

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

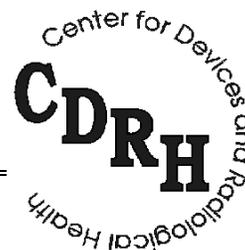
APPLICATION NUMBER:

205750Orig1s000

PHARMACOLOGY REVIEW(S)

Medical Officer
MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration



Date: 7/21/14

Subject: NDA 205750

To: Wen-Yi Gao, M.D. CDER /DGIEP

From: Prakash Jha, MD,MPH, Medical Officer/Pathologist, CDRH/OIR/DMGP

Bile Acid Treatment Alters Hepatic Disease and Bile Acid Transport in Peroxisome-Deficient PEX2 Zellweger Mice

MOUSE MODEL: *PEX2* control and mutant mice were analyzed on a Swiss Websterx129SvEv genetic background. Control mice had either or *PEX2*^{+/+} or ^{-/-} genotypes as biochemical and morphologic measures did not differ.

IMPORTANT FINDINGS:

Liver: Early postnatal *PEX2*^{-/-} mice had severe intrahepatic cholestasis, with numerous brownish-yellow deposits in bile canaliculi and small bile ducts. Cholestatic deposits were observed in newborn *PEX2*^{-/-} livers, and their density rapidly increased until about P9. In untreated mutants this was followed by a decrease between P12 and P18. This cholestatic pattern was observed in untreated mutants regardless of animal size, viability, or rearing with control mice, suggesting an evolution in the disease process and that the less severe phenotype in older mutants cannot be entirely explained by a less penetrant phenotype. The ductular cholestasis was often associated with cholangitis, suggesting severely reduced bile flow. Oil redOstaining demonstrated mild hepatic steatosis in P9 untreated mutants, which was further exacerbated by BA therapy. The hepatic steatosis increased further in BA-fed mice between P9 and P18 diffusely involving the hepatic lobule, again independent of the viability or size of the mutant mouse. By P36, variable degrees of steatohepatitis had developed in untreated *PEX2*^{-/-} mice, with persistently fatty livers, scattered dying hepatocytes, and a mixed neutrophilic/lymphocytic inflammatory infiltrate. Hyperplasia of the hepatocytes, with enlarged nuclei and abundant glassy eosinophilic cytoplasm, was evident in P36 untreated mutants. Bile deposits were less frequently observed and were found predominantly in hepatic sinusoids and occasionally in bile canaliculi. P36 BA-fed mutants did not have inflammatory infiltrates in the liver but still had increased hepatic steatosis relative to that in untreated mutants. There was significant clearing of fat in the pericentral zone in all P36 *PEX2*^{-/-} mice.

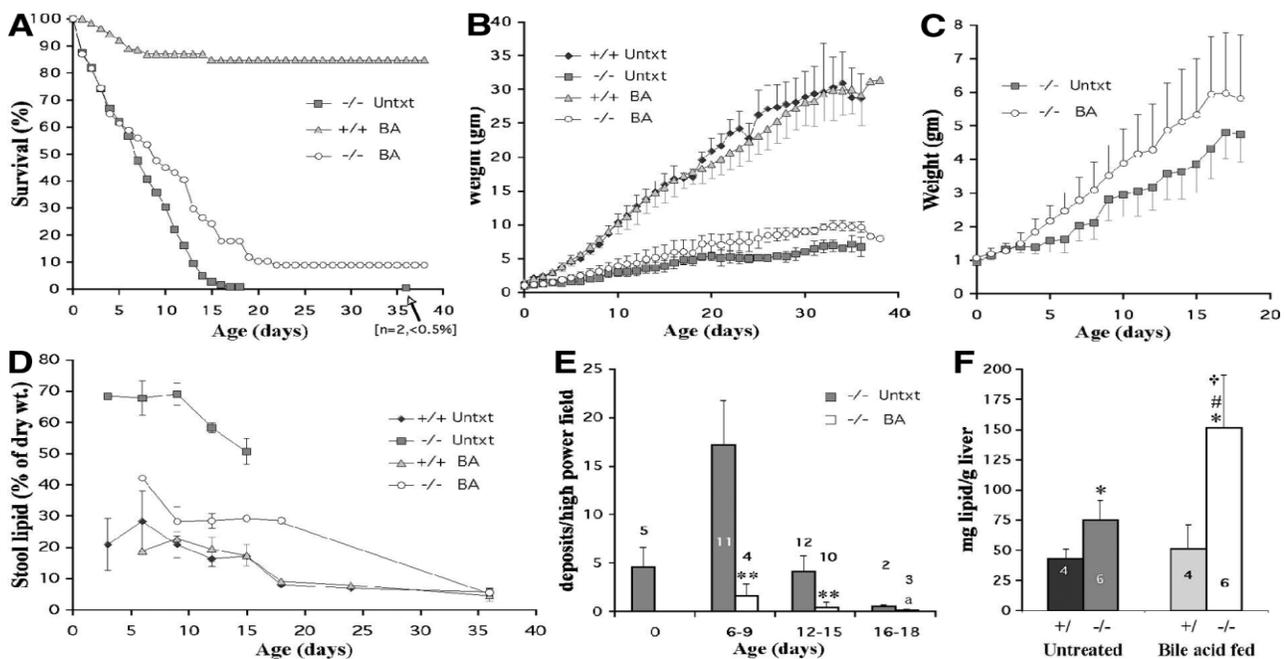
Electron Microscopy Finding:

