# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 205750Orig1s000

# <u>OTHER REVIEW(S)</u>

**PMR/PMC Development Template**

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

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| | |
|---|---|
| NDA/BLA # | 205750 |
| Product Name: | Cholbam (cholic acid) |
| PMR # | 2882-1 |

PMR/PMC Description: 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.

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| PMR/PMC Schedule Milestones: | | |
|---|---|---|
| | Final Protocol Submission: | September 2015 |
| | Study/Trial Completion: | September 2028 |
| | Final Report Submission: | March 2029 |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   X Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   X Theoretical concern



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☐ Other

Safety issues associated with cholic acid may be confounded by the underlying disease. The population of patients with [redacted] (b) (4) is small. The use of cholic acid outside of this patient population is limited. The safety of FDA-approved cholic acid should be monitored. Potential safety signals include cholestasis and worsening cholestasis, elevated bile acids, and liver function tests (SGOT, serum bilirubin, etc.), gastroenteritis/diarrhea, coagulopathy, and convulsions.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Safety issues associated with cholic acid use in patients with [redacted] (b) (4) include risks of worsening 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.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
***If not a PMR, skip to 4***.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
X FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
X Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk



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X Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments? ***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A postmarketing prospective, long-term, observational study in a routine clinical setting of patients aged (b) (4) 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. (see above)

Required

X Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

*Continuation of Question 4*

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?



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X Does the study/clinical trial meet criteria for PMRs or PMCs?
X Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☒ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)



Reference ID: 3716327

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/s/

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BRIAN K STRONGIN
03/16/2015

LARA DIMICK-SANTOS
03/16/2015

# 505(b)(2) ASSESSMENT

| Application Information | | |
|---|---|---|
| NDA # 205750 | NDA Supplement #: S- N/A | Efficacy Supplement Type SE- N/A |
| Proprietary Name: Cholbam<br>Established/Proper Name: cholic acid<br>Dosage Form: capsules<br>Strengths: 50 mg and 250 mg | | |
| Applicant: Asklepion Pharmaceuticals, LLC. | | |
| Date of Receipt: November 21, 2013 | | |
| PDUFA Goal Date: October 21, 2014 | Action Goal Date (if different):<br>March 18, 2015 | |
| RPM: CDR Anissa Davis-Williams | | |
| Proposed Indication(s): for the treatment of (b) (4) | | |

## GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



Reference ID: 3716788

## INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

| Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph) | Information relied-upon (e.g., specific sections of the application or labeling) |
|---|---|
| Published Literature | Nonclinical toxicology, Clinical and Clinical Pharmacology |

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)
The applicant provided a scientific justification for how the literature that is necessary for approval is scientifically sound and relevant to the proposed 505(b)(2) product.

## RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

## RELIANCE ON LISTED DRUG(S)



Reference ID: 3716788

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO ☒

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

| Name of Listed Drug | NDA # | Did applicant specify reliance on the product? (Y/N) |
|---|---|---|
| | | |
| | | |

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:



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d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*



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(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



Reference ID: 3716788

Pharmaceutical alternative(s):

## PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☒ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*



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☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐



Reference ID: 3716788

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/s/

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BRIAN K STRONGIN
03/16/2015

**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**
**Office of Prescription Drug Promotion**

# ****Pre-decisional Agency Information****

## Memorandum

**Date:** March 6, 2015

**To:** Brian Strongin, R.Ph., MBA, Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products (DGIEP)

**From:** Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

**CC:** Kathleen Klemm, Pharm.D., RAC, Team Leader, OPDP

**Subject:** NDA # 205750 - CHOLBAM (cholic acid) capsules, for oral Use

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Reference is made to DGIEP's consult request dated December 5, 2013, requesting review of the proposed Package Insert (PI) and Carton/Container Labeling for CHOLBAM (cholic acid) capsules, for oral use (Cholbam).

OPDP has reviewed the proposed PI entitled, "FDA package-insert-CHOLBAM word-version-red-lined 2-27-15.docx" that was available in SharePoint on February 27, 2015. OPDP's comments on the proposed PI are provided directly on the attached copy of the labeling (see below).

OPDP has also reviewed the proposed Carton/Container labeling submitted by the sponsor on December 23, 2014, and located in the EDR at \\cdsesub1\evsprod\nda205750\0044\m1\us\114-labeling\draft-labeling\draft-carton-container-labels\250-mg-bottle.pdf and \\cdsesub1\evsprod\nda205750\0044\m1\us\114-labeling\draft-labeling\draft-carton-container-labels\50-mg-bottle.pdf. OPDP has no comments at this time on the proposed Carton/Container labeling.

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



Reference ID: 3712392

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/s/

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ADEWALE A ADELEYE
03/06/2015

**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Food and Drug Administration
Office of New Drugs (OND)
Office of Drug Evaluation-IV (ODE-IV)
Division of Pediatric and Maternal Health
(DPMH)
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

# MEMORANDUM TO FILE

| | |
|---|---|
| **From:** | Ethan D. Hausman, MD<br>Pediatric and Maternal Health Staff (DPMH)<br>Office of New Drugs (OND) |
| **Through:** | Hari Cheryl Sachs, MD<br>Medical Team Leader, DPMH, OND<br><br>Lynne Yao, MD<br>OND Associate Director, DPMH, OND |
| **To:** | Division of Gastroenterology and Inborn Errors of Metabolism (DGIEP) |
| **NDA:** | 205,750 |
| **Sponsor:** | Asklepion Pharmaceuticals, LLC |
| **Drug:** | Cholic acid |
| **Dosage form and route of administration**: | 50 and 100 mg capsules for oral administration |
| **Proposed Dose**: | 10-15 mg/kg/day (once daily administration) |
| **Proposed Indication:** | For the treatment of [redacted] (b) (4) |
| **Consult Request:** | The Division of Gastroenterology and Inborn Error Products (DGIEP) request that DPMH "assist in the labeling review." |



