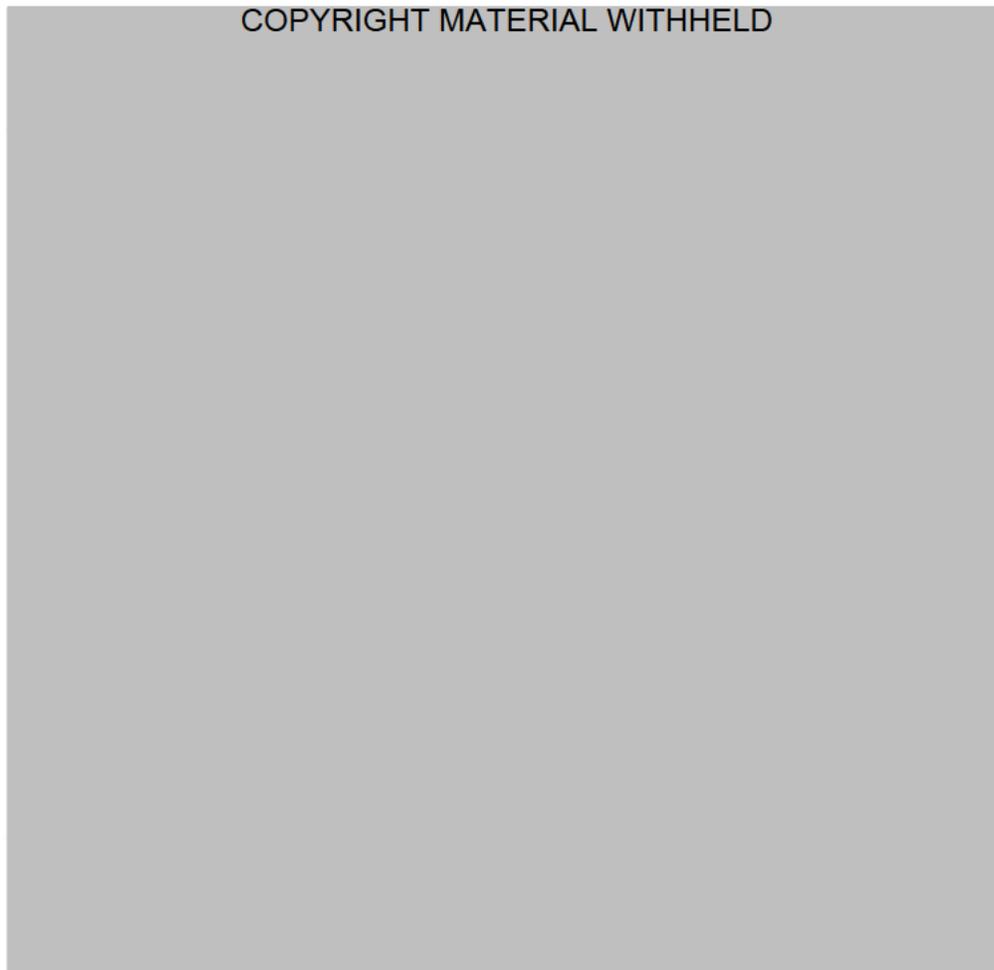
⁵ Song X, Kaimal R, Yan B, Deng R. Liver receptor homolog 1 transcriptionally regulates human bile salt export pump expression. *J Lipid Res* 2008; 49(5):973-84.

⁶ The alternative “acidic” pathway is responsible for the remainder of bile acid synthesis; oxysterols rather than cholesterol serve as substrates for 7 α -hydroxylation. Enzymes involved in this pathway include CYP27A1. This pathway produces mainly chenodeoxycholic acid, is the major pathway for bile acid synthesis in the first year of life, and is involved in the control of cholesterol levels in extrahepatic tissues, particularly in the nervous system.

⁷ THCA is (25R) 3 α ,7 α ,12 α -trihydroxy-5 β -cholestanoic acid; DHCA is (25R)3 α ,7 α ,12 α -dihydroxy-5 β -cholestanoic acid.

After conjugation, “mature” C₂₄-bile acids are transported out of the peroxisome, and then out of the hepatocyte into bile via BSEP. In livers of normal subjects, total C₂₇-bile acid intermediates amounted to only 2 nmol/gr wet weight vs. a total mature C₂₄-bile acid wet weight of 52 nmol/gr.⁸

The schematic below adapted from Ferdinandusse and Houten (2006) depicts the enzymatic pathways involved in bile acid synthesis.⁹ Known enzyme defects are shown by solid bars over the arrows. Atypical bile acid intermediates specific to each defect form above the block. In patients with non-functional peroxisomes, or defects in peroxisomal enzymes, C₂₇-bile acid intermediates (THCA and DHCA) can accumulate.



II. Bile Acid Deficiency States

1. Pathophysiology

⁸ Ferdinandusse S, Denis S, Faust PL, Wanders RJA. Bile acids: the role of peroxisomes. *J Lipid Res* 2009; 50:2139-2147.