Electron microscopy revealed additional hepatic degeneration, which was modified by BA feeding in older *PEX2*^{-/-} mice. In a P36 untreated mutant, there were numerous large vacuolated cells that predominantly clustered around central veins. These were not macrophages and did not label with cleaved caspase-3 antibody, and their vacuoles were largely devoid of neutral lipids. Rather, these were degenerating hepatocytes with enlarged cytolysosomes containing flocculent material or

circular membranes but also associated with tightly whorled myelin figure membranes. These myelin figures appeared to be bile products as they were observed around hepatocytes, in bile canaliculi, and in hepatocyte cytosol. In BA-fed mutants, vacuolated hepatocytes were associated with smaller autophagic vacuoles and a profound increase in smooth endoplasmic reticulum.

Electron microscopy demonstrated mitochondrial abnormalities typically seen in peroxisomal disorders in both early postnatal and P36 untreated *PEX2* mutant livers, and these defects persisted in all BA-fed *PEX2*^{-/-} mice. However, BA feeding was associated with significantly increased mitochondrial autophagy and increased matrix density, particularly in older mutants.

This study demonstrated that peroxisome-deficient mice develop severe postnatal liver disease, with transient intrahepatic cholestasis in the juvenile period that progresses to steatohepatitis. BA treatment of *PEX2*^{-/-} mice alleviated the cholestasis, enabling a subset of *PEX2* mutants to survive past the early postnatal period and preventing the onset of steatohepatitis by Day36.



Bile acid-fed mutants had increased tonus and activity, mild improvement in growth, increased body fat, reduction in hepatic cholestasis and near complete normalization of stool fat content.

In their response to the Paper the sponsor's position is the following:

1. The paper by Keane *et al.* is internally inconsistent. Although the authors highlight morphologic changes that in their opinion seem worse in *PEX2*^{-/-} mice treated with cholic acid and ursodeoxycholic acid, the treated homozygous mice actually do significantly better clinically than their untreated counterparts.
2. Many of the morphologic changes highlighted by Keane *et al.* as concerns are either benign

reversible changes or are likely to represent well-known artifacts.

3. The differences in bile acid metabolism between rodents and humans are so significant as to require extreme caution in extrapolating findings from rodent models to humans. Indeed, the untreated natural phenotype inborn errors of bile acid metabolism may differ significantly between human patients and rodents engineered to be deficient in the comparable gene.

Comment:

The hepatic histopathological findings in Zellweger syndrome have not been consistent, and some cases have shown no or only minimal, nonspecific alterations. Portal inflammation, periportal fibrosis, focal necrosis with progression to parenchymal fibrosis, cholestasis, and haemosiderosis have been recorded. In a survey of the literature, Gilchrist et al. found reduction of ‘cholangioles’ in 23% of cases. Cases with severe fibrosis and disruption of the parenchyma and even cirrhosis have been described.

The absence of peroxisomes in liver cells, first described by Goldfischer et al., has been a consistent finding in subsequent ultrastructural studies. In some cases, however, small bodies resembling incompletely developed peroxisomes could be found. Another ultrastructural feature is the occurrence within macrophages of large angulate lysosomes filled with fine double lamellae. Mitochondria show disarrangement and twisting of their cristae and have a dense matrix. The absence of catalase, a peroxisomal enzyme, was demonstrated at the ultrastructural level in a liver biopsy specimen from a patient with Zellweger syndrome.