Reference ID: 3704951

## INTRODUCTION

On November 21, 2013, Asklepion Pharmaceuticals, LLC submitted an original NDA in support of marketing approval of cholic acid for the treatment of (b) (4) . The proposed indication is for treatment of (b) (4)

In July 2003, FDA granted orphan designation for cholic acid (cholic acid (3 alpha, 7 alpha, 12 alpha trihydroxy 5-beta cholanolic acid) for the treatment of inborn errors of cholesterol and bile acid synthesis and metabolism.[1] The drug has been under development for this indication under IND 45,470. The product development plan included affected patients of all ages and no pediatric assessment/plan has been submitted.

*Reviewer comment: Additionally, PREA does not apply to products that have received orphan designation..*[2]

The Division of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP) consulted the Pediatric and Maternal Health Staff (PMHS) – Pediatrics to perform a pediatric focused labeling review.

## BACKGROUND

A PubMed/Online Mendelian Inheritance in Man (OMIM) search using various combinations of the disease terms intended for labeling produced several thousand results. Review of the disorders is therefore limited to listing of the disorders for which the sponsor seeks an indication (Table 1; derived from (b) (4) clinical study report), a brief summary of the disorders by group (i.e., inborn errors of cholesterol and bile acid synthesis and metabolism, and inherited peroxisomal disorders) which follows the table, and referral of the reader to the review by the DGIEP Medical Officer (Gao, WY; review pending).

[1] http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm; website accessed June 9, 2014.

[2] Guidance for Industry How to Comply with the Pediatric Research Equity Act; http://www fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf; website accessed June 9, 2014



Reference ID: 3704951

| **Table 1: Disorders for Requested Indication (page** |
|---|
| Alpha-methylacyl-CoA racemase (AMACR) |
| Cholesterol 7 a-hydroxylase (CYP7A1) |
| Peroxisomal disorder (not otherwise specified) |
| Adrenoleukodystrophy |
| Peroxisomal biogenesis disorder: Type unknown |
| Smith-Lemli-Opitz |
| 3ß-HSD or HSD3ß7 |
| Peroxisomal Biogenesis Disorder: Generalized |
| Peroxisomal biogenesis disorder: neonatal |
| Peroxisomal biogenesis disorder: Refsum |
| Peroxisomal biogenesis disorder: Zellweger |
| Sterol 27-hydroxylate (CTX) |
| Unknown |

*Reviewer Comment: Due to clinical difference outlined in the following paragraphs, DGIEP is grouping the disorders that were studied into two categories. The first category is comprised of a heterogeneous group of inborn errors of cholesterol and bile acid synthesis and metabolism due to single enzyme defects (SEDs). The second category is comprised of a heterogeneous group of peroxisomal disorders (PDs). Patients with both groups of disorders may be diagnosed as soon as several weeks of age; however in some disorders such as x-linked adrenal leukodystrophy (X-ALD) diagnosis may occur at several years of age.*

Inborn Errors Cholesterol and Bile Acid Metabolism

Inborn errors of cholesterol and bile acid synthesis and metabolism are a heterogeneous group of rare disorders that share some overlap in phenotype, typically hepatic dysfunction. They are inherited through a variety of mechanisms, but are most commonly inherited as autosomal traits.

Endogenous cholic and chenodeoxycholic acid are primary bile acids produced in the liver. When primary bile acids are conjugated to glycine or taurine, the products are conjugated bile salts which help emulsify fats for digestion. In patients with inborn errors of bile acid synthesis, there is a lack of the enzymes needed to synthesize the primary bile acids. As a consequence, these patients produce high concentrations of atypical bile acids and bile acid intermediates. These atypical bile acids and bile acid intermediates are hepatotoxic and cause progressive cholestasis.

Peroxisomal Disorders

Peroxisomal disorders are etiologically distinct from inborn errors of cholesterol and bile acids; however, they similarly affect bile acid metabolism. The defects in these various disorders affect “down-stream” side-chain modification of primary bile acids. Inheritance is most commonly autosomal recessive (e.g., Zellweger syndrome and



Reference ID: 3704951

Zellweger spectrum diseases [ZSDs]), however, adrenal leukodystrophy (ALD) is inherited in x-linked hemizygous fashion (males and females affected).

