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APPLICATION NUMBER:

205750Orig1s000

SUMMARY REVIEW

NDA 205750

Cholbam

Addendum

March 23, 2015

The submitted studies in NDA 205,750 were single arm trials in which on-treatment measurements of efficacy were compared to baseline measurements. The reference to these studies as "uncontrolled" on page 12 of my previous review dated March 16th, 2015, should not be construed that efficacy was assessed as isolated measurements, without comparison to a baseline measurements.

Andrew E. Mulberg, MD

Division Deputy Director

DGIEP

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/s/

ANDREW E MULBERG
03/23/2015

Summary Review for Regulatory Action

Date	
From	Andrew E. Mulberg, MD, FAAP, CPI
Subject	Division Deputy Director Summary Review
NDA/BLA # Supplement #	205750
Applicant Name	Asklepiion Pharmaceuticals, LLC
Date of Submission	November 21, 2013
PDUFA Goal Date	7/21/2014 major amendment 10/21/2014
Proprietary Name / Established (USAN) Name	Cholbam/cholic acid
Dosage Forms / Strength	Capsules/ 50 and 250 mg 10-15 mg/kg once daily in both pediatric and adult patients
Proposed Indication(s)	<ul style="list-style-type: none"> • Treatment of bile acid synthesis disorders due to single enzyme defects (SEDs). • Adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea or complications from decreased fat soluble vitamin absorption
Recommended Action for NME to Signatory, Dr. Julie Beitz	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Wen-Yi Gao, MD, PhD
CDTL Reviews:	Lara Dimick, MD
Statistical review	Benjamin P Vali, MS Yeh-Fong Chen, PhD
Nonclinical Reviewer	Ke Zhang, PhD David Joseph, PhD
Clinical Pharmacology	Insook Kim, PhD Sue Chih-Lee, PhD
Biopharmaceuticals Reviewer	Kareen Riviere, PhD

**Deputy Division Director Review
Cholbam (cholic acid)
March 16, 2015**

	Tapash Ghosh, PhD
Labeling Reviewers – DMEPA, OMEPRM	Matthew Barlow, RN, BSN Kendra Worthy, PharmD
PMHS	Tamara Johnson, MD Carrie Ceresa, PharmD
Bioequivalence and GLP Compliance	Gajendiran Mahadevan, PhD William H. Taylor, Ph.D.
Compliance Reviewer - DSI	Susan Leibenhaut, MD
CMC Review	Gene Holbert, PhD Moo Jhong Rhee, PhD
Microbiology Reviewer	Bryan Riley Stephen Langille

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Asklepiion Pharmaceuticals LLC has submitted the NDA for Cholbam (cholic acid)) for the following indication:

Treatment of bile acid synthesis disorders involving single enzyme defects (SED) and peroxisomal disorders (PD).

This submission was comprised of a single open-label trial and an extension trial CAC-002-01, of significant duration to support primary efficacy. The substantial evidence of efficacy and safety was based on a review of effectiveness and safety, primarily based on an open-label, single arm, treatment (expanded access trial (CAC-91-10-10). The study was conducted for 18 years, and the data were collected from 54 SED patients and 31 PD patients (ITT population, 85 patients). There were multiple gaps in data collection with missing records for many efficacy parameters and missing data to confirm compliance. I agree with the assessment of the CDTL, Dr. Dimick who states: “Though the applicant submitted the application with both populations and primarily analyzed the data for the two populations together, these are in reality very different diseases with different phenotypic expressions and different outcomes. Single Enzyme Defects (SEDs) have primarily hepatic pathology (with the exception of Cerebrotendinous Xanthomatosis [CTX] disease, which has systemic and neurological manifestations). However, peroxisomal disorders, including Zellweger’s Spectrum Disorders, are systemic diseases that affect multiple organs and have prominent neurological manifestations.” Dr. Dimick notes, “On initial review of the data from trial CAC-91-10-10 by the Medical Officer, Wen-Yi Gao, MD did not show efficacy in the PD population by his initial responder criteria. However, the MO did not review the data from the extension trial CAC-002-01 that was submitted very late in the review. When the data from the extension trial are included, as well as including improvements in coagulopathy, there are 10 of 30 responders in the PD population. Additionally, I do not agree with Dr. Gao’s conclusion that survival is significantly worse in the trial population than in the historical control data submitted by the applicant or in the paper reviewed by Dr. Gao.” This Signatory also would like to provide concerns, regarding certain provisos for the nosology used in labeling this product depends on the single enzyme defects including mitochondrial oxidation defects and side chain modification of the cholesterol nucleus that may not necessarily promote the benefit of cholic acid for all single enzyme defects. This concern is raised especially in the context of the treatment of peroxisomal disorders with cholic acid. Peroxisomal type disorders may not express hepatobiliary type defects which would support a rationale for a putative benefit of cholic acid supplementation.

Based on review, despite numerous issues discussed below, I have concluded that there is sufficient evidence of clinical benefit to justify a recommendation of approval of this NDA to Dr. Beitz, as evidence of efficacy and safety, as fulfilled for the SEDs. I have expressed some concerns regarding the approvability of the evidence to support labeling for (b) (4)