The paper under review acknowledges markedly improved clinical picture produced by bile acid therapy by showing prolonged survival, mildly improved growth, alleviated intrahepatic cholestasis and intestinal malabsorption, reduced trihydrocholestanic acid and dihydrocholestanic acid levels, temporarily normalized hepatic primary bile acid levels and protected older mutants from developing steatohepatitis. However they also noted that the therapy exacerbated the degree of hepatic steatosis and worsened the already severe mitochondrial and cellular damage and the persistence of significantly increased mitochondrial autophagy and increased matrix density in older mutants.

I agree with the sponsors that the treated homozygous mice actually do significantly better clinically however their interpretation of significant increase in the steatosis as being benign or reversible is questionable. Severe steatosis has been shown to lead to cirrhosis and this question has not been settled yet.

The second point regarding the mouse model and the assertion of the sponsor regarding extrapolating findings from rodent models to humans needs to be addressed. It is true that rodent models are being developed to mimic human liver disease. However, no model to date can completely recapitulate the “corresponding” human disorder. Limiting factors are the time frame required in humans to establish a certain liver disease and the fact that rodents possess a distinct immune system compared with humans and have different metabolic rates affecting liver homeostasis.

In this case if we look at another mouse model we find significant differences in the finding as compared to the model used in the paper.

Different mouse model:

A mouse model with hepatocyte-selective elimination of peroxisomes was generated by In breeding *Pex5-loxP* and albumin-*Cre* mice to investigate the consequences of peroxisome deletion on the functioning of hepatocytes(DIRKX ET AL. HEPATOLOGY, Vol. 41, No. 4, 2005)

The severe hepatic pathology found in Zellweger patients is only partly mimicked in the *L-Pex5* knockout mouse model. Hepatomegaly and fibrosis do develop, but micronodular cirrhosis, hyperbilirubinemia, and elevation of aminotransferases were not observed. This could be due to the specific situation that peroxisomes are only depleted in hepatocytes, and other tissues/cells can convert and exchange peroxisomal metabolites with the hepatocytes.

Severe changes in mitochondrial ultrastructure were observed in 60% to 70% of the mitochondrial population in hepatocytes from 10-week-old *L-Pex5* knockout mice. The most common finding was the proliferation of pleomorphic mitochondria with rarefication of cristae. Other abnormalities primarily involved the inner mitochondrial membrane as previously reported in newborn generalized *Pex5* knockout mice. Mitochondria with curled and stacked cristae, tubulation of the inner membrane and invagination of the cytoplasm, as well as mitochondrial ghosts, were observed. In addition, some mitochondria showed increased matrix density, and a few were found inside autophagic vacuoles. Interestingly, mitochondria were normal in the few hepatocytes in which catalase-positive peroxisomes were found, indicating that this is a cell-autonomous phenomenon. Additional ultrastructural changes in hepatocytes lacking peroxisomes were the proliferation of the smooth endoplasmic reticulum and the appearance of lipid droplets and large groups of lysosomes with electron-dense deposits around dilated bile canaliculi, which were all more numerous than in control mice. This model indicates that in addition to hepatocytes lacking peroxisomes their seems to be abnormality in mitochondria which may be significant.

Being a rare disease only few studies are published in the literature on this issue. The most relevant one being “**Oral Bile Acid Treatment and the Patient with Zellweger Syndrome** **SETCHELL ET AL. HEPATOLOGY Vol. 15, No. 2, 1992**”. A significant improvement in biochemical indices of liver function occurred with a normalization of the serum bilirubin and liver enzymes and a histological improvement in the extent of inflammation and bile duct proliferation and disappearance of cannalicular plugs. Serum and urinary cholestanic acids showed a significant decrease within a few days. A striking and sustained increase in growth was observed after therapy, and an improvement in neurological symptoms was noted. In conclusion, this study indicates that primary bile acid therapy improves liver function and growth in the patient with peroxisomal dysfunction and should be considered in the supportive therapies for this condition.