⁹ Ferdinandusse S and Houten SM. Peroxisomes and bile acid synthesis. *Biochimica et Biophysica Acta* 2006; 1763:1427-1440.

Patients with inherited single enzyme defects in bile acid synthesis and those with peroxisomal disorders (involving peroxisomal enzyme defects or non-functional peroxisomes) fail to synthesize the primary bile acids (cholic acid and chenodeoxycholic acid). This can lead to:

- **Reduction in bile flow.** The secretion of bile by the liver is driven by the pumping of bile acids into the canaliculi. When there is a failure to synthesize the primary bile acids, bile flow is reduced leading to cholestasis and retention of compounds normally excreted in the bile.
- **Fat malabsorption.** Bile acids are detergents and are needed in the intestine for digestion and absorption of fat and fat-soluble vitamins. In this role, the taurine and glycine conjugates of cholic acid and chenodeoxycholic acid are more efficient than other bile acids. Fat malabsorption can lead to steatorrhea, failure to thrive and deficiencies of fat-soluble vitamins (most commonly manifested as rickets, and vitamin E and K deficiencies).
- **Lack of the physiologic down-regulation of bile acid synthesis.** Atypical bile acids that accumulate as a result of single enzyme defects may function poorly as FXR agonists, failing to repress CYP7A1 expression allowing for the sustained production of high concentrations of atypical bile acid intermediates.

As a result, there is accumulation of:

- **Potentially hepatotoxic atypical bile acid intermediates in the liver.** Liver pathology usually involves giant cell hepatitis and steatosis; extramedullary hematopoiesis may be present.
- **Atypical bile acid intermediates in extrahepatic tissues.** Conversion of atypical bile acid intermediates to cholestanol in extrahepatic tissues can lead to excess deposition in various organs, including the CNS, as seen in patients with defects in CYP27A1 function in CTX.
- **Very long chain fatty acids in the CNS.** In patients with neonatal adrenoleukodystrophy (NALD), peroxisomal function is impaired leading to accumulation of very long chain fatty acids in neuronal cell membranes and neurologic injury.

2. Common Single Enzyme Defects of Bile Acid Synthesis

3 β -hydroxy- Δ^5 -C₂₇-steroid oxidoreductase (3 β -HSD) and Δ^4 -3-oxosteroid 5 β -reductase (Δ^4 -3-oxo-R or AKR1D1) defects. These are rare autosomal recessive diseases and the most frequent inborn errors of primary bile acid synthesis causing early cirrhosis and liver failure. They result from dysfunction of 3 β -HSD and AKR1D1, respectively, which leads to the hepatic accumulation of atypical bile acid intermediates that cannot be transported across the canalicular membrane; rather they are excreted in urine. The presence of atypical bile acid intermediates, specific for each defect, concomitant with a lack of primary bile acids in the urine and serum is the basis for diagnosis of these genetic defects. Of note, pruritus is absent, and serum GGT activity is normal.¹⁰ Thus, there is both a failure to synthesize adequate amounts of cholic acid, and unregulated production of cholestatic atypical bile acid intermediates that accumulate proximal to the enzyme defect. Recently, two of the atypical bile acid intermediates arising from a defect in 3 β -HSD function were shown to be unable to function as FXR agonists and exert the hepatoprotective effects which are efficiently coordinated by primary bile acids under normal conditions. Their inability to repress CYP7A1 expression could account for the sustained

¹⁰ Bile acids facilitate the detachment of GGT from the canalicular membrane. Thus, if there are reduced amounts of bile acids entering the canaliculi, as in disorders of bile acid synthesis (unlike other causes of cholestasis), soluble GGT is not released and plasma GGT is not elevated.

production of high concentrations of atypical bile acid intermediates.¹¹ Steatorrhea and fat-soluble vitamin deficiencies result from the reduced levels of intraluminal cholic acid in these patients.¹²

Cerebrotendinous xanthomatosis (CTX). This is a rare autosomal recessive disease caused by a defect in CYP27A1 function which results in reduced bile acid synthesis and tissue accumulation of cholestanol. Patients presenting in early infancy can have cholestatic liver disease which may be fatal. Clinical manifestations in older children are related to the presence of cholestanol deposits and can include tendon xanthomas, learning difficulties (low IQ) or psychiatric illness. Adults may present with spastic paraparesis (due to spinal xanthomas), falling IQ and frank dementia with ataxia and seizures or peripheral neuropathy. Adults may also experience premature atherosclerosis and coronary heart disease, and early onset osteoporosis.¹³

3. Peroxisomal Single Enzyme Defects

AMACR defect. Although most patients with a defect in AMACR function present in adolescence with a neuropathy resembling that of Refsum disease, two siblings presenting in the first weeks of life have been described.¹⁴ The index (female) patient presented with cholestatic liver disease, coagulopathy and malabsorption of fat-soluble vitamins; the deceased (male) patient presented with cholestatic liver disease, coagulopathy and died of a subdural hematoma. His liver was harvested for orthotopic transplantation; the recipient developed the same urinary bile acid profile (elevated levels of THCA) as the donor's sister.