*Reviewer comments: The NDA submission is still under review and DGIEP has not yet determined the adequacy of the data. Therefore, this labeling review is limited to general comments regarding Pediatric Use (section 8.4) and Clinical Studies (section 14). Review of Pregnancy (section 8.1) is discussed in the Maternal Health review (T. Johnson, December 15, 2014). Nevertheless, pediatric information should be distributed appropriately throughout the label since the studies to support included affected pediatric patients of all ages, and since the drug is likely to be used in children of all ages.*

**Proposed labeling**

**1 Indications and Usage**

(b) (4)

*Reviewer comment: In verbal and email communications between DPMH and DGIEP on December 16, 2014, and January 22 and 23, 2015, DGIEP informed DMPH that data in the NDA were adequate to support approval for treatment of SEDs and as adjunctive treatment for some or all of the PDs studied including ZSDs.*

*Due to clinical differences described in the summaries of SEDs and PDs provided above, DPMH recommends that following language which more accurately describe the populations studied:*

**1 Indications and Usage**

(b) (4)

**8.4 Pediatric Use**

(b) (4)

*Reviewer comment: Section 8.4 should briefly summarize the data upon which pediatric indications are based, and refer to key sections that describe those data (e.g., section 14 CLINICAL STUDIES). Section 8.4 is to be used also to summarize pediatric ages for whom the drug is not indicated, and to summarized failed studies or conditions for which the drug is not indicated for specific reasons (e.g., patients in clinical studies treated with the candidate drug die faster than patients in the comparison group).*



Reference ID: 3704951

*In the aforementioned communications (December, 2014, and January 2015), DGIEP stated that the youngest patients studied (3 weeks old) did not appear to experience dose/concentration associated toxicities and DGIEP therefore intends to provide weight-based dosing recommendation based on data in the clinical studies.*

*DPMH therefore, recommends the following language for section 8.4*

### 8.4 Pediatric Use (Recommended)

The safety and efficacy 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 (b) (4) [see Clinical Studies (14)].

## 14 CLINICAL STUDIES

Review and comment on the clinical studies section is deferred to DGIEP; however, the sponsor has proposed the following statement:

"(b) (4)

*Reviewer comment: DPMH does not agree that this statement should appear in labeling. The integrated summary of efficacy (ISE) and the (b) (4) were briefly reviewed.* (b) (4) *Therefore, DPMH recommends deleting this information.*

***Additional Comment**:*

*In different portions of the proposed labeling describes dosing volume is described in tablespoons and in milliliters (mL). There is no accepted standard definition for tablespoon volume. All descriptions in labeling must be in standardized metric units, such as mL*

**Conclusion**: DPMH participated in internal labeling discussions and provided the above recommendations to DGIEP. Final labeling will be negotiated with the sponsor may contain additional changes not contained in this document.



Reference ID: 3704951

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/s/

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ETHAN D HAUSMAN
02/20/2015

HARI C SACHS
02/23/2015

LYNNE P YAO
02/24/2015

# REVIEW OF CONSULT REQUEST FOR RARE PEDIATRIC DISEASE DETERMINATION

FILE COPY

| | |
|---|---|
| Date Submitted by Sponsor: | December 12, 2014 |
| Date Received by FDA: | December 15, 2014 |
| Date Received by Reviewer: | December 22, 2014 |
| Date Review Completed: | February 4, 2015 |
| Designation Number: | 03-1705C |
| Trade Name: | Cholbam™ |
| Generic Name: | Cholic Acid |
| Sponsor: | Asklepion Pharmaceuticals, LLC<br>729 E. Pratt Street<br>Baltimore, MD 21202 |
| Primary Contact: | Gary Pasternack, M.D., Ph.D.<br>Chief Executive Officer<br>Asklepion Pharmaceuticals, LLC<br>729 E. Pratt Street<br>Baltimore, MD 21202<br>Telephone: (410) 545-0494 X107<br>Email: gary.pasternack@asklepionpharm.com |
| Manufacturer: | [redacted] (b) (4) |
| Regulatory Status: | The sponsor has submitted an NDA (#205-705) for Cholbam™ (cholic acid) for treatment of [redacted] (b) (4) (b) (4) The sponsor also states that Cholbam™ (cholic acid) has been studied under IND #45,470 for treatment of [redacted] (b) (4) (b) (4) This IND is currently active. |
| Proposed Orphan Designation: | Treatment of inborn errors of cholesterol and bile acid synthesis and metabolism. |
| Orphan Drug Designation History: | Cholic acid received orphan drug designation for the treatment of inborn errors of cholesterol and bile acid synthesis and metabolism on July 18, 2003. Cholic acid received Orphan Designation from the European Agency for the Evaluation of Medicinal Products (EMEA) on December 18, 2002 (excerpted from review #03-1705). |

**1. Background of Disease or Condition** (excerpted from review #03-1705)
The human liver synthesizes two primary bile acids, cholic acid and chenodeoxycholic acid. These bile acids are critical to the development and maintenance of enterohepatic circulation. The primary functions of bile acids are: 1) to promote bile flow; 2) to solubilize cholesterol and phospholipid in the gall bladder; and 3) to enhance gastrointestinal lipid digestion and absorption.[1] Bile acids are also essential for elimination of endogenous and exogenous toxic substances. Bile acid pools are maintained through an efficient process of intestinal reabsorption and hepatic extraction, with less than 5% of bile acid being lost per day.[2,3] Bile acid synthesis and homeostasis is subject to a negative feedback loop by the flux of bile acids returning to the liver.[3] In response to decreased levels of bile acids, the liver catabolizes cholesterol to primary bile acids. The synthesis pathway involves a complex sequence of reactions regulated by at least 14 enzymes which act at various steps to modify cholesterol's steroid ring structure or nucleus, and to oxidize and shorten sterol side chains. To date, six defects in enzyme activity involved in primary bile acid synthesis have been identified, and involve the following enzymes: 3βhydroxy-C27-steroid dehydrogenase/isomerase, $\Delta^4$-3 oxosteroid 5β-reductase, oxysterol-7α-hydroxylase, sterol 27-hydroxylase, 2-methylacyl-CoA racemase, and enzymes involved in side chain conjugation and amidation.