Liver Biopsy. The pretreatment liver biopsy specimen examined by light microscopy revealed portal tracts filled and distended by proliferating bile ductules and scattered inflammatory cells. Ductular lumen were inconspicuous, and plugs were not seen. Lobular hepatocytes were disorganized with pseudodudular transformation and were full of inflammation, including some neutrophils. Occasional necrotic hepatocytes were observed, and some hepatocytes were swollen and finely granular. Canalicular plugs and golden pigmentation of some hepatocytes were present.

By electron microscopy, hepatocytes were well formed and contained a normal amount of glycogen. Nuclei were unremarkable. Mitochondria were present in relatively normal numbers, and some had dilated cristae. Well-formed peroxisomes could not be recognized. Numerous residual bodies were seen. Bile canaliculi were well formed with numerous microvilli but tended to be flat and empty. The morphological picture was consistent with the peroxisomal disorder of Zellweger.

After 3 mo of treatment with cholic acid and chenodeoxycholic acid, the light microscopy revealed significant changes, most notably a decrease in the extent of bile duct proliferation and inflammation. By electron microscopy, however, peroxisomes could not be identified in the post treatment sample.

One other study which can tangentially address the long-term effectiveness and safety of cholic acid (CA) therapy is in Hereditary Defects of Primary Bile Acid Synthesis disorders. The data shows that in these patients after at least 5 years of treatment resolution of cholestasis and inflammation and a decrease or reversal of the extent of fibrosis/cirrhosis.

In conclusion, given the improvement of clinical picture both in the animal model (with caution in extrapolating findings from rodent models to humans) as well as similar finding of improvement seen in the human studies I don't have much concern on the long-term effectiveness and safety of the drug, however marked increase in steatosis is a concern and need to be monitored.

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/s/

BRIAN K STRONGIN
11/11/2014

MEMORANDUM

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

FROM: David B. Joseph
Lead Pharmacologist

DATE: November 7, 2014

SUBJECT: NDA 205,750 (SD # 1 dated November 21, 2013)

Sponsor: Asklepion Pharmaceuticals, LLC

Drug Product: CHOLBAM (cholic acid) capsules

Comments: None.

Recommendations:

There are no nonclinical issues which preclude the approval of CHOLBAM. I concur with Dr. Zhang's recommendation for approval and his recommended revisions in the label.

David B. Joseph, Ph.D. Date
Lead Pharmacologist
Division of Gastroenterology and Inborn Errors Products

cc:
NDA 205,750
DGIEP
DGIEP/PM
DGIEP/D. Joseph
DGIEP/K. Zhang

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/s/

DAVID B JOSEPH
11/07/2014

Comments on N205,750 CHOLBAM (cholic acid capsules)

Date 7/16/14

From A. Jacobs

1. No nonclinical studies were conducted to support approval, but this is OK, since cholic acid is an abundant bile acid in humans
2. I concur that there are no outstanding pharm/tox approval issues
3. I concur with the recommendations from the division regarding labeling of pharm-tox sections

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/s/

ABIGAIL C JACOBS
07/30/2014

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 205,750
Supporting document/s: 1
Applicant's letter date: November 21, 2013
CDER stamp date: November 21, 2013
Product: CHOLBAM (cholic acid) capsules
Indication: (b) (4)
[REDACTED]
Applicant: Asklepion Pharmaceuticals, LLC
Review Division: Division of Gastroenterology and Inborn Errors
Products (DGIEP)
Reviewer: Ke Zhang, Ph.D.
Supervisor/Team Leader: David Joseph, Ph.D.
Division Director: Donna Griebel, M.D.
Project Manager: Anissa Davis

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205,750 are owned by Asklepion Pharmaceuticals, LLC or are data for which Asklepion Pharmaceuticals, LLC has obtained a written right of reference. Any information or data necessary for approval of NDA 205,750 that Asklepion Pharmaceuticals, LLC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of the NDA.

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1. Executive Summary

1.1 Introduction

Cholbam capsule contains cholic acid. Supplementation of exogenous cholic acid is intended to replace this physiological bile acid in cases of inborn errors of bile acid synthesis. The sponsor seeks marketing approval of Cholbam (b) (4)

1.2 Brief Discussion of Nonclinical Findings

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 levels 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.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical standpoint, the NDA application should be approved for the proposed indication.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

Established Pharmacologic Class (HIGHLIGHTS and section 11)

The EPC text phrase in the Sponsor's proposed label is: (b) (4)
However, "bile acid" is the EPC text phrase shown in the PRPLL for the structurally related drug, ursodiol. The inclusion of (b) (4) in the proposed EPC text phrase for CHOLBAM (cholic acid) is not justified, since this term is not clinically meaningful. The EPC text phrase "bile acid" is considered to be scientifically valid and clinically meaningful for cholic acid based on the chemical structure (the Medical team concurs that "bile acid" is clinically meaningful). Therefore, "bile acid" should be used as the EPC text phrase for CHOLBAM.