A defect in AMACR function results in accumulation of the R isomers of C₂₇-bile acid intermediates (THCA and DHCA) which are more hydrophobic than their C₂₄-products, and less efficiently conjugated and excreted into the bile. These factors contribute to the retention of these intermediates in the liver, cholestasis and, consequently, to hepatic injury. Moreover, C₂₇-bile acid intermediates are more hepatotoxic than mature C₂₄-bile acids.¹⁵ In addition, the primary bile acid substrates for BSEP are low in concentration, thus limiting bile flow; concentrations of C₂₄-bile acid measured from duodenal aspirates are decreased. Reduced intraluminal bile acid concentrations, in turn, lead to malabsorption of dietary fat and fat-soluble vitamins.¹⁶

4. Zellweger Spectrum Disorders

These inherited disorders include Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD) and have overlapping clinical, biochemical and genetic phenotypes. The failure to form functional peroxisomes is common to all these disorders. Clinically, patients have

¹¹ Gioiello A, Cerra B, Zhang W, Vallerini GP, Constantino G, DeFranco F, Passeri D, Pellicciari R, Setchell KD. Synthesis of atypical bile acids for use as investigative tools for the genetic defect of 3 β -hydroxy- Δ^5 -C₂₇-steroid oxidoreductase deficiency. *J Steroid Biochemistry & Molecular Biology* 2014; 144:348-360.

¹² Gonzales E, Gerhardt MF, Fabre M, Setchell KD, Davit-Spraul A, Vincent I, Heubi JE, Bernard O, Jacquemin E. Oral cholic acid for hereditary effects of primary bile acid synthesis: A safe and effective long-term therapy. *Gastroenterology* 2009; 137:1310-1320.

¹³ Clayton PT. Disorders of bile acid synthesis. *J Inherit Metab Dis* 2011; 34:593-604.

¹⁴ Setchell KDR, Heubi JE, Bove KE, O'Connell NC, Brewsaugh T, Steinberg SJ, Moser A, Squires Jr RH. Liver disease caused by failure to racemize trihydrocholestanic acid: Gene mutation and effect of bile acid therapy. *Gastroenterology* 2003; 124:217-232.

¹⁵ Ferdinandusse et al. 2009

¹⁶ Setchell et al. 2003

cognitive and motor dysfunction, retinopathy, sensorineural hearing impairment, hepatic involvement, and growth failure.

A published report of the natural history of 31 patients with Zellweger spectrum disorders who survived beyond one year found that long-term survival was possible. Nine patients died at a mean age of 8 years (range 1.2 to 22.5 years) from a variety of causes including respiratory problems, dehydration and shock, and renal failure. One patient died of liver failure and another from gastrointestinal bleeding due to gastric varices.¹⁷

Zellweger syndrome (ZS). Patients diagnosed with Zellweger syndrome exhibit a wide variety of abnormalities involving multiple organs, including the liver. Hepatomegaly was reported in 78% of 114 patients; histology varied from near normal to diffuse fibrosis and micronodular cirrhosis depending on the age of the patient.¹⁸ Invariably, there is distortion of mitochondria and either total absence or a severe reduction in peroxisomes in the liver. There is accumulation of hepatotoxic R and S isomers of C₂₇-bile acid intermediates, due to the block in beta-oxidation to mature C₂₄-bile acids. In livers of ZS patients, total C₂₇-bile acid intermediates amounted to 63.5 nmol/gr wet weight vs. a total C₂₄-bile acid wet weight of 16.7 nmol/gr.¹⁹ As noted above, C₂₇-bile acid intermediates are less efficiently conjugated and excreted into the bile, and more hepatotoxic than mature C₂₄-bile acids.

Accumulation of C₂₇-bile acid intermediates also occurs in other organs, including the brain. Serum levels of these intermediates range from normal to 50-fold higher than normal; urine levels are also elevated. In contrast, biliary bile acid concentrations measured in duodenal aspirates are decreased.²⁰

Neonatal adrenoleukodystrophy (NALD) and infantile Refsum disease (IRD). NALD and IRD are considered milder forms of the Zellweger disease spectrum. Patients with NALD, IRD and less severe presentations of ZS (i.e., patients surviving more than 1 year) have generally lower serum levels of C₂₇-bile acid intermediates and less cholestasis.²¹

NALD is characterized by the accumulation of very-long-chain fatty acids (VLCFA) resulting from a β -oxidation defect caused by mutations in the *ABCD1* gene, the gene encoding the peroxisomal enzyme ABCD1 (ATP-binding cassette [ABC] transporter subfamily D member 1). ABCD1 transports CoA-activated VLCFA from the cytosol into the peroxisome for degradation.