Deputy Division Director Review
Cholbam (cholic acid)
March 16, 2015

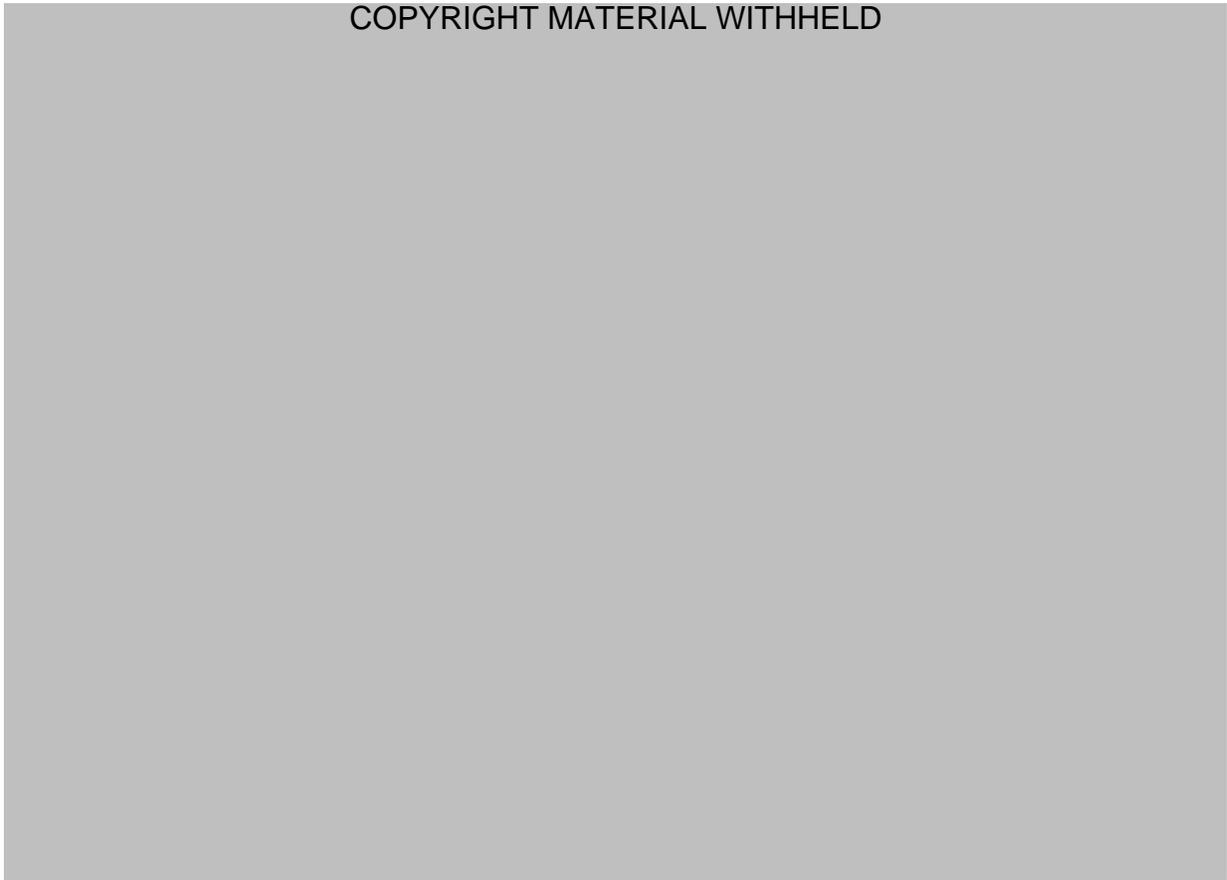
(b) (4) infants and children with peroxisomal defects in bile acid synthesis but ultimately support the final labeling language through review of the available data in this application. The PD type of defects will be reflected in the label reflecting a specific cohort of patients with hepatobiliary manifestations of disease or other surrogates of hepatobiliary disease, including (b) (4), fat soluble vitamin deficiency or (b) (4) for the population of peroxisomal disorders. The final labeling in toto does address my review concerns and herein summarized below. My review will focus on the salient issues related to this risk/benefit assessment as a recommendation for Approval to the Signatory, Dr. Julie Beitz.

2. Background

Bile acid synthetic defects are uncommon inborn errors of metabolism. Inborn errors of bile acid metabolism are recognized as a category of metabolic liver disease. Individuals with inborn errors of bile acid synthesis lack the enzymes needed to synthesize the primary bile acids, cholic acid and chenodeoxycholic acid (CDA). These primary bile acids are important for the regulation of bile flow and production of atypical bile acids and bile acid intermediates. The absence of feedback inhibition of CYP7A1 results in overproduction of these potentially hepatotoxic bile acids and intermediates. Liver disease does result from the accumulation of hepatotoxic bile acids and intermediates leading to cholestasis, bile acid plugs, giant cell hepatitis and cirrhosis in varying cohorts of infants, children and rarely adult patients.

Bile acid biosynthesis is complex with synthesis of bile acids requiring at least 17 enzymes. The biosynthetic pathway is reproduced below in **Figure 1**:

Figure 1: the Biosynthetic Pathway of Bile acids and their Intermediates



The enzymes required for bile acid biosynthesis are located in different hepatocyte organelles; C27 hydroxylation occurs in the mitochondria and ring modification of the bile acid nucleus occurs in the cytoplasm. Side-chain modification and conjugation occur in the peroxisomes. Deficiency of primary bile acids may be related to the early onset giant cell hepatitis, liver failure in infancy and/or progressive neuropathy in adults. Fat-soluble vitamin and fat deficiency can lead to malabsorption syndromes. Disorders of bile acid biosynthesis can be primary or secondary: The primary defects in synthesis of cholic acid and CDCA include the following disorders:

- 3β -hydroxy- Δ^5 -C27 steroid oxidoreductase also known as 3β -HSD or HSD3 β 7
- Δ^4 -3-oxosteroids 5β -reductase or AKR1D1 deficiency
- Sterol-27 hydroxylase presenting as cerebrotendinous xanthomatosis (CTX) deficiency
- Defective bile acid amidation due to failure to conjugate to glycine or taurine
- AMACR deficiency-2-methacyl-CoA racemase
- Oxysterol 7α -hydroxylase (CYP7A1) deficiency
- Tri-hydroxycholestanoic acid (THA) CoA oxidase deficiency

- Side chain oxidation defect in the sterol 25-hydroxylation pathway

Secondary metabolic defects that impact primary bile acid synthesis include peroxisomal biogenesis disorders, such as Zellweger's cerebro-hepato-renal syndrome and related disorders. These disorders present as rare autosomal recessive disorders with progressive cholestasis, presenting as liver failure and fat-soluble vitamin deficiency. Liver diseases due to defects in Bile acid biosynthesis are characterized by hepatocyte destruction, acute or chronic liver failure and giant cell hepatitis. Clinical severity is variable. Biochemical abnormalities include elevated transaminases, elevated serum and urine bile acids or metabolites and normal γ -glutamyltranspeptidase (γ -GT). When elevated, γ -GT suggests bile duct epithelial injury. Histological evidence of liver injury includes intralobular cholestasis, giant cell transformation, necrotic hepatocytes including giant cell forms and cholangiolitis. Periportal is classically progressive. Furthermore, peroxisomal disorders exhibit multi-organ defects affecting the mitochondrion and peroxisome with concomitant expression of hepatic pathology related to defects in conjugation and transport of bile acids.