Sponsor's Proposed Version:

8.1. Pregnancy

[Redacted text block with (b) (4) in the top right corner]

Evaluation: The [Redacted] (b) (4) information in the proposed version is not appropriate for inclusion in the label [Redacted] (b) (4). The recommended version shown below was developed in collaboration with the Maternal Health team (Tamara Johnson and Jeanine Best).

Recommended Version:

8.1. Pregnancy

[Large redacted text block with (b) (4) in the top right corner]

Risk Summary

[Redacted text block with (b) (4) in the top right corner]

Sponsor's Proposed Version:

12.1 Mechanism of Action

[Redacted text block with (b) (4) in the top right corner]

12.2 Pharmacodynamics

[Redacted text block with (b) (4) in the top right corner]

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

Evaluation:

The proposed mechanism of action that is described in subsections 12.1 and 12.2 is supported by literature cited by the sponsor (Kim, I, et al., J Lipid Res, 48: 2664-2672, 2007; Gonzales, E, et al., Gastroenterology, 137:1310-1320, 2009; Matsubara, T, et al., Mol Cell Endocrinol, 368: 17-29, 2013). However, the Medical and Clinical Pharmacology reviewers recommend the inclusion of additional mechanistic information from other publications, related to the up-regulation of UDP-glucuronosyltransferase. The following sentence should be removed: [Redacted] (b) (4)

[Redacted] The recommended version shown below was developed in collaboration with the Medical and Clinical Pharmacology teams.

Recommended Version:

12.1 Mechanism of Action

[Redacted] (b) (4)

[Redacted text block]

(b) (4)

12.2 Pharmacodynamics

[Redacted text block]

(b) (4)

Sponsor's Proposed Version:

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

[Redacted text block]

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

(b) (4)

[Redacted text block]

Evaluation:

The studies described in the sponsor’s proposed version are not appropriate for inclusion in the label. In addition, the quality and reliability of these studies cannot be evaluated.

Recommended Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genetic toxicology, and (b) (4) fertility studies have not been performed with cholic acid.

Sponsor’s Proposed Version:

13.2 Animal Toxicology and/or Pharmacology

(b) (4)

[Redacted text block]

Evaluation:

The (b) (4) data presented in this subsection is not necessary for safe and effective use of Cholam in humans. Therefore, the inclusion of this subsection is not in accord with 21 CFR 201.57. This subsection should be removed.

Recommended Version: None.

2 Drug Information**2.1 Drug**

Trade Name: Cholbam

Code Name: N/A

Chemical Name:

Table 2.3.S.1.1-1: Cholic Acid Nomenclature

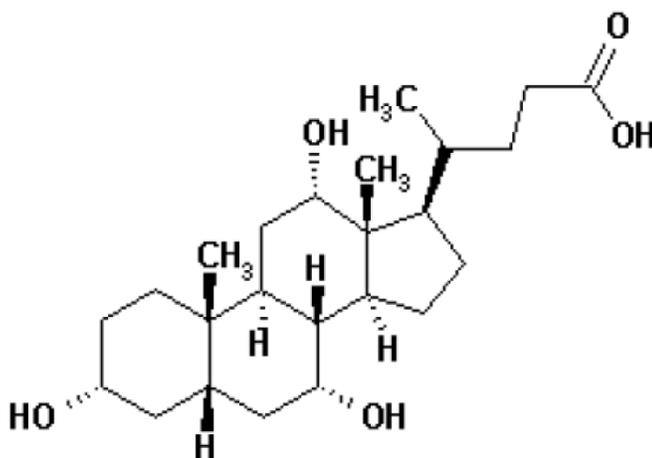
Recommended International Nonproprietary Name (INN)	Cholic Acid
Chemical name(s)	(3 α , 5 β , 7 α , 12 α)-3 α , 7 α , 12 α -trihydroxy-5 β -cholanic-24-oic acid Cholan-24-oic Acid P321
EINECS	201-337-8
Chemical Abstracts Service (CAS) registry number	81-25-4

EINECS: European Inventory of Existing Commercial Chemical Substances

Molecular Formula: C₂₄H₄₀O₅

Molecular Weight: 408.57

Structure or Biochemical Description:



Pharmacologic Class: bile acid

2.2 Relevant INDs, NDAs, and DMFs: IND 45,470

2.3 Drug Formulation

Cholic Acid Capsules contain 50 or 250 mg of cholic acid.