While dysfunction of peroxisomal beta-oxidation results in accumulation of VLCFA in all tissues, clinically NALD primarily affects the nervous system and the adrenal glands. The typical manifestation of mutations in *ABCD1* is adrenomyeloneuropathy, a slowly progressive dying-back axonopathy affecting both ascending and descending spinal cord tracts as well as in some cases, a peripheral neuropathy. In about 60% of male patients, either in childhood (35-40%) or in adulthood (20%), an initial, clinically silent, myelin destabilization results in conversion to a devastating, rapidly progressive form of cerebral inflammatory demyelination.

¹⁷ Poll-The BT, Gootjes J, Duran M, de Klerk JBC, Maillette de Buy Wenniger-Prick LJ, Admiraal RJC, Waterham HR, Wanders RJA, Barth PG. Peroxisome biogenesis disorders with prolonged survival. *American Journal of Medical Genetics* 2004; 126A:333-338.

¹⁸ Wanders RJA, Heymans HSA, Schutgens RBH, Barth PG, van den Bosch H, Tager JM. Peroxisomal disorders in neurology. *J Neurol Sci* 1988; 88:1-39.

¹⁹ Ferdinandusse et al. 2009

²⁰ Ferdinandusse and Houten, 2006

²¹ Ibid.

In IRD the function of peroxisomal enzyme, phytanoyl-CoA 2-hydroxylase, which catalyzes the conversion of phytanic acid to pristanic acid, is defective; phytanic acid accumulates in tissues. The clinical signs of the disease include retinitis pigmentosa, cerebellar ataxia and polyneuropathy, whereas liver abnormalities are rarely reported.

Efficacy of Exogenous Oral Cholic Acid Treatment

I. Literature Reports

In the published literature, beneficial effects of exogenous cholic acid treatment have been described in patients with bile acid synthesis disorders due to single enzyme defects, and in patients with AMACR defects or Zellweger spectrum disorders. These effects are summarized below.

1. **Administration of exogenous cholic acid restores the physiologic feedback inhibition on bile acid synthesis** thereby reducing the formation of potentially hepatotoxic atypical bile acid intermediates. As noted above, primary bile acids are more effective than atypical bile acid intermediates in down-regulating their own biosynthesis via activation of the nuclear receptor farnesoid X receptor (FXR).

In 15 patients with either 3 β -HSD or AKR1D1 deficiency on chronic cholic acid treatment (median 12.4 years), excretion of total urinary bile acid, and specific intermediates was reduced; urinary excretion was predominantly cholic acid and its metabolite, deoxycholic acid. All 9 patients with pre-existing jaundice experienced resolution, and 14 of 15 patients experienced resolution of hepatosplenomegaly. Liver biochemistries normalized in all patients. In 14 patients, liver histology showed resolution of cholestasis and inflammation and a decrease or reversal of the extent of liver fibrosis and cirrhosis.²²

A patient with a defect in AKR1D1 who initiated cholic acid therapy at 8 months of age (at a dose of 10 mg/kg/day) was reported to be alive and well.²³ The authors noted that AKR1D1 patients with an INR greater than 1.4 did not respond to bile acid treatment and died or were transplanted. The authors also noted that cholic acid had been used successfully in the treatment of cholestatic liver disease in patients with CTX but no details were provided; they noted that there is no information on the effectiveness of cholic acid in treating neurologic manifestations in patients with CTX.

The case report of a child with AMACR deficiency²⁴ treated with cholic acid for 7 years noted reduction of C₂₇ bile acid intermediates in urine, and normalization of liver function and fat-soluble vitamin status, without the need for supplementation.

The first report of treatment with cholic acid (and concomitant chenodeoxycholic acid) in a 6 month old patient with Zellweger syndrome noted improvement in liver function and liver histology, and reduction in serum and urinary C₂₇-bile acid intermediates.²⁵ Despite these

²² Gonzales et al. 2009

²³ Clayton PT. Disorders of bile acid synthesis. *J Inherit Metab Dis* 2011; 34:593-604.

²⁴ Setchell et al. 2003

²⁵ Setchell KD, Bragetti P, Zimmer-Nechemias L, Daugherty C, Pelli MA, Vaccaro R, Gentili G, Distrutti E, Dozzini G, Morelli A et al. Oral bile acid treatment and the patient with Zellweger syndrome. *Hepatology* 1992; 15:198-207.

improvements, the patient died at one year of age, consistent with the presence of additional metabolic derangements that were not responsive to cholic acid treatment.