The nosology used in labeling this product depends on the SEDs to include mitochondrial oxidation defects and side chain modification, including that exhibited in cerebrotendinous xanthomatosis (CTX) syndrome. This nosology may extend treatment to disorders which may not necessarily benefit from cholic acid supplementation based on an understanding of their individual pathobiology. I raise this same concern in the context of treatment of all peroxisomal disorders globally whose presentation and clinical features may not express hepatobiliary type defects.

Using the example of cerebrotendinous xanthomatosis, based on the seminal work of Salen and colleagues in patients with CTX, there indeed is a deficiency of C24 bile acids. Salen described¹ that the biliary bile acid composition in subjects with CTX was abnormal with virtually no chenodeoxycholic acid present in the bile. This suggested that the increased production of neutral sterols might be related to a deficient hepatic pool of chenodeoxycholic acid. Salen provided clear evidence that the administration of chenodeoxycholic acid reduced elevated sterol synthesis in patients with this disease. Furthermore, in analysis of bile acid pools, he showed that in three patients described (in **Figure 2**) below that the endogenous cholic acid was elevated and secondarily inhibited by CDCA:

¹ Salen G, Meriwether TW and Nicolau G. Chenodeoxycholic Acid Inhibits Increased Cholesterol and Cholesterol Synthesis in Patients with Cerebrotendinous Xanthomatosis. *Biochemical Medicine* 1975; 14, 57-74.

Figure 2: Effect of Chenodeoxycholic acid on Biliary Bile Alcohol and Bile Acid Composition



Treatment for SEDs including CTX has classically involved cholic acid supplementation. Cholbam (cholic acid) is a new molecular entity (**Figure 3**).

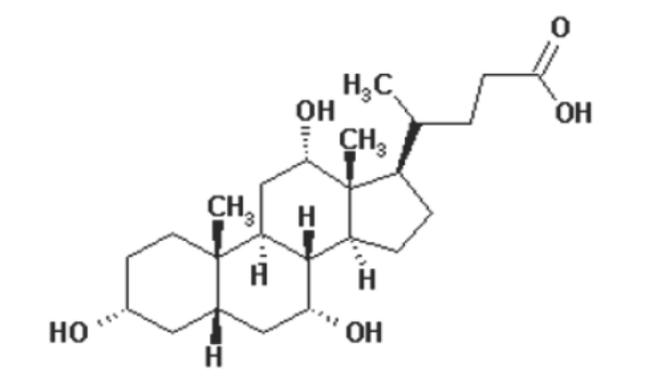
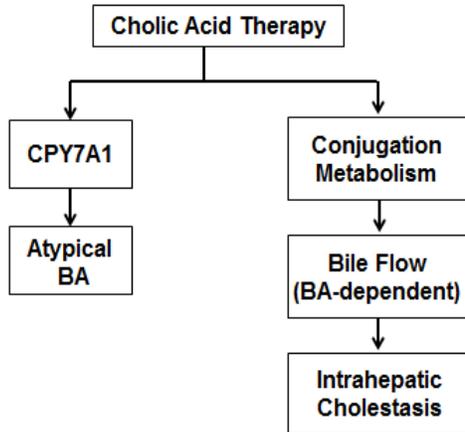


Figure 3: Cholic acid (chemical structure)

Pharmacological class: Bile acid

The exact mechanism of benefit of cholic acid likely reflects a number of putative mechanisms of effect in treatment (**Figure 4, below**). Particularly, important is the inhibition of CYP7A1. The mechanism of cholic acid action includes stimulation of hepatic metabolic conjugation, increase of BA-dependent bile flow, and reduces of intrahepatic cholestasis. Hepatocytes secrete bile-acid dependent bile; Cholangiocytes contribute to bile-acid independent bile flow but the effect of CA on BA independent (glutathione) bile flow is not clear.

Figure 4: Putative Mechanisms of Cholic Acid Therapy on Hepatocyte and Bile Flow



Dietary lipid is in the form of long-chain triglycerides (LCTs). Absorption of fat requires several stages: (1) a digestive phase that includes both lipolysis and micelle formation requiring pancreatic lipase and conjugated bile acids in the duodenum; (2) an absorptive phase for mucosal uptake and re-esterification; and (3) a post-absorptive phase that includes chylomicron formation and exit from the intestinal epithelial cell via lymphatics. The digestive phase has two components, *lipolysis* and *micellar formation*. Although dietary lipid is in the form of LCTs, the intestinal mucosa does not absorb triglycerides; they must first be hydrolyzed **Figure 5**):

Figure 5²: Schematic representation of lipid digestion and absorption

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The initial step in lipid digestion is the formation of emulsions of finely dispersed lipid, which is accomplished by mastication and gastric contractions. Lipolysis, the hydrolysis of triglycerides to free fatty acids, monoglycerides, and glycerol by lipase, is initiated in the stomach by a gastric lipase that has a pH optimum of 4.5–6.0. About 20–30% of total lipolysis occurs in the stomach. Lipolysis is completed in the duodenum and jejunum by pancreatic lipase, which is inactivated by a pH < 7.0. Pancreatic lipolysis is greatly enhanced by the presence of a second pancreatic enzyme, colipase, which facilitates the movement of lipase to the triglyceride. The exact mechanism of action for cholic acid remains ultimately unclear but its putative effect is by restituting normal intraluminal concentration of the bile acid to ensure adequate effects on micellar solubilization which facilitates fatty acid and monoglyceride formation into triglycerides and its subsequent absorption, especially of lipids and fat-soluble vitamins. Treatment by oral administration of cholic acid could potentially establish an adequate pool of these exogenous bile acids leading to(an) improvement in the micellar