Table 2.3.P.1-1: Composition of Cholic Acid Capsules 50 mg/250 mg

Each Cholic Acid Capsule Contains the Following	% (w/w)	mg per capsule
Active Ingredient:		
Cholic acid	(b) (4)	50.0/250.0 mg
Other Ingredients:		
Silicified microcrystalline cellulose NF*	(b) (4)	(b) (4)
Magnesium stearate Ph. Eur./NF*	(b) (4)	(b) (4)
Total:		
Swedish Orange Capsule Shells Size 2:		
Red iron oxide	(b) (4)	(b) (4)
Titanium dioxide	(b) (4)	(b) (4)
Gelatin	(b) (4)	(b) (4)
Opaque White Capsule Shells Size 0:		
Titanium dioxide	(b) (4)	(b) (4)
Gelatin	(b) (4)	(b) (4)

* Ph. Eur. - European Pharmacopoeia
 NF - National Formulary
 Reference is to the current version of the compendium.

2.4 Comments on Novel Excipients: None.

2.5 Comments on Impurities/Degradants of Concern:

(b) (4)
 The structure (b) (4) is shown below.



The sponsor proposes a specification limit for (b) (4) in the drug substance at ≤ (b) (4) %, based on the qualification threshold stated in ICH guidance Q3B(R2), Impurities in New Drug Products (qualification threshold is 0.2% or 3 mg total daily intake (TDI), whichever is lower, for the dose range of > 100 mg – 2 g). The maximum proposed clinical dose is 15 mg/kg/day, or 900 mg/day if a 60-kg body weight is assumed. The calculated TDI (b) (4) is (b) (4) mg at the proposed limit, based on a 60-kg bodyweight, which is lower than the TDI of 3 mg stated in ICH Q3B(R2). Although (b) (4) is not a degradation product of the drug substance, the proposed limit in accordance with the qualification threshold in ICH Q3B(R2) is deemed acceptable to support approval (b) (4)

In conclusion, the specification limit of (b) (4) % (b) (4) is deemed as acceptable.

2.6 Proposed Clinical Population and Dosing Regimen

(b) (4)
The proposed oral dose is 10-15 mg/kg administered once daily in both pediatric and adult patient populations.

2.7 Regulatory Background

Cholbam was developed under IND 45,470. In the pre-NDA meeting on January 25, 2010, the Agency agreed that nonclinical studies may not be needed to support approval. However, this depended on whether the proposed dose levels are expected to produce a total body content of cholic acid (i.e., endogenous cholic acid + exogenous cholic acid) that exceeds the normal body content of cholic acid in the pediatric population. The sponsor was asked to provide the following information to address this issue: the amount (endogenous pool) and synthetic rate of cholic acid in normal neonates, infants, and children, and any available information on the quantity of endogenous cholic acid in infants with inborn errors of bile acid synthesis. The sponsor submitted such information in this NDA.

3 Studies Submitted

Pharmacokinetics (b) (4) in Male Sprague-Dawley Rats Following a Single IV and PO Dose and Stability in Human Blood

3.1 Studies Reviewed

Pharmacokinetics (b) (4) in Male Sprague-Dawley Rats Following a Single IV and PO Dose and Stability in Human Blood

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

The pharmacology review of IND 45,470 dated September 4, 1994 was referenced.