Inborn errors in bile acid synthesis are associated with progressive cholestatic liver disease and fat-soluble vitamin malabsorption syndromes, and are characterized by markedly reduced or complete lack of cholic and chenodeoxycholic acid. Diagnosis is accomplished by mass spectrometry of bile acid profiles of the urine. Deficiencies in specific enzymes result in decreased production of primary bile acids. As a result, down-regulation of bile acid synthesis is inhibited, and the liver synthesizes increased amounts of sterol and bile acid intermediates involved in the synthesis pathway proximal to the enzyme defect. Liver injury is the result of failure to synthesize adequate concentrations of primary bile acids required to stimulate bile acid-dependent bile flow and increased production of cholestatic and hepatotoxic atypical metabolites that accumulate in the hepatocytes. Early diagnosis of these inborn errors is important because these conditions are inevitably fatal. Death is usually caused by cirrhosis and liver failure or a consequence of internal hemorrhage secondary to fat-soluble vitamin malabsorption. Cerebrotendinous xanthomatosis (CTX), caused by sterol 27-hydroxylase deficiency, is also associated with premature cardiovascular disease and progressive neurologic dysfunction.

The only therapy currently available for many of these primary bile acid synthesis defects is liver transplantation, however, this procedure is limited by the availability of a suitable donor and is associated with the risk of transplant rejection.

**2. Population Estimate**
The Office of Orphan Products Development (OOPD) has accepted a target population estimate for inborn errors of primary bile acid synthesis of 500 (see review #03-1705). Due to the expected course of the disease/condition the target population estimate would not be expected to have increased to any great extent since 2003.



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To support its request for a Rare Pediatric Disease Voucher, the sponsor states that for three of the four specific enzyme defects treated by cholic acid untreated patients die within the first decade of life; and patients with sterol 27 hydroxylase deficiency tend to live to adulthood even if untreated. The sponsor states that 27 hydroxylase deficiency patients would comprise no more than 25% of all patients with inborn errors of primary bile acid synthesis and thus 75% of all persons with inborn errors of primary bile acid synthesis are children.

The sponsor submits demographic data from subjects enrolled in a clinical trial (Protocol CAC-91-10-10) to support its contention that inborn errors of primary bile acid synthesis primarily affects children (see table below excerpted from the application).

| **Characteristic** | | **ITT (N = 85)** | **Safety (N = 79)** | **mITT (N = 70)** |
|---|---|---|---|---|
| Gender [N (%)] | Female | 31 (36) | 29 (37) | 25 (36) |
| | Male | 50 (59) | 48 (61) | 45 (64) |
| | Unknown | 4 (5) | 2 (3) | 0 (0) |
| Race [N (%)] | Arabic | 1 (1) | 1 (1) | 1 (1) |
| | Asian Indian | 2 (2) | 2 (3) | 2 (3) |
| | Black/African American | 1 (1) | 1 (1) | 1 (1) |
| | Egyptian | 1 (1) | 1 (1) | 1 (1) |
| | Haitian | 1 (1) | 1 (1) | 1 (1) |
| | Hispanic | 10 (12) | 10 (13) | 10 (14) |
| | Middle Eastern | 7 (8) | 7 (9) | 6 (9) |
| | Persian/Iranian | 1 (1) | 1 (1) | 1 (1) |
| | Portuguese | 2 (2) | 2 (3) | 2 (3) |
| | UNK | 29 (34) | 23 (29) | 16 (23) |
| | White | 30 (35) | 30 (38) | 29 (41) |
| Age at diagnosis [years] | Mean ± SD | 2 ± 4 (n = 74) | 2 ± 4 (n = 71) | 2 ± 4 (n = 62) |
| | Min, Max | 0, 13 (n = 74) | 0, 13 (n = 71) | 0, 13 (n = 62) |
| Age group at diagnosis [N (%)] | <3 months | | 23 (27) | |
| | 3-6 months | | 19 (22) | |
| | 7-12 months | NA | 13 (15) | NA |
| | 13-36 months | | 12 (14) | |
| | >36 months | | 18 (21) | |
| Age at treatment start [years] | Mean ± SD | 3 ± 4 (n = 77) | 3 ± 4 (n = 77) | 3 ± 4 (n = 68) |
| | Min, Max | 0, 16 (n = 77) | 0, 16 (n = 77) | 0, 16 (n = 68) |
| Baseline height percentile | Mean ± SD | 33 ± 31 (n = 16) | 33 ± 31 (n = 16) | 34 ± 31 (n = 15) |
| | Min, Max | 0, 92 (n = 16) | 0, 92 | 0, 92 (n = 15) |
| Baseline weight percentile | Mean ± SD | 39 ± 36 (n = 16) | 39 ± 36 (n = 16) | 35 ± 35 (n = 15) |
| | Min, Max | 0, 98 (n = 16) | 0, 98 (n = 16) | 0, 98 (n = 15) |

N = number of patients, n = number of patients with data available, NA = not assessed, SD = standard deviation.