In two Japanese patients with Zellweger syndrome, treatment with bile acids decreased THCA levels and serum transaminases.²⁶

- 2. Administration of exogenous cholic acid restores bile acid-dependent bile flow by replenishing the decreased levels of C₂₄ primary bile acids.** Treatment with exogenous primary bile acids leads to their transport from the intestine to the liver where they can be conjugated and fuel bile flow. Patients with bile acid synthesis disorders due to single enzyme defects and those with peroxisomal disorders have low concentrations of the primary bile acid substrates for BSEP, including the glycine and taurine conjugates of cholic acid, and hence, impaired bile flow. In one patient with a defect in 3 β -HSD function, biliary bile acid analysis performed while on cholic acid treatment showed enrichment with cholic acid.²⁷ Restoration of bile flow ameliorates cholestasis, and results in improvement of liver function.
- 3. Administration of exogenous cholic acid increases the amount of intraluminal cholic acid, and thereby, enhances micellar solubilization of dietary fats and absorption of fat-soluble vitamins.** In 13 patients diagnosed with either 3 β -HSD or AKR1D1 defects who had pre-existing steatorrhea, all experienced resolution on chronic cholic acid treatment. Resolution of fat malabsorption was associated with improved growth and development. Vitamin E deficiency resolved in all 14 patients with pre-existing deficiency and levels remained normal after vitamin supplementation ceased.²⁸

The published report of a child with a defect in AMACR function²⁹ treated with cholic acid for 7 years noted normalization of fat-soluble vitamin levels without the need for supplementation.

The first report of cholic acid treatment in a 6 month old patient with Zellweger syndrome noted improvement in steatorrhea and growth, although the patient died at one year of age.³⁰

- 4. CNS effects.** In an animal model of Zellweger syndrome (*PEX2*^{-/-} knockout mouse), cholic acid treatment improved balance and spasticity and was associated with increased dendritic arborization of cerebellar Purkinje cells.³¹ There are as yet no reports of improved balance or spasticity in humans treated with cholic acid.

II. Review of Submitted Cases in the NDA

Exposure. The applicant provided information regarding exogenous oral cholic acid treatment (10-15 mg/kg daily) administered to 62 patients with bile acid synthesis disorders due to single enzyme defects

²⁶ Maeda K, Kimura A, Yamato Y, Nittono H, Takei H, Sato T, Mitsubuchi H, Murai T, Kurosawa T. Oral bile acid treatment in two Japanese patients with Zellweger syndrome. *J Pediatric Gastroenterol Nutr* 2002; 35(2):227-230.

²⁷ Gonzales et al. 2009

²⁸ *Ibid.* Additionally, sexual maturation progressed normally in all patients, including two sisters with AKR1D1 deficiency who experienced menarche at age 11.5 years. Four normal pregnancies were reported in two patients with 3 β HSD deficiency while on cholic acid treatment, resulting in the birth of four healthy infants.

²⁹ Setchell et al. 2003

³⁰ Setchell et al. 1992

³¹ Keane et al. 2007

and 31 patients with peroxisomal disorders, including Zellweger spectrum disorders, in a series of uncontrolled studies beginning in 1992. Study CAC-91-10-10 enrolled 50 patients with single enzyme defects and Study CAC-92-8-19 enrolled 29 patients with peroxisomal disorders.

In anticipation of commercialization, Asklepiion introduced a new capsule formulation of cholic acid in 2010. Fifteen patients with single enzyme defects initially enrolled in Study CAC-91-10-10 were enrolled in crossover Study CAC-001-01 that assessed the safety and efficacy of switching from the CCHMC formulation to the TBM formulation after 30 days; one additional treatment naïve patient was also enrolled. No substantive changes in efficacy or safety were noted as a result of the formulation switch.

These 16 patients, along with additional patients from Studies CAC-91-10-10 and CAC-92-8-19, and several treatment naïve patients were enrolled on extension Study CAC-002-01 and continued to receive the TBM formulation. A total of 44 unique patients with single enzyme defects were evaluable for efficacy, 39 from Study CAC-91-10-10 and 5 treatment naïve patients enrolled on Study CAC-002-01. A total of 24 unique patients with peroxisomal disorders were evaluable for efficacy (23 from Study CAC-91-10 and 1 treatment naïve patient enrolled on Study CAC-002-01). See table below.

Study	Number of Patients Enrolled	Number of Patients Evaluable - Safety	Number of Patients Evaluable - Efficacy
CAC-91-10-10	50 SED	50 SED	39 SED
CAC-92-9-18	29 ZSD	29 ZSD	23 ZSD
CAC-001-01	16 SED (15 from CAC-91-10-10; 1 treatment naïve)	16 SED	16 SED
CAC-002-01 Interim Efficacy (as of Sep 30, 2012)	43 31 SED (21 from CAC-91-10-10; 10 treatment naïve) 12 ZSD (10 from CAC-92-9-18; 2 treatment naïve)	N/A	6 5 SED (treatment naïve) 1 ZSD (treatment naïve)
CAC-002-01 Interim Safety (as of Nov 30, 2013)	45 33 SED (21 from CAC-91-10-10; 12 treatment naïve); 12 ZSD (10 from CAC-92-9-18; 2 treatment naïve)	62 SED 31 ZSD	N/A