4 Pharmacology

4.1 Primary Pharmacology

N/A

4.2 Secondary Pharmacology

N/A

4.3 Safety Pharmacology

N/A

5 Pharmacokinetics/ADME/Toxicokinetics

Pharmacokinetics (b) (4) in Male Sprague-Dawley Rats Following a Single IV and PO Dose and Stability in Human Blood (Report # ASK-R2210R1)

Methods: (b) (4) is present as an impurity in the cholic acid drug substance. To determine the pharmacokinetics (b) (4), male Sprague-Dawley rats were dosed intravenously (1 mg/kg) or orally (5 mg/kg) (b) (4) (3 rats/group). Blood samples were collected at 5 min, 0.5, 1, 2, 4, 6, 8, and 24 hr following intravenous administration, and at 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hr following oral administration. Plasma concentrations (b) (4) were determined using LC-MS/MS. The limit of quantitation was 1 ng/mL. The authors stated that plasma concentrations of cholic acid derived from metabolism (b) (4) could not be measured due to interference from endogenous cholic acid.

The stability (b) (4) was evaluated in human whole blood. This study was conducted by incubating (b) (4) (1 and 10 µM) in blood for 120 minutes at 37 °C in duplicate. In addition, the stability (b) (4) was investigated in human whole blood spiked with NaF (2 mg/mL). NaF is a non-specific esterase inhibitor.

Results: The results indicated that following intravenous administration, (b) (4) had a clearance of 97 mL/min/kg, and a volume of distribution of 0.016 L/kg. (b) (4) was detected in plasma only at the 5-min time-point following intravenous

administration. The authors noted that the estimated clearance value exceeded hepatic blood flow.

In 2/3 orally treated rats, (b) (4) was detected in plasma only at 0.25 - 2 hr post-dose; (b) (4) was not detected in plasma in the third rat. The oral bioavailability (b) (4) was determined to be approximately 15%. However, the oral bioavailability is an index of systemic exposure to the unchanged compound. The rapid clearance (b) (4) in rat plasma following intravenous administration may have been mediated by plasma esterases, yielding the metabolites cholic acid and methanol. Furthermore, (b) (4) it is possible that (b) (4) undergoes enterohepatic circulation following oral administration, similar to other bile acids. Given the uncertainties related to the possible metabolism and enterohepatic circulation (b) (4) the data in this study cannot be used to estimate the proportion of absorbed (b) (4) from oral administration. However, it is clear that absorption did occur in 2/3 rats dosed orally (b) (4)

The stability data obtained from the study with human whole blood showed that approximately (b) (4) had degraded after two hours, using either 1 or 10 μM (b) (4) as the starting concentration. Furthermore, no degradation was observed in the presence of NaF, which indicates that degradation was mediated by plasma esterase activity.

6 General Toxicology

No toxicity studies were conducted to support approval of this NDA. The sponsor was asked to provide the following information to assure that the proposed dose levels would not produce a total body content of cholic acid that exceeds the normal body content of cholic in the pediatric population: the amount (endogenous pool) and synthetic rate of cholic acid in normal neonates, infants, and children, and any available information on the quantity of endogenous cholic acid in infants with inborn errors of bile acid synthesis. This information was submitted in this NDA and is summarized below.

Table 1. Relationship of Exogenous Cholic Dosing to Normal Cholic Acid Pool Size and Biosynthetic Rates.

Age	25 th Percentile			50 th Percentile			75 th Percentile		
	Patient Cholic Acid Dose (mg/day)	Normal Cholic Acid Synthesis (mg/day)	Normal Chololate Pool Size (mg)	Patient Cholic Acid Dose (mg/day)	Normal Cholic Acid Synthesis (mg/day)	Normal Chololate Pool Size (mg)	Patient Cholic Acid Dose (mg/day)	Normal Cholic Acid Synthesis (mg/day)	Normal Chololate Pool Size (mg)
2 weeks	57	25.3	60.5	60	27.0	64.4	63	28.1	67.3
1 year	143	211	415	161	227	446	168	236	462
3 years	198	186	583	216	198	619	225	205	641
10 years	435	332	1041	480	353	1106	555	385	1207

Heights and weights for the indicated percentiles and ages were obtained from the CDC Growth Charts for the United States using Length for Age Percentiles: Boys, Birth to 36 Months, Weight for Age Percentiles: Boys, Birth to 36 Months, Stature for Age Percentiles: Boys 2 to 20 Years, and Weight for Age Percentiles: Boys, 2 to 20 Years (<http://www.cdc.gov/growthcharts/charts.htm#Set3>). The height and weight were then converted to the corresponding surface area using the Mosteller equation in an automated calculator (www.medcalc.com/body.html). Dosages of cholic acid were calculated by multiplying the weight in kg by 15 mg/kg. Cholic acid synthetic rates were calculated using values of 110 mg/m²/day for neonates, 478 mg/m²/day for infants of 1 year, and 319 mg/m²/day for children of 3 and 10 years. Standard errors of the mean for synthetic rates were on the order of ± 20 to 25%. The chololate pool size was calculated using values of 263 mg/m² for neonates, 938 mg/m² for infants of 1 year, and 999 mg/m² for children of 3 and 10 years. These values were obtained from Heubi et al, 1982 and Heubi, 1996. Standard errors for pool size measurements clustered around $\pm 10\%$.