² https://www.google.com/search?q=effect+of+cholic+acid+on+intraluminal+lipid+digestion&client=firefox-a&hs=dDQ&rls=org.mozilla:en-US:official&source=lnms&tbm=isch&sa=X&ei=9hbiVNzVJ6z-sATZjoJw&ved=0CAgQ_AUoAQ&biw=1366&bih=622#imgdii=_&imgsrc=ICuYcYhN95I3M%253A%3BCWpMkCVlhCpkXM%3Bhttp%253A%252F%252Fduallibra.com%252Fwp-content%252Fuploads%252F2012%252F04%252F037800~1%252FPart%25252013.%252520Disorders%252520of%252520the%252520Gastrointestinal%252520System%252520Section%2525201.%252520Disorders%252520of%252520the%252520Alimentary%252520Tract%252520288_files%252520loadBinary_002.gif%3Bhttp%253A%252F%252Fduallibra.com%252Fwp-content%252Fuploads%252F2012%252F04%252F037800~1%252FPart%25252013.%252520Disorders%252520of%252520the%252520Gastrointestinal%252520System%252520Section%2525201.%252520Disorders%252520of%252520the%252520Alimentary%252520Tract%252520288.htm%3B619%3B315

solubilization of fats and fat soluble vitamins, (b) stimulation of bile flow and hence elimination of toxic substances from the liver, and (c) inhibition of cholesterol 7 α -hydroxylase. This may diminish the production of toxic metabolites from cholesterol. The impact of exogenous supplementation of cholic acid on non-hepatic manifestations which are not etiologically related to this pathobiology especially those with PD type disorders remains unclear to me. The remainder of this review will focus on further discussion of the benefit risk and review of the review of cholic acid relative to these particular issues.

3. CMC

The CMC review was conducted by Gene Holbert, PhD who recommended approval. Further details are provided in his individual review. Particular concerns regarding labeling of cholic acid in foods particularly relevant to infants and children including stability in infant formula and breast milk has been addressed. The submission indicates that the product is stable in applesauce (b)(4), which would be the most acidic of the foods listed and Cholic acid is stable when (b)(4). Therefore, there is no concern regarding stability of Cholbam in exogenous food substrates. The reader is referred to the review of Dr. Dimick regarding the issue of bioavailability and concerns regarding bioequivalence studies with cholic acid. In conclusion I concur with Dr. Dimick that the bioequivalence study was not adequate alone to prove bioequivalence between the formulation used in the initial studies and the to-be marketed formulation. Based on the adequacy of the data and clinical experience with the to-be marketed formulation in trial CAC-001-01 and trial CAC-002-01, the CDTL concurred with the Biopharmaceutics reviewer. Dr. Riviere.

4. Nonclinical Pharmacology/Toxicology

Preclinical Pharmacology and Toxicology were reviewed by Drs. Ke Zhang and David Joseph. They did not identify an issue that would preclude approval (DARRTS on July 21, 2014).

Dr. Zhang commented that “No nonclinical studies of cholic acid were conducted to support approval of this application. Since cholic acid is the most abundant bile acid in humans, there is minimal concern about its safety from a nonclinical viewpoint. In response to a request from the Agency, the sponsor provided data which indicate that the total body content of cholic acid at the proposed dose level in pediatric patients with defects in bile acid synthesis (the target patient population) will not exceed that of the normal pediatric population. Thus, the drug product (Cholbam) can be accurately described as a bile acid replacement therapy in the context of the proposed indication.” “From a nonclinical standpoint, the NDA application should be approved for the proposed indication”. The Associate Director of Pharmacology/Toxicology, OND, Dr. Abby Jacobs commented, “No nonclinical studies were conducted to support approval, but this is OK, since cholic acid is an abundant bile acid in humans. I concur that there are no outstanding pharm/tox approval issues”; and “I concur with the recommendations for the division regarding labeling of pharm-tox sections”. (DARRTS, July 30, 2014)

I provide additional comment to the review of the PEX2^{-/-} mouse model of Zellweger syndrome³ as discussed by Dr. Dimick in her CDTL review. In a study of this animal model, Dr. Dimick notes that “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.” Furthermore, total hepatic lipids analysis found a 1.75-fold increase in untreated PEX2^{-/-} mouse livers compared with control animals, but 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.” She states that “though there is some concern about findings of exacerbation of hepatic steatosis and mitochondrial and cellular damage in the PD deficient mice model, the relevance is difficult to interpret since the mice received both CA and UDCA”. As per the investigators, they note that there were adequate controls including Control and PEX2^{-/-} mice were fed a mixture of cholic acid (CA) and ursodeoxycholic acid (UDCA) starting on postnatal day 1 (P1). Bile acids were analyzed in bile and liver from untreated and BA-fed control and PEX2^{-/-} mice that ranged in age from P12 to P36. Based on these controls, it is difficult to agree with Dr Dimick that there was confounding on the concomitant use of UDCA. The reader is referred to the data presentation in the paper for further discussion.

My perspective in developing some putative concern regarding the potential hepatotoxicity of cholic acid, relates exactly to the histopathology evidenced in the PEX2^{-/-} animal model. It is unlikely that UDCA contributes to the histopathology since it is recognized that UDCA conjugates prevent liver damage and cholestasis caused by conjugates of cholic acid, and other more hydrophobic bile acids including CDCA, deoxycholic acid, and lithocholic acid in experimental animals, the isolated perfused liver, or isolated hepatocytes. Amidation of UDCA seems to be a prerequisite for its protective effect⁴. The authors themselves cite that “Peroxisome deficiency widely disturbs bile acid homeostasis and hepatic functioning in mice, and the high sensitivity of the peroxisome-deficient liver to bile acid toxicity limits the effectiveness of bile acid therapy for preventing hepatic disease”. It is this perspective that this

³ Keane MH, Overmars H, Wikander TM et al. Bile acid treatment alters hepatic disease and bile acid transport in peroxisome-deficient PEX2 Zellweger mice. *Hepatology* Volume 45, Issue 4, pages 982–997, April 2007.

⁴ Uers, Boyer and Paumgartner. Ursodeoxycholic Acid in Cholestasis: Potential Mechanisms of Action and Therapeutic Applications. *Hepatology* Vol. 28, No. 6, 1998

reviewer is concerned with the specific use and recommendation to use cholic acid in the treatment of patients with non-hepatic manifestations of PD and Zellweger's disease. It is unclear whether the cholic acid supplementation has a negative effect on either morbidity or mortality in these patients and the data in this submission are inadequate to make a definitive assessment in this regard. Dimick notes,

"some concern about findings of exacerbation of hepatic steatosis and mitochondrial and cellular damage in the PD deficient mice model, the overall clinical picture is of improvement. However, the relevance of the mice model to the human population is always debatable and the fact that these mice received both UDCA and cholic acid further confounds the interpretation of the relevance of this data. From a safety perspective, if it is the patients with the more severe peroxisomal defects that may be more susceptible to the toxic effects of cholic acid, because changes in bile acid transporter (BSEP) expression that limit hepatic excretion of bile acids, persistent canalicular damage, and limits to bile acid conjugation capacity, then close screening at the initiation of treatment should show worsening of liver function and treatment should be stopped. For patients that are treated long term, screening for early onset hepatic steatosis may be considered. Though there is no treatment currently available to treat steatosis, steatohepatitis or liver fibrosis there are currently several drugs under investigation for these indications. The post-marketing Registry trial should allow more information to be gathered to assess the implications for treatment in the PD population."