SED = Single Enzyme Defect; ZSD = Zellweger Spectrum Disorder

Measurement of urinary bile acid intermediates. Investigators at CCHMC developed a qualitative assay using FAB-MS (fast atom bombardment mass spectrometry) to detect bile acid profiles in spot urine samples. The bile acid profile or imprint of patient samples is compared to that of normal controls to

discern whether atypical bile acid metabolites are present. Individual bile acid intermediates of interest are subsequently identified by molecular structure prediction based on mass fragmentation pattern, thereby permitting diagnosis of specific enzyme defects. The FAB-MS assays as performed at CCHMC are based on methods validated, certified and accredited by the Centers for Medicare and Medicaid Services Clinical Laboratory Improvement Amendments (CLIA) and by the College of American Pathologists. In addition to diagnosis, the investigators have utilized on-treatment urinary bile acids as a non-invasive measure of treatment compliance and effect. For example, the applicant observed that while 50% of patients with single enzyme defects presented with marked elevations of urinary atypical bile acids, only about 10% showed marked increases following oral cholic acid treatment. FDA has acknowledged the utility of urinary atypical bile acid measurement for diagnostic purposes but has raised concerns with its reliance as a potential measure of cholic acid efficacy in patients with bile acid synthesis disorders. This is because synthetic standards for atypical bile acid intermediates were not available until recently³², precluding validation of the FAB-MS method for the detection of urinary atypical bile acid intermediates as a quantitative method of assessment.

To partly address these concerns, Asklepiion submitted information obtained using a liquid chromatography-mass spectrometry (LC-MS) assay. Although LC-MS was not used for the analysis of urine samples from patients enrolled in the submitted studies, it was performed with synthesized standards; results supported the identities of mass peak characteristics of atypical bile acid intermediates found in the urine from patients with 3 β -HSD deficiency.

The **Dosage and Administration** section, **Treatment Monitoring** subsection of product labeling will state: "Assessment of serum or urinary bile acid levels using mass spectrometry (b) (4) in the diagnosis of bile acid synthesis disorders due to single enzyme defects and peroxisomal disorders including Zellweger spectrum disorders. The utility of bile acid measurements in monitoring the clinical course of patients and in decisions regarding dose adjustment has not been demonstrated."

Asklepiion has agreed to develop post-approval a quantitative urinary bile acid assay method with relevant standards for bile acid synthesis disorders.

Assessment of response. Response to exogenous oral cholic acid treatment was assessed by the applicant using changes in pre- and on-treatment urinary atypical bile acids (as determined by FAB-MS), serum transaminases and bilirubin, height/weight percentiles, and liver histology.

FDA has relied on available measures of efficacy other than urinary bile acid measurement and has conducted a post-hoc analysis of response using the following laboratory criteria: (1) ALT or AST values reduced to < 50 U/L, or baseline levels reduced by 80%; (2) total bilirubin values reduced to \leq 1 mg/dL; (3) no evidence of cholestasis on liver biopsy, and the following clinical criteria: (1) body weight increased by 10% or stable at > 50th percentile; and (2) alive for at least 3 years on cholic acid treatment or at the efficacy data cut-off date for Study CAC-002-01 (September 30, 2012). Responders were defined as patients who either (1) met at least two of the laboratory criteria and were alive at the last follow-up; or (2) met at least one laboratory criterion, had increased body weight and were alive at the last follow-up. Only patients with pre-treatment abnormalities in ALT, AST, or bilirubin were deemed evaluable for response.

³² Gioiello et al. 2014

The original protocols for Study CAC-91-10-10 and Study CAC-92-8-19 specified ursodeoxycholic acid in combination with cholic acid as study medications. In June 2001, the use of ursodeoxycholic acid was discontinued. Thus, assessments of cholic acid treatment response were performed subsequent to the patients' discontinuation of ursodeoxycholic acid, up to the data cut-off date of December 31, 2009. As noted above, incomplete data collection in these studies limited the assessment of efficacy.

With the initiation of Study CAC-002-01 in 2010, data collection was enhanced over previous efforts. The interim report of Study CAC-002-01 submitted in January 2015 provided updated laboratory results, and long-term weight and survival data for patients continuing on cholic acid treatment from earlier studies, and was critical to the assessment of response in these patients. Responses in additional treatment naïve patients were also noted. At the Agency's request, updated narratives on several potential responders were provided for review. Importantly, the findings from Study CAC-002-01 support the efficacy of the TBM formulation of Cholbam.

1. Bile Acid Synthesis Disorders due to Single Enzyme Defects

On average, patients were 4 years of age at the start of cholic acid treatment (range 3 weeks to 36 years). The mean duration of treatment was 6 years. Additional interventions in some patients included fat-soluble vitamin supplementation.

Overall, 28/44 (64%) of evaluable patients with bile acid synthesis disorders due to single enzyme defects were responders by the above criteria.

Response by Type of Enzyme Defect

Single Enzyme Defect	Number of Responders/Number Treated
3β-HSD	22/37
AKR1D1	3/4
CTX	2/2
AMACR	1/1
CYP7A1	N/A
Smith-Lemli-Opitz	N/A

N/A indicates no evaluable patients in the defect subgroup

Forty-three percent of responders met the two clinical criteria plus 1 to 3 laboratory criteria, and 55% percent of patients met the weight criteria. Liver biopsy information was limited; in six patients with pre- and post-treatment biopsies, reduced or absent inflammation, and reduced or absent giant cell formation was noted.