In children with inborn errors of bile acid synthesis and metabolism, there is no endogenous synthesis of cholic acid, suggesting that any detected cholic acid in body fluids or tissue is exogenous. The summary information from sponsor's table 1 shows that the proposed clinical dose of cholic acid does not produce a total body content of cholic acid that exceeds the normal body content in these pediatric patients (Heubi JE et al., Bile salt metabolism in the first year of life. *J Lab Clin Med* 100: 127-136, 1982; Heubi JE, Bile acid metabolism and enterohepatic circulation of bile acids. *In: Pediatrics and Perinatology: The Scientific Basis. 2nd ed.* Gluckman, PD and Heymann, MA, 1996).

7 Genetic Toxicology

N/A

8 Carcinogenicity

N/A

9 Reproductive and Developmental Toxicology

N/A

10 Special Toxicology Studies

N/A

11 Integrated Summary and Safety Evaluation

Cholbam (cholic acid) was developed under IND 45,470. [REDACTED] (b) (4)
[REDACTED] Cholic acid is the most abundant endogenous bile acid in humans. Cholbam acts as a supplement of exogenous cholic acid to replace endogenous cholic acid in cases of inborn errors of bile acid synthesis. In the current NDA, the sponsor seeks market approval of Cholbam [REDACTED] (b) (4)
[REDACTED]

In the pre-NDA meeting on January 25, 2010, the Agency agreed that nonclinical studies may not be needed to support approval. However, this would depend on whether the proposed dose levels are expected to produce a total body content of cholic acid (i.e., endogenous cholic acid + exogenous cholic acid) that exceeds the normal body content of cholic acid in the pediatric population. The sponsor was asked to provide the following information to address this issue: the amount (endogenous pool) and synthetic rate of cholic acid in normal neonates, infants, and children, and any available information on the quantity of endogenous cholic acid in infants with inborn errors of bile acid synthesis. The sponsor submitted such information in this NDA.

In children with inborn errors of bile acid synthesis and metabolism, there is no endogenous synthesis of cholic acid, suggesting that any detected cholic acid in body fluids or tissue is exogenous. Thus, only exogenous cholic acid is considered for safety assessment in this case. The information submitted by the sponsor indicates that the proposed clinical dose of cholic acid will not produce a total body content of cholic acid that exceeds the normal body content in the pediatric population from age of 2 weeks up to 10 years. Therefore, from a nonclinical standpoint, the NDA application should be approved for the proposed indication. The labeling should be revised as recommended.

12 Appendix/Attachments

N/A

cc:

Orig NDA 205,750

DGIEP

DGIEP/PM

DGIEP/D. Joseph

DGIEP/K. Zhang

DGIEP/L. Dimick

OND IO/A. Jacobs

R/D Init.: D. Joseph 7/2/14

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/s/

KE ZHANG
07/21/2014

DAVID B JOSEPH
07/21/2014
I concur.

Comments on N205,750 CHOLBAM (cholic acid capsules)

Date 7/16/14

From A. Jacobs

1. No nonclinical studies were conducted to support approval, but this is OK, since cholic acid is an abundant bile acid in humans
2. I concur that there are no outstanding pharm/tox approval issues
3. I concur with the recommendations from the division regarding labeling of pharm-tox sections

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/s/

ABIGAIL C JACOBS
07/17/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205,750

Applicant: Asklepion
Pharmaceuticals, LLC

Stamp Date: December 4,
2013

Drug Name: Cholbam
(cholic acid)

NDA Type: 505 (b) 2

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			N/A
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			N/A
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	x		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		x	

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Ke Zhang, Ph.D.

Reviewing Pharmacologist

Date

David Joseph, Ph.D.

Team Leader/Supervisor

Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

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/s/

KE ZHANG
01/07/2014

DAVID B JOSEPH
01/07/2014