Exact understanding of the narrow therapeutic risk benefit is critical especially with the potential of overdosing in certain patients. The reader is referred to the excellent reference for further analysis. This issue is also addressed in the PMR for the Sponsor discussed in Section 13 as well as addressed in final labeling.

5. Clinical Pharmacology

The pharmacology review was conducted by the following reviewers: Drs. Insook Kim and Sue Chih-Lee who provide an Approval recommendation to Dr. Beitz. This Signatory concurs with the following comments on this recommendation.

A. Dose Selection for Administration

The dose selection of 10-15 mg/kg is supported based on review of data that demonstrates changes in serum transaminases and bilirubin and the extent of reduction of atypical bile acids in urine. As Dr. Dimick notes, "the documentation on the dosage adjustment with relevant clinical observations and biomarkers at the time of dosage adjustment was not adequate for review." (b) (4)

The labeling will reflect the dose as 10-15mg/kg and (u) (4)
instructions for monitoring patients and discontinuing cholic acid for evidence of deteriorating hepatic function. Further data on dose and adjustment of dose using quantitative methods of measurement of urinary bile acids will be requested from the applicant as a part of the post-marketing registry."

I agree with Dr. Dimick that the scientific rationale to propose a starting dose of cholic acid is based on restitution of likely deficient intraluminal bile acid pools in the PD and SED populations. What are not accounted for are the potential differences in the entero-hepatic circulation that may exist by virtue of incomplete feedback inhibition of CYP7A1 and its impact on endogenous cholic acid and chenodeoxycholic acid biosynthesis. There are no data provided in this application to justify fully the final dose of what is currently recommended in labeling. No intraluminal biliary concentrations of bile acids have been provided at a patient level as compared to what has been reported by Salen and colleagues in CTX patients⁵. What is reasonable is providing a starting dose as recommended with the provisos that serum transaminases, and GGT are monitored for potential toxicity to the liver. In these diseases, GGT is abnormally low or normal and reflects as in all biliary duct and ductular disease inflammatory condition. Therefore, in the context of monitoring an individual patient, these serum biomarkers are critical although the extent to which labeling should reflect guidance is difficult to elucidate definitively. The decades of experience with management of these patients at Cincinnati Children's Hospital does make this Signatory at least confident that this type of monitoring will maximize patient tolerability and safety. As noted by Dr. Dimick, clear follow up of the monitoring of these patients through the PMR will be critical to ensure adequate labeling. The specific focus on developing a more quantitative approach to urinary bile acid monitoring will be critical. More comment on the urinary bile acid screening methodology below will be discussed below.

B. Urinary Bile Acid Measurement- FAB-MS

The reader is referred to the excellent summary reviews of Dr. Dimick and Dr. Kim on this issue. The utility of urinary bile acid FAB-MS has been described over decades by the excellent work of Setchell and colleagues who developed this technique for the diagnosis of this rare group of inborn errors of metabolism. Literature extensively supports this diagnostic testing aptly represented by the description of an infant with cholestatic jaundice whose urine contained unusual labile sulfated C24 bile acids with two or three hydroxyl groups and a double bond. Application of mild isolation procedures and mass spectrometry permitted the identification of $3\beta,7\alpha$ -dihydroxy-5-cholenoic acid and $3\beta,7\alpha,12\alpha$ -trihydroxy-5-cholenoic acid. The presence of these compounds in the urine and the absence of chenodeoxycholic acid and cholic acid from the urine and plasma suggested a defect of the 3β -hydroxy- Δ^5 steroid dehydrogenase/isomerase involved in bile acid synthesis⁶. As noted by the authors, the patient suffered from a unique form of giant cell hepatitis that can be diagnosed by testing through FAB-MS and confirmed by GC-MS analysis of the urine bile acids if appropriate methodology is used. The applications of FAB-MS to diagnose the presence of abnormal urinary bile acids and their intermediates have been well-established through the submitted application.

Concerns with the current application focus on the inadequacy of the urinary bile acid measurement to quantitate and make dosing decisions in individual patients. Dr. Dimick notes

⁵ Salen G, Meriwether TW and Nicolau G. Chenodeoxycholic Acid Inhibits Increased Cholesterol and Cholestanol Synthesis in Patients with Cerebrotendinous Xanthomatosis. *Biochemical Medicine* 1975; 14, 57-74.

⁶ Clayton PT, Leonard JV, Lawson AM et al. Familial Giant Cell Hepatitis Associated with Synthesis of $3\beta,7\alpha$ -Dihydroxy and $3\beta,7\alpha,12\alpha$ -Trihydroxy-5-Cholenoic Acids. *J Clin Invest*. 1986;79:1031-1038.

that, “Unfortunately, the applicant was unable to provide actual data to match urinary bile acid scores to dose adjustments made in the clinical trials, therefore the significance of reduction of atypical bile acids to the clinical outcome and usefulness for dose adjustment will need to be further established. In addition, the team did not agree (b) (4)

The applicant has verbally committed to developing and appropriate method to quantitatively measure urine bile acids (e.g. liquid chromatography) and we will request data on urinary bile acid measurements and dose adjustments as part of the post-marketing registry data.” This Signatory agrees with these recommendations and are reflected in the requested Post-marketing commitment to develop a quantitative urinary bile acid analysis assay method along with standards for bile acid synthesis disorders. The reader is referred to the CDTL and Clinical Pharmacology memoranda for further details of this issue and to Section 13 below

6. Clinical Microbiology

The Product Quality, microbiology reviewer, Bryan S. Riley, Ph.D., noted that the Microbial Limits specification for Cholic Acid Capsules (50 mg and 250 mg) were acceptable from a Product Quality Microbiology perspective, and recommend approval.

7. Clinical/Statistical-Efficacy

I do concur with the reviews of Drs. Gao and Dimick who have recommended approval of cholic acid for the treatment of SEDs and do not agree that the PD population should be approved for treatment without certain restrictions noted in final labeling. The final labeling does reflect the limitations of use as discussed below.