It is difficult to evaluate long term survival in these patients since there is little natural history survival data for comparison. Overall, 41 of 62, or 67% of patients with single enzyme defects survived greater than 3 years while on cholic acid treatment. Thirteen of these 41 patients, or 32%, were "long-term" survivors (range of 10 to 24 years on treatment).

Four patients in Study CAC-91-10-10 underwent liver transplant, including two patients diagnosed with AKR1D1 deficiency, one with 3 β -HSD deficiency, and one with CYP7A1 deficiency. Two patients with AKR1D1 deficiency in Study CAC-002-01 also underwent liver transplantation.

2. Peroxisomal Disorders, including Zellweger Spectrum Disorders

The majority of patients with peroxisomal disorders, including Zellweger spectrum disorders, were less than 2 years of age at the start of cholic acid treatment (range 3 weeks to 10 years). The mean duration of treatment was 4.8 years. Most patients received concomitant DHA (docosahexaenoic acid) and fat-soluble vitamin supplementation.

Overall, 11/24 (46%) of evaluable patients with peroxisomal disorders, including Zellweger spectrum disorders, were responders by the above criteria.

Response by Type of Disorder

Peroxisomal Disorder	Number of Responders/Number Treated
Zellweger Syndrome	3/8
Neonatal Adrenoleukodystrophy	3/6
Infantile Refsum Disease	3/4
Generalized Peroxisomal Disorder	1/1
Peroxisomal Disorder, Type Unknown	1/5

Thirty-eight percent of responders met the two clinical criteria plus 1 to 3 laboratory criteria, and 63% met the weight criteria. No patient underwent liver transplantation.

No evidence of improvement in survival over that seen in historical controls could be demonstrated. Overall, 13 of 31 patients, or 42%, survived greater than 3 years while on cholic acid treatment. Eight of these 13 patients, or 62%, were “long-term” survivors (range of 10 to 17 years on treatment).

III. Summary of Efficacy Findings

Published and submitted cases of cholic acid-responsive patients with bile acid synthesis disorders due to single enzyme defects have reported improvement or normalization of laboratory parameters of liver function, weight gain and prolonged survival. Resolution of steatorrhea and hepatosplenomegaly, achievement of developmental milestones, and sexual maturation including normal pregnancy have also been reported. These outcomes are consistent with the expected actions of exogenous cholic acid in patients with cholic acid deficiency and support Cholbam’s effectiveness in this population.

Published and submitted cases of cholic acid-responsive patients with peroxisomal disorders have reported improvement in laboratory parameters of liver function, weight gain, and prolonged survival. In rare cases, improvement in developmental milestones was also noted. These outcomes are consistent with the expected actions of exogenous cholic acid in patients with cholic acid deficiency and support Cholbam’s effectiveness in this population.

The effectiveness of oral exogenous cholic acid treatment on the extrahepatic manifestations of bile acid synthesis disorders due to single enzyme defects, and of peroxisomal disorders, including Zellweger spectrum disorders, has not been established.

The lower rates of response and survival observed in patients with peroxisomal disorders (relative to patients with single enzyme defects) likely reflect complications related to extrahepatic manifestations of disease, and/or more severe biochemical abnormalities (e.g., absence of peroxisomes vs. a defect in a single enzyme) which can negatively impact the patient's overall clinical course, growth trajectory and prospect for survival.

Concomitant use of bile acid binding resins (e.g., cholestyramine) or aluminum-based antacids can reduce the efficacy of Cholbam. Product labeling will recommend that Cholbam be taken either 1 hour before or 4-6 hours after ingestion of these drug products. Concomitant use of inhibitors of the bile salt efflux pump (e.g., cyclosporine) should be avoided as these drugs may exacerbate the accumulation of conjugated bile acids in the liver.

Safety

A total of 62 patients with bile acid synthesis disorders due to single enzyme defects, and 31 patients with peroxisomal disorders including Zellweger spectrum disorders, are evaluable for safety.

Deaths. Of the 62 patients with single enzyme defects evaluable for safety, 7 patients died. In all but 2 patients, the cause of these deaths was attributed to progression of underlying liver disease.

Of the 31 patients with peroxisomal disorders including Zellweger spectrum disorders evaluable for safety, 16 patients died. In the majority of these patients (11/16), the cause of death was attributed to progression of underlying liver disease or to a worsening of their primary illness.

Hepatic impairment. Evidence of liver impairment was present before treatment with Cholbam in 86% of patients with bile acid synthesis disorders due to single enzyme defects and in 50% of patients with peroxisomal disorders, including Zellweger spectrum disorders. Five patients (3 with single enzyme defects and 2 with peroxisomal disorders) with liver impairment at baseline experienced worsening serum transaminases, elevated bilirubin values, or worsening cholestasis on liver biopsy following treatment. An additional 5 patients (2 with single enzyme defects and 3 with peroxisomal disorders) who did not have baseline cholestasis experienced an exacerbation of their liver disease while on treatment. Exacerbation of liver impairment by Cholbam in these patients cannot be ruled out. These findings will be described in the **Warnings and Precautions** section of product labeling.