*Reviewer's Comments:*



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*The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 defines a rare pediatric disease as 1) a disease that primarily affects individuals aged from birth to 18 years including neonates, infants, children and adolescents; and 2) the disease is a rare disease or condition (affecting fewer than 200,000 persons in the United States).*

*The disease or condition that is the subject of this request is inborn errors of cholesterol and bile acid synthesis and metabolism. OOPD accepts that the prevalence of inborn errors of cholesterol and bile acid synthesis and metabolism in the United States is less than 200,000.*

*OOPD contacted* [redacted] (b) (4) *that of all persons diagnosed with a bile acid synthesis defect, who are resident in the United States, 69% are currently <18 years of age (see Appendix A).*

*OOPD notes that inborn errors of cholesterol and bile acid synthesis and metabolism are due to peroxisome biogenesis disorders (PBD) in addition to single enzyme defects. PBDs are divided into two groups: Zellweger spectrum disorders and Rhizomelic Chondrodysplasia Punctua spectrum. The Zellweger spectrum is comprised of three disorders that have considerable overlap of features. These include Zellweger syndrome (ZS, the most severe form), neonatal adrenoleukodystrophy (NALD), and Infantile Refsum disease (IRD, the least severe form). The PBDs of the Zellweger spectrum are associated with defects of bile synthesis, while the Rhizomelic Chondrodysplasia Punctua spectrum cause disruption in endochondral bone formation[7,8]. The prognosis for Zellweger spectrum is poor with most infants not surviving past 6 months of age[7]. IRD patients rarely survive beyond their teens[9], and NALD patients do not survive beyond 10 years of age[10].*

*It is estimated that the incidence of Zellweger spectrum disorders is 1/50,000 births[11]. This translates to an annual incidence of 80 cases in the United States, assuming an annual birth rate of 4 million. Given the poor prognosis of Zellweger spectrum disorders the estimated U.S. prevalence of Zellweger spectrum disorders would be 1,600 assuming a disease duration of 20 years.*

*The data provided by Dr. Setchell provides adequate evidence that inborn errors of cholesterol and bile acid synthesis and metabolism, including peroxisomal disorders, primarily affect individuals aged from birth to 18 years including neonates, infants, children and adolescents.*

**3. Scientific Rationale** (excerpted from review #03-1705)
In inborn errors of primary bile acid synthesis, little to no primary bile acid is produced. Instead, the liver synthesizes increasing amounts of sterol and bile acid intermediates proximal to the enzyme defect. Cholestasis and liver injury result from inadequate amounts of primary bile acid, and the production of hepatotoxic atypical metabolites. The sponsor hypothesizes that primary bile acid replacement therapy may be effective in these defects by increasing the primary bile acid pool size thus stimulating bile flow and



Reference ID: 3706582

by down regulating endogenous bile acid synthesis by negative feedback inhibition thereby limiting production of hepatotoxic atypical bile acid intermediates. The sponsor also states that administration of primary bile acids will facilitate the absorption of fats and fat-soluble vitamins. By identifying these patients early, the sponsor hopes that primary bile acid therapy may help avoid the need for liver transplantation.

Literature included in this designation request support the use of cholic acid in the treatment of various enzyme deficiencies, including CTX, 3βhydroxy-C27-steroid dehydrogenase/isomerase deficiency, 2-methylacyl-CoA racemase deficiency, and $\Delta^4$-3 oxosteroid 5β-reductase deficiency. Various sources have reported favorable effects of this therapy including marked reduction in the production of atypical metabolites, normalization of liver enzymes, improvement in liver function and histology, and improvement in clinical symptoms.[3,4,5] Changes in liver morphology have also been reported.[6] There is also evidence in the literature of cholic acid being used to treat Zellweger syndrome with improvement in liver function and a decrease in hepatic inflammation[12].

**4. Same Drug vs. Different Drug**

Cholbam™ (cholic acid) has not received marketing approval in the United States for the treatment, diagnosis or prevention of any disease or condition.

**5. Evaluation and Recommendations**

Asklepion Pharmaceuticals, LLC requests Pediatric Rare Disease designation for Cholbam™ (cholic acid) [redacted] (b) (4) OOPD has been consulted by CDER ODEIII/DGEIP [redacted] (b) (4) The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 defines a rare pediatric disease as 1) a disease that primarily affects individuals aged from birth to 18 years including neonates, infants, children and adolescents; and 2) the disease is a rare disease or condition (affecting fewer than 200,000 persons in the United States). OOPD accepts that the prevalence [redacted] (b) (4) in the United States is less than 200,000. The concern with this request is that the sponsor has not adequately demonstrated that [redacted] (b) (4) primarily affects individuals aged from birth to 18 years including neonates, infants, children and adolescents. The data presented by the sponsor is based on the age at diagnosis and does not provide an age distribution of all persons currently living in the United States who have been diagnosed [redacted] (b) (4) In order to meet the criteria that a disease or condition primarily affects persons from birth through 18 years of age greater than 50% of the affected population in the U.S. is between birth and 18 years of age.

OOPD contacted [redacted] (b) (4) that of all persons diagnosed with a bile acid synthesis defect, who are resident in the United States, 69% are currently <18 years of age (see Appendix A). The data provided [redacted] (b) (4)



Reference ID: 3706582

provides adequate evidence that [redacted] (b) (4) primarily affect individuals aged from birth to 18 years including neonates, infants, children and adolescents.

John D. Milto, M.D.

Concur: _____ Date: 2/5/2015

Henry H. Startzman III, M.D.
Director, Orphan Drug Designation Program
Office of Orphan Products Development

cc: HF-35/ Designation file 03-1705
HF- 35/ Chron file
HF-35/ J. Milto



Reference ID: 3706582

**References** (excerpted from review #03-1705)

1. http://www.harrisonsonline.com

2. Setchell KDR, O'Connell NC, Squires RH, Heubi JE. Congenital defects in bile acid synthesis cause a spectrum of disease manifest as severe cholestasis, neurological disease, and fat-soluble vitamin malabsorption. In: Northfield TC, Ahmed H, Jazwari R, Zentler-Munro R, eds. Bile Acids in Hepatobiliary Disease. Dordrecht: Kluwer Academic Publishers; 1999. P 55-63.