A. Definition of Responder Used to Determine Efficacy for the SED and PD Populations:

The reader is referred to the Clinical review of Dr. Gao for further information on clinical trial specific information. I do concur with Dr. Dimick that a post-hoc method to assess efficacy in these populations using the limited amount of data that was available to confirm improvements in transaminases and bilirubin and resolution of cholestasis on histology, and the clinical outcomes of survival and weight gain. It is important to understand and appreciate that the post-hoc identification of responder criteria are consistent with the clinical benefit observed in patients treated with cholic acid supplementation. It is obvious that the statistical team stated that because of the lack of real placebo data and no pre-specified statistical plan for this trial, that no statistical analysis were valid and the interpretation of these data relied on clinical judgment. It is critical to support this notion of efficacy based on the understanding of the natural history of these types of disorders which will be discussed below. In addition the utility of the responder definitions proposed by Dr. Gao to include main efficacy endpoints compared to baseline including the following parameters makes clinical sense to this reviewer’s perspective:

These include:

Laboratory criteria:

- ALT or AST values reduced to < 50 U/L, or baseline levels reduced by 80%
- total bilirubin values reduced to < 1 mg/L
- normalization of prothrombin time
- no evidence of cholestasis on liver biopsy

Clinical Criteria:

- body weight increased by 10% or stable at > 50th percentile
- alive at the last follow-up

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 met at least one laboratory criterion, as well as body weight and survival criteria **was changed to: survival for at least 3 years on treatment, or alive at the end of CAC-002-01**

The protocol CAC-91-10-10 enrolled infants and children with Infants and children with cholestasis: conjugated bilirubin >2 mg/dL or ↑serum bile acids and urine FAB-MS analysis positive for bile acid metabolites consistent with the bile acid metabolism disorder. The CAC-92-8-19 (sub-study) identified patients with PD, with manifestations supported by a neurologic evaluation plus serum long-chain fatty acids and urine FAB-MS analysis positive assay for bile acid metabolites. Additional key entry criteria for SED included cholestasis defined as a serum conjugated bilirubin >2 mg/dL or increased serum bile acids (normal range: 4.5-24.6 μmol/L) and urine atypical BA analysis positivity. Key entry criteria for PD include neurologic evaluation, plus serum very long-chain fatty acids positivity (Phytanic acid ≥4 μmol/L) and the presence of urine atypical BA analysis positivity.

Overall, 28 of the 44 patients with single enzyme defects (64%) were responders by the above criteria and reflected below in **Table 1: Response by Type of Enzyme Defect**

Table 1: 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

B. Hepatobiliary Disease and Efficacy of Cholbam in Peroxisomal Diseases

One of the issues is the inclusion of patients with peroxisomal defects that did not have observable evidence of hepatobiliary disease. As discussed by Dr. Gao, **Table 2** below reflects the predominance of the patient population enrolled in CAC-91-10-10 with PD as not having the presence of cholestasis and no data available. As noted by Dr. Gao in the data representing the Responder Analysis & Baseline Cholestasis: PD ITT population, it is clear that the greatest percentage of patients were non-responders based on the responder definition. Dr. Dimick notes in **Table 3** below the response criteria that were met in the PD population. What is evidenced is that the responders included patients only with hepatobiliary disease. Coagulopathy, survival and weight gain were evidenced throughout the cohort and supported that the likely benefit of cholic acid supplementation in PD patients represents an impact on the effects on intraluminal digestion yielding impact either on fat soluble vitamin efficiency, coagulation parameters and nutritional effects. The lack of appropriate monitoring of weight and growth parameters in this study makes conclusions difficult. In addition survival analysis offered by Dr. Gao does not lend support for the efficacy of CA supplementation in the PD disorders.

Table 2: Summary of Baseline Cholestasis and CA Treatment Responder: PD ITT

PD/Subtype: N	Baseline			CA Treatment		
	Cholestasis	No Cholestasis	Data N/A	Responder	Non-Responder	Data N/A
PD: 29	8/29=28%	16/29=55%	5/29=17%	0	22/29=76%	7/29=24%
Zellweger's: 11	4	5	3	0	5	6
NALD: 8	2	5	1	0	7	1
Unknown: 5	1	3	1	0	5	0
Refsum's: 4	2	2	0	0	4	0
Generalized: 1	0	1	0	0	1	0

From Table 2 of clinical reviewer's notes

Table 3: Response Criteria Met by Type of Disorder

Response Criteria Met	Types of Parameters Met	Number and Types of Disorder (Patient IDs)
3 Clinical + 2 Laboratory	S, W, D, E, B	1 1: Zellweger syndrome (703)
2 Clinical + 2 Laboratory	S, W, E, B	3 1: Zellweger syndrome (32) 2: NALD (30, 35)
	S, W, E, C	2 2: Refsum's disease (20, 21)
	S, W, D, E	1 1: Generalized (92)
2 Clinical + 1 Laboratory	S, W, E	3 2: Zellweger syndrome (46,

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	173) 1: NALD (12)
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S: Survivor; W: body weight increased; D: improved developmental/cognitive milestones; B: total bilirubin improved; C: coagulopathy resolved; E: ALT or AST improved; Bx: liver biopsy improved

Overall, Dr Dimick notes 11 of 24 patients (46%) in the PD population were responders by the criteria as outlined above .

Table 4: Response by Type of Disorder

Peroxisomal Disorder	Number of Responders/Number Treated
Zellweger Syndrome	3/8
Neonatal Adrenoleukodystrophy	3/6
Infantile Refsum Disease	¾
Generalized Peroxisomal Disorder	1/1
Peroxisomal Disorder, Type Unknown	1/5
Total	11/24

Table 5 reflected below reproduced from Dr. Gao’s review represents the PD Sub-type analysis of Cholic acid effectiveness endpoints. Clinically relevant changes in transaminases, bilirubin total, weight and survival are recorded in the data presented. In the presence of hepatobiliary diseases manifested either by elevated total bilirubin, or transaminase elevations, weight gain markedly decreased in these patients (patients with Zellweger’s syndrome and neonatal adrenoleukodystrophy). If the cholic acid supplementation truly was exhibiting any benefit, weight gain would have reflected positive benefits.