Other adverse reactions. The most common adverse reaction on Cholbam was diarrhea, reported in approximately 3% of patients. All other events were reported in 1% of patients: reflux esophagitis, malaise, jaundice, skin lesion, nausea, abdominal pain, intestinal polyp, urinary tract infection, and peripheral neuropathy. Only one of these reactions, peripheral neuropathy, resulted in discontinuation of study medication.

In the literature, symptomatic overdose was reported in four pediatric patients with bile acid synthesis disorders due to single enzyme defects. In one patient, an accidental overdose of 56 mg/kg as a single dose was reported; pruritus, diarrhea and elevations of serum GGT and ALT were noted. Transient

elevations of serum GGT and ALT were observed in the other three patients. Reduction of the cholic acid dose led to resolution of the clinical signs and correction of abnormal laboratory parameters.³³

Pediatric Considerations

Pediatric use. The **Use in Specific Populations** section, **Pediatric Use** subsection, of the product label will state that the safety and effectiveness of Cholbam has been established in pediatric patients 3 weeks of age and older for the treatment of bile acid synthesis disorders due to single enzyme defects and for adjunctive treatment of peroxisomal disorders, including Zellweger spectrum disorders, in patients who exhibit manifestations of liver disease, steatorrhea or complications from decreased fat-soluble vitamin absorption.

Required pediatric studies. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product has received orphan designation for the treatment of inborn errors of bile acid synthesis and metabolism, Asklepiion is exempt from this study requirement.

Tradename Review

The applicant's proposed tradename "Cholbam" is acceptable from both a promotional and safety perspective. The applicant was informed of this determination on February 20, 2014.

Postmarketing Requirement under 505(o)

The applicant will be required to conduct the following postmarketing study to identify unexpected serious risks of cholestasis, steatorrhea leading to poor growth, fat-soluble vitamin deficiency, or neuropathic process related to a vitamin deficiency, reduced survival, and adverse effects on pregnancy, pregnancy outcomes and infant status in patients with bile acid synthesis disorders:

- A prospective observational study to assess the long-term safety of treatment with Cholbam (cholic acid) capsules with respect to the aforementioned risks. Information on dosing regimens and reasons for dose modification will also be collected. Patients with bile acid synthesis disorders treated with, and not treated with, Cholbam will be enrolled. Patient follow-up will be a minimum of 10 years from the time of enrollment or until death, whichever comes first.

Rare Pediatric Disease Priority Review Voucher

Section 908 of the Food and Drug Administration Safety and Innovation Act (FDASIA) modified the Rare Pediatric Disease Priority Review Voucher Incentive Program to allow the issuance of a "priority review voucher" to the sponsor of a rare pediatric disease product application. The holder of such voucher is entitled to priority review of a single human drug application submitted under section 505(b)(1) after

³³ Gonzales et al. 2009

the date of approval of the rare pediatric disease product application. Under the statute, “rare pediatric disease” is defined as:

1. The disease primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents.
2. The disease is a rare disease or condition, within the meaning of section 526.

The term “rare pediatric disease product application” means a human drug application that:

1. is for a drug or biological product—
 - a. that is for the prevention or treatment of a rare pediatric disease; and
 - b. that contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of this Act or section 351(a) or 351(k) of the Public Health Service Act;
2. is submitted under section 505(b)(1) of this Act or section 351(a) of the Public Health Service Act;³⁴
3. the Secretary deems eligible for priority review;
4. that relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population;
5. that does not seek approval for an adult indication in the original rare pediatric disease product application; and
6. is approved after the date of the enactment of the Prescription Drug User Fee Amendments of 2012.

Asklepiion submitted a Pediatric Rare Disease Priority Review Voucher Request for Cholbam (cholic acid) capsules on December 9, 2014 (later resubmitted on December 11, 2014).

In a memo dated February 4, 2015, the Office of Orphan Products Development concluded that “inborn errors of cholesterol and bile acid synthesis and metabolism, including peroxisomal disorders,” primarily affect individuals aged from birth to 18 years. FDA has further determined that the Cholbam NDA submission represents a rare pediatric disease product application as defined above. While Cholbam’s indication encompasses an adult population, it is understood that the indication in the adult population is merely a continuum of the pediatric indication, and does not represent a different adult indication. Therefore, a Rare Pediatric Disease Priority Review Voucher will be granted at the time of approval.

³⁴ See *Rare Pediatric Disease Priority Review Vouchers, Guidance for Industry*, draft issued November 17, 2014, footnote 8, which states: “Because 505(b)(2) new drug applications (NDAs) are submitted under section 505(b)(1), all references to NDAs submitted under section 505(b)(1) include 505(b)(2) applications.”

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/s/

JULIE G BEITZ
03/17/2015