3. Setchell KDR, O'Connell NC. Disorders of bile acid synthesis and metabolism. In: Walker WA, Durie PR, Hamilton JR, Walker-Smith JA, Watkins JB, eds. Pediatric Gastrointestinal Disease. Hamilton, Ontario, Canada: B.C. Decker Inc.; 2000. P 1138-1170.

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

5. Setchell KDR, Balistreri WF, Piccoli DA, Clerici C. Oral bile acid therapy in the treatment of inborn errors in bile acid synthesis associated with liver disease. In: "Bile Acids as Therapeutic Agents; From Basic Science to Clinical Practice" (Paumgartner G, Stiehl A, Gerok W, eds.), Klumer Academic Publishers, Dordrecht/Boston/London. 1990, p 367-373.

6. Daugherty CC, Setchell KDR, Heubi JE, Balistreri WF. Resolution of liver biopsy alterations in three siblings with bile acid treatment of an inborn error of bile acid metabolism ($\Delta^4$-3 oxosteroid 5β-reductase deficiency). Hepatology 1993; 18: 1096-1101.



Reference ID: 3706582

## References for this Review

7. http://www.ninds.nih.gov/disorders/zellweger/zellweger.htm.

8. http://themedicalbiochemistrypage.org/rcdp.html.

9. http://www.ninds.nih.gov/disorders/refsum_infantile/refsum_infantile.htm.

10. http://www.nlm.nih.gov/medlineplus/ency/article/001182.htm.

11. http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=912.

12. Setchell, K.D., et al., Oral bile acid treatment and the patient with Zellweger syndrome. *Hepatology* 1992;15:198-207.

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BRIAN K STRONGIN
02/24/2015

**Rare Pediatric Disease Priority Review Voucher eligibility checklist**

Under section 529 of the Food, Drug, and Cosmetic Act, the sponsor of a human drug application (as defined in section 735(1) of the FD&C Act ) for a rare pediatric disease drug product may be eligible for a voucher that can be used to obtain a priority review for a subsequent human drug application submitted under section 505(b)(1) of the FD&C Act or section 351 of the Public Health Service (PHS) Act after the date of approval of the rare pediatric disease drug product.

This checklist is intended to help determine if an NDA or BLA is eligible for a **Rare Pediatric Disease Priority Review Voucher.**

| **NDA/BLA** | **Review Division** |
|---|---|
| **NDA 205750 cholic acid** | **DGIEP** |
| **Requirement** | **Meets? (yes/no)** |
| | |
| For prevention or treatment of a *rare pediatric disease? (OOPD makes determination)* | Yes |
| | |
| 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 the FD&C Act or section 351(a) or 351(k) of the PHS Act? | Yes |
| | |
| FDA deems eligible for priority review? | Yes 1/8/14 |
| | |
| Submitted under section 505(b)(1) (includes 505(b)(2) applications) of the FD&C Act or section 351(a) of the Public Health Service Act? | Yes |
| | |
| Relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population? | Yes |
| | |
| Does not seek approval for an adult indication in the original rare pediatric disease product application? | Yes |
| | |

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LARRY J BAUER
02/24/2015

**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Food and Drug Administration
Office of New Drugs
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

# Division of Pediatric and Maternal Health – Maternal Health Review Addendum

**Date:** December 12, 2014

**From:** Tamara Johnson, MD, MS, Medical Officer
Division of Pediatric and Maternal Health

**Through:** Carrie Ceresa, PharmD, MPH, Acting Team Leader- Maternal Health,
Division of Pediatric and Maternal Health, and

Lynne P. Yao, MD, Acting Division Director,
Division of Pediatric and Maternal Health

**To:** Division of Gastroenterology and Inborn Errors Products (DGIEP)

**NDA:** 205750

**Drug:** Cholbam (cholic acid)

**Applicant:** Asklepion Pharmaceuticals, LLC.

**Proposed Indication:** Treatment of [redacted] (b) (4)

**Consult Request:** "The reason for this consult is to invite the Maternal Health team to attend meetings and assist in the labeling review pertaining to this NDA and offer any assistance as necessary."

**Materials Reviewed:** (labeling, reviews)

- Original NDA 205750, Cholic Acid, received November 21, 2013
- Draft Cholic Acid Labeling, received November 21, 2013
- DPMH- Maternal Health consult review, by T. Johnson, dated June 30, 2014

## INTRODUCTION

This original NDA for the new molecular entity Cholbam (cholic acid) is submitted as the proposed [redacted] (b) (4) This marketing application is presented to the Agency with clinical evidence from two single-arm clinical trials for efficacy and safety and one pharmacokinetic study in healthy adult male volunteers. A waiver for required nonclinical studies was granted in 2004. The waiver decision was based upon the abundant nonclinical data available in published literature and because cholic acid is a natural component of the human body.