Table 5: PD Sub-type Analysis of CA Effectiveness Endpoints (ITT)

ITT (n=31)	ALT/AST	Bilirubin (Total)	Weight	Sibling Study	Survival ⁸
Zellweger’s (n=12)	Imp ¹ (n=8)	Wnd ⁴ (n=4)	Wnd ⁶ (n=11)	N/A	5/11 (45%)
Neonatal adrenoleukodystrophy (n=8)	ALT Imp ² (n=7) AST Wnd ³ (n=7)	Normal ⁵ (n=4)	Wnd ⁷ (n=8)	N/A	3/6 (50%)

From the clinical reviewer’s notes based on Asklepiion Supplement SN028 (with on imputation) on July 7, 2014.

Imp¹: median of ALT of Zellweger’s improved from 97 to 82; median of AST also improved from 373 to 202;

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ALT Imp²: median of ALT of NALD improved from 148 to 63;

AST Wnd³: median of AST of NALD worsened from 164 to 186;

Wnd⁴: median of total bilirubin of Zellweger's worsened from 0.500 to 1.050;

Normal⁵: median of total bilirubin of NALD was in the normal range at baseline (0.825) and post-TMT (0.347), respectively;

Wnd⁶: median of weight percentile of Zellweger's worsened from 5.83 to 0.18 percentile;

Wnd⁷: median of weight percentile of NALD worsened from 1.76 to 0.40 percentile;

Survival⁸: the overall historical survival rate of PD=10/31 (32%); the total PD on treatment=15/29 (52%); Sub-types historical control is not available.

As noted by Dr. Gao, "because there was only small numbers of patients who had both pre- and post-treatment evaluations, the sensitivity analyses were considered to be explorative. However, the trend of SED sub-type analyses supports the clinical benefits of cholic acid therapy for SED patients. In contrast, there was no consistent trend of biomarker analyses in PD; while the clinical weight and height percentile worsened on treatment for both ZS and NALD."

In addition Dr. Dimick notes that "In the absence of definitive historical control data substantiating the efficacy of CA on survival in PD patients or at least some description of the effect of CA on those PD patients who exhibited classical hepatic injury since we have used those criteria to be components of the responder definition, I am not convinced with this proposal to include in labeling. Data need to be provided at least that supports CA treatment as adjunctive in the population with cholestasis at least."

Dr. Dimick comments that additional data from the extension trial CAC-92-9-18 included 12 ZSD patients who are referred to as partial responders. She adds additional analyses that lend support to slight differences in the numbers of the PD population that appears in final labeling than Dr. Gao's review. Ultimately, with regards to interpreting the efficacy in the PD population, she correctly notes that peroxisomal disorders have a heterogeneous phenotype and several of the patients in the trial and in literature reports did have prominent hepatic dysfunction/cholestasis, steatorrhea and/or coagulopathy. She correctly notes that these types of patients would be expected to benefit from cholic acid treatment. In addition, some patients with milder phenotypic presentations of PD with longer life expectancy and milder hepatic disease would be expected to benefit from prevention of progression of liver disease.

Therefore, it is the opinion of Dr. Dimick that there is evidence of efficacy from the combined trial data including the extension trial data which was uncontrolled. Dr. Dimick in my opinion correctly cites that the mechanism of action of cholic acid and literature support that cholic acid is effective in the SED population and also in PD patients who have evidence of hepatic injury, cholestasis, malabsorption with steatorrhea, or fat soluble vitamin deficiency.

In toto, this Signatory concurs that there is a positive benefit for cholic acid supplementation in the SED cohort but should be restricted to those patients in the PD population with evidence of hepatobiliary disease or certain clinical features that portend response with cholic acid supplementation. There is largely inadequate data to review to confirm a clinical benefit of

Cholic acid for treatment of all patients with PD and this needs further study which will be mandated as part of the PMR and (b) (4).

8. Safety

The reader is referred to the review of Dr. Gao for specific details. This Signatory will focus on particular elements of concern of potential safety with cholic acid. Dr. Dimick notes that “Cholic acid is a normal component of bile and therefore is a relatively safe drug. However, in cases of bile obstruction or reduced bile flow bile acids can have a deleterious detergent effect and should be stopped. In addition, over dose of bile acids can occur and there use must be monitored by a physician experienced with liver diseases. In addition, a post-marking safety registry study will be conducted as a PMR to assess further signals of hepatic toxicity.” She continues by stating that: “To mitigate the risk of use the Dosage and Administration section, Treatment Monitoring subsection of product labeling will note that:

- Treatment with Cholbam should be initiated and monitored by an experienced hepatologist or pediatric gastroenterologist;
- Serum transaminases, γ -glutamyltransferase (γ -GT), alkaline phosphatase, bilirubin and INR 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. Monitoring should occur more frequently during periods of rapid growth, concomitant disease, and pregnancy. The lowest dose that effectively maintains hepatic function should be used.
- Treatment with Cholbam should be discontinued if hepatic function does not improve within 3 months of the start of treatment; and Treatment with Cholbam should be discontinued at any time if there are clinical or laboratory indicators of worsening hepatic function or cholestasis.

To this Signatory, specific mention of worsening cholestasis including rising γ -GT levels should be precautionary to the prescribing physician. In the types of disorders as the single enzyme defects and the PD noted, there is by definition reduced bile flow as a component of their disorder. This is the reason for cholestasis. It would appear more appropriate for labeling this NME to identify concerns of dosing in the context of biliary obstruction evidenced by elevated γ -GT levels. As has been discussed in the section on Nonclinical, there are reports of severe pre-existing mitochondrial defects in PD pts reported from clinical cases and animal studies. Specific animal models in PD mice has demonstrated that supplementation with cholic acid has worsened hepatic damage with notable defects in bile acid conjugation and transportation. It is important to identify appropriately in labeling that ingesting bile acids by patients with cholestatic liver may cause delayed hepatic damage, specifically mitochondrial toxicity.

9. Advisory Committee Meeting

During this review cycle, an advisory committee meeting was not convened to discuss the current supplement

10. Pediatrics

The relevant population of neonates, infants and children has been the focus of this pivotal trial and no other studies can be mandated due to the orphan designation of this product since the application is not subject to PREA regulation.