The Division of Gastroenterology and Inborn Errors Products (DGIEP) requested meeting attendance and input from the Division of Pediatric and Maternal Health - Maternal Health Team (DPMH-MHT) for the proposed full prescribing information of Cholbam, as well as any additional assistance as necessary. A review providing recommendations for the Pregnancy [redacted] (b) (4) labeling sections, as well as a pregnancy surveillance program within the product registry, was provided to DGIEP on June 30, 2014. This addendum review provides an update to the DPMH-MHT labeling recommendations such that the Cholbam full prescribing information complies with the finalized Pregnancy and Lactation Labeling Rule regulatory requirements.[1]

## BACKGROUND

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[1] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule[2] format to include information about the risks and benefits of using these products during pregnancy and lactation.

## LABELING RECOMMENDATIONS

DPMH-MHT amended labeling recommendations for sections 8.1 and 8.2 to comply with the PLLR. These labeling revisions are shown below; deleted text has a strikethrough, while new text is underlined. Recommendations made by the DGIEP review team are included in this version of the labeling.

---

[1] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

[2] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).



Reference ID: 3672448

(b) (4)

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy (b) (4)

(b) (4)

Pregnancy Exposure Registry

There is a pregnancy (b) (4) surveillance program that monitors pregnancy outcomes in women exposed to (b) (4) Cholbam during pregnancy. - (b) (4)

Women who become pregnant during Cholbam treatment are encouraged to enroll. Patients or their (b) (4) should call (b) (4) to enroll.

Risk Summary

No studies in pregnant women or animal reproduction studies (b) (4) have (b) (4) been conducted with Cholbam (b) (4) -Limited published case reports discuss (b) (4) pregnancies in (b) (4) women taking cholic acid for 3β-HSD deficiency (b) (4) resulting in healthy infants. These reports (b) (4) may not adequately inform (b) (4) the presence or absence of drug-associated risk with the use of Cholbam during pregnancy. (b) (4)

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

(b) (4)



Reference ID: 3672448

(b) (4)

## 8.2 Lactation (b) (4)

Risk Summary

(b) (4) Endogenous cholic acid is (b) (4) present in human milk. Clinical lactation studies have not been conducted to assess the presence of Cholbam in human milk, the effects of Cholbam on the breastfed child, or the effects of Cholbam on milk production. There are no animal lactation data and no data from case reports available in the published literature. (b) (4) The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Cholbam and any potential adverse effects on the breastfed child from Cholbam or from the underlying maternal condition.

## 17 PATIENT COUNSELING INFORMATION

- Pregnancy: There is a pregnancy surveillance program that monitors pregnancy outcomes in women exposed to Cholbam during pregnancy *[see Use in Specific Populations (8.1)]*. (b) (4)



Reference ID: 3672448

*APPENDIX*

***Applicant's Original Proposed Labeling***
****
(Highlights)

(b) (4)

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

(b) (4)

(b) (4)

(b) (4)

## 17 PATIENT COUNSELING INFORMATION

(b) (4)



Reference ID: 3672448

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/s/

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TAMARA N JOHNSON
12/12/2014

CARRIE M CERESA
12/12/2014

LYNNE P YAO
12/15/2014

# MEMORANDUM

## REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| **Date of This Memorandum:** | December 12, 2014 |
| **Requesting Office or Division:** | Division of Gastroenterology & Inborn Error Products (DGIEP) |
| **Application Type and Number:** | NDA 205750 |
| **Product Name and Strength:** | Cholbam (cholic acid) capsules 50 mg and 250 mg |
| **Submission Date:** | March 21, 2014 |
| **Applicant/Sponsor Name:** | Asklepion Pharmaceuticals, LLC |
| **OSE RCM #:** | 2013-2752 |
| **DMEPA Primary Reviewer:** | Matthew Barlow, RN, BSN |
| **DMEPA Team Leader:** | Kendra Worthy, PharmD |

## 1 PURPOSE OF MEMO

DGIEP requested that we review [redacted] (b) (4)

## 2 CONCLUSIONS

We reviewed [redacted] (b) (4)

[1] [redacted] (b) (4)

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/s/

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MATTHEW J BARLOW
12/12/2014

KENDRA C WORTHY
12/12/2014

**M E M O R A N D U M**

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

---

DATE: September 23, 2014

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology & Inborn Errors Products
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

Young Moon Choi, Ph.D.
BE Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Charles Bonapace, Pharm.D.
Chief, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

and

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 205-750, Cholic acid capsules, 50 and 250 mg

At the request of the Division of Gastroenterology and Inborn Errors Products (DGIEP), the Division of Bioequivalence and GLP Compliance (DBGLPC) arranged inspections of the clinical and analytical portions of the following *in vivo* bioequivalence study:

**Study Number:** CAC-003-01
**Study Title:** "Comparative bioavailability of three formulations of cholic acid in healthy male

subjects using a multiple dose repeated measures approach"

**Clinical**:

The inspection of the clinical portion of the study was conducted by Peter Lenahan (ORA) during May 12-20, 2014 at **Frontage Clinical Services, Inc., Hackensack, NJ.** The inspection included a thorough examination of the protocol, protocol amendments, protocol deviations, study records, informed consent forms, SOPs, IRB approvals, case report forms, and interviews/discussions with the firm's staff and management.

At the conclusion of the inspection, Form FDA 483 was issued (**Attachment-1**). The firm responded to Form FDA 483 on June 3, 2014 (**Attachment-2**). The Form FDA 483 observation, the firm's response to Form FDA 483, and DBGLPC's evaluation follow.