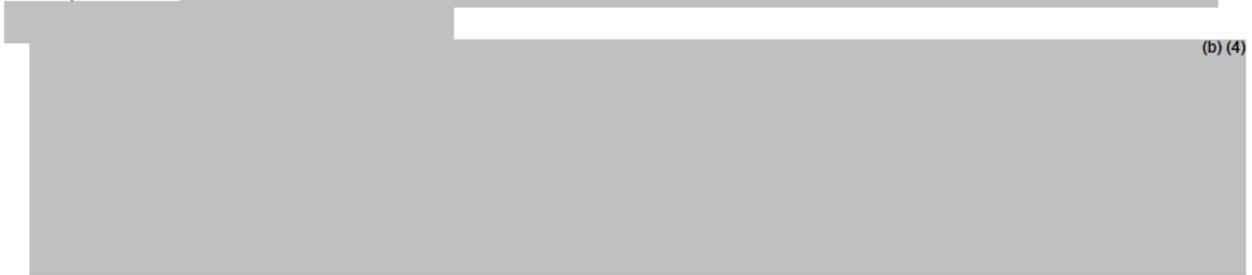
11. Other Relevant Regulatory Issues

A. DSI audits

The Reader is referred to the CDTL memorandum for further discussion of this issue. No relevant observations were made.

B. Pediatric Rare Disease Voucher Designation

Asklepiion Pharmaceuticals, LLC submitted a Rare Pediatric Disease Voucher Request for Cholbam (cholic acid) capsules on December 9, 2014 (later resubmitted on December 11, 2014) for the (b) (4)



In a memo dated February 24th, 2015, the Office of Orphan Products Development concluded that inborn errors of bile acid metabolism meet the FDASIA definition of a rare pediatric disease. 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 Priority Review Voucher will be granted at the time of approval.

12. Labeling

There was agreement with the final labeling and important aspects are herein described for the final indications of:

- Treatment of bile acid synthesis disorders due to single enzyme defects (SEDs).
- Adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea or complications from decreased fat soluble vitamin absorption

As noted for the peroxisomal disorders, it was critical to reinforce that the patients determined to be treated for peroxisomal disorders (PDs) including Zellweger spectrum disorders in patients must exhibit manifestations of liver disease, steatorrhea or complications from decreased fat soluble vitamin absorption. As noted in earlier discussion

above, the adjunctive treatment of these clinical signs and symptoms related to intrinsic liver disease are appropriate.

There is the important documentation for Limitations of Use to include the following verbiage in the label:

Limitation of use:

The safety and effectiveness of CHOLBAM on extra-hepatic manifestations of bile acid synthesis disorders due to SEDs or PDs including Zellweger spectrum disorders have not been established.

Additional important labeling language to mitigate the risk of use the Dosage and Administration section, Treatment Monitoring subsection of product labeling will note that:

- Treatment with Cholbam should be initiated and monitored by an experienced hepatologist or pediatric gastroenterologist;
- Serum transaminases, gamma glutamyltransferase (GGT), alkaline phosphatase, bilirubin and INR 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. Monitoring should occur more frequently during periods of rapid growth, concomitant disease, and pregnancy. The lowest dose that effectively maintains hepatic function should be used.
- Treatment with Cholbam should be discontinued if hepatic function does not improve within 3 months of the start of treatment; and
- Treatment with Cholbam should be discontinued at any time if there are clinical or laboratory indicators of worsening hepatic function or cholestasis.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action:

All of the review divisions recommended an Approval which gained concurrence from the Clinical reviewer and CDTL. I have concluded that the data in these submissions do reflect a risk and benefit of Cholbam for the indication: as follows

- *Treatment of bile acid synthesis disorders due to single enzyme defects (SEDs).*
- *Adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea or complications from decreased fat soluble vitamin absorption*

The product has a favorable risk/benefit profile for this indication.

13.2 Risk Benefit Assessment:

The treatment of vulnerable infants and children with bile acid SEDs, including peroxisomal defects with hepatobiliary disease should require cholic acid supplementation. The critical

issue is that the proper patient cohort that requires definitive diagnosis of this inborn error of metabolism and monitoring of cholic acid supplementation for prevention of additional toxicity is needed. There are multiple deficiencies in this application but the weight of evidence supports a positive risk benefit assessment for the acceptability of a labeled indication for the

- Treatment of bile acid synthesis disorders due to single enzyme defects (SEDs).
- Adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea or complications from decreased fat soluble vitamin absorption

Limitation of use:

The safety and effectiveness of CHOLBAM on extrahepatic manifestations of bile acid synthesis disorders due to SEDs or PDs including Zellweger spectrum disorders have not been established.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:

There are no requirements for postmarketing risk evaluation and mitigation strategies.

Recommendation for other Postmarketing Requirements and Commitments:

POSTMARKETING REQUIREMENTS UNDER 505(o):

Postmarketing Requirement:

2882-1

A prospective, long-term, observational study in a routine clinical setting of patients aged 3 weeks or older with bile acid synthesis disorders due to single enzyme defects and patients with peroxisomal disorders, including Zellweger spectrum disorders, who exhibit manifestations of liver disease, steatorrhea, fat soluble vitamin deficiency, or a neuropathic process related to a vitamin deficiency. The purpose of the study is to assess primarily the long term safety of treatment with Cholbam (cholic acid) capsules with respect to incidence rates of worsening cholestasis, steatorrhea leading to poor growth, fat soluble vitamin deficiency, or neuropathic process related to a vitamin deficiency, and the incidence of death and adverse effects on pregnancy, pregnancy outcomes and infant status. Additional evaluations will include dosing regimens and reasons for any dose modifications, weight gain, length/height and developmental outcomes. Specify concise case definitions and validation algorithms for all outcomes. Enroll at least 55 patients (25 receiving cholic acid and 30 not receiving cholic acid) including at least 20 peroxisomal disorder patients, with liver dysfunction, steatorrhea, fat soluble vitamin deficiency or a neuropathic process related to the latter. Enroll over an initial 3-year period and follow for a minimum of 10 years from the time of enrollment or until death, whichever comes first.

Final Protocol Submission: September 2015

Study Completion: September 2028

Final Report Submission: March 2029

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Post-Marketing Commitment:

2882-2

Develop a quantitative urinary bile acid analysis assay method along with standards for bile acid synthesis disorders.

Final Report Submission: March 2017

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREW E MULBERG
03/16/2015
Division Deputy Director Review