1) [redacted] (b) (4) [redacted] (b) (4) **for study CAC-003-01.**

In their response (**Attchment-2**), [redacted] (b) (4) (b) (4)

[redacted] (b) (4)

In the opinion of these reviewers, [redacted] (b) (4) (b) (4)

**Analytical**:

The inspection of the analytical portion of the study was conducted by [redacted] (b) (4) (ORA), Young Moon Choi, Ph. D. (OSI), and Gajendiran Mahadevan, Ph.D. (OSI) [redacted] (b) (4) [redacted] (b) (4) The inspection included a thorough examination of study records, facilities and equipment, and interviews and discussions with the firm's staff and management.

At the conclusion of the inspection, Form FDA 483 was issued (**Attachment-3**). The firm responded to Form FDA 483 on May 14, 2014 (**Attachment-4**). The Form FDA 483 observations, the firm's response to Form FDA 483, and DBGLPC's evaluation follow.

**Failure to fully validate LC-MS/MS assay for cholic acid (CA), glycholic acid (GCA), and taurocholic acid (TCA). Specifically,**

a. **Long-term stability of the above analytes was not evaluated.**

[redacted] (b) (4) acknowledged the observation and stated that the lack of long-term stability data was an oversight. The firm conducted a long-term stability study and submitted the data on September 12, 2014 (**Attachment-5**). The data support that each analyte is stable for 96 days at -70°C, the longest duration between sample collection and sample analysis.

b. **Accuracy and precision for the analytes in the plasma were not demonstrated with appropriate sensitivity. Specifically, 44 samples for CA, 253 samples for GCA, and 346 samples for TCA were below the level of 56, 244, and 24 ng/mL, respectively. These were the lowest concentrations of bile acids in the plasma used to determine accuracy and precision during validation, and represent the LLOQ for each analyte.**

In their response, [redacted] (b) (4) stated that because the analytes are endogenous, they used phosphate buffer as a surrogate matrix for the preparation of the select calibrators, resulting in a lower limit of quantitation (LLOQ) of 2 ng/mL for cholic acid (CA), glycocholic acid (GCA), and taurocholic acid (TCA). However, the pooled plasma used in the method validation had endogenous concentrations of 56/244/24 ng/mL for CA, GCA, TCA, respectively. Thus, these mean endogenous concentrations of CA, GCA, and TCA in blank plasma are the lowest concentration

determined with adequate sensitivity and represent the LLOQ for each analyte.

The steady-state $C_{max}$ and $AUC_{tau}$ based on cholic acid were the primary endpoints, whereas the steady-state $C_{max}$ and $AUC_{tau}$ of total CA (CA+GCA+TCA) were secondary endpoints. Of the 18 subjects enrolled in the study, 17 subjects completed all three dosing regimens and were included in the PK analysis. One subject received only one dosing regimen and was excluded from the analysis.

Based on the primary endpoint, the analytical method demonstrated sufficient sensitivity to estimate the steady-state $C_{max}$ and $AUC_{tau}$ based on CA concentrations from 14 subjects; the CA concentrations from subjects 7, 13, & 15 were below the lower limit of quantitation (BLOQ) at the beginning or end of the dosing interval and impacted the estimation of $AUC_{tau}$.

GCA and TCA plasma concentrations were BLOQ in most subjects at most time points (except subjects 4, 9, & 14 for GCA and subject 14 for TCA); thus, the analytical method failed to demonstrate sufficient sensitivity to estimate the steady-state $C_{max}$ and $AUC_{tau}$ based on GCA and TCA concentrations.

In these reviewers' opinion, the analytical method used in this *in vivo* bioequivalence study demonstrated sufficient sensitivity to measure the plasma concentrations of CA necessary to determine the primary endpoints.

**Recommendations:**

Following the inspections and review of the firm's responses, the data from study CAC-003-01 were found not to be reliable. Therefore, these DBGLPC reviewers recommend that the data not be accepted for Agency review since the authenticity of the data cannot be assured (b) (4) (b) (4).

Gajendiran Mahadevan, Ph.D.
GLP Branch, DBGLPC, OSI

Young Moon Choi, Ph.D.
BE Branch, DBGLPC, OSI

**Final Classification:**

**OAI: Frontage Clinical Services, Hackensack, NJ**
FEI: 3005134380

**VAI:** [redacted] (b) (4)
FEI: [redacted] (b) (4)

CC:
OSI/DBGLPC/Taylor/Bonapace/Dasgupta/Mahadevan/Dejernett/Fenty-Stewart/Nkha/Johnson
OSI/DBGLPC/Haidar/Skelly/Choi
CDER/OND/DGIEP/Griebel/Lostritto/Riviere

ORA/NWJ-DO/Rolli/Lenahan
ORA/ [redacted] (b) (4) DO/ [redacted] (b) (4)

Draft: GM 07/23/2014; 9/17/14
Edit: YMC 09/14/2014; CB 09/22/2014

OSI File: BE6667; O:\BE\EIRCOVER\205750.bio.ch
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/ [redacted] (b) (4) /NDA 205-750_Cholic acid

**FACTS: 8745501**

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/s/

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GAJENDIRAN MAHADEVAN
09/23/2014

YOUNG M CHOI
09/23/2014

ARINDAM DASGUPTA
09/23/2014

CHARLES R BONAPACE
09/25/2014

WILLIAM H TAYLOR
09/26/2014

**M E M O R A N D U M**

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

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DATE: September 10, 2014

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Office of Drug Evaluation III

FROM: Hansong Chen, Ph.D., Pharm.D.
Pharmacologist
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 205-750, Cholic Acid Capsules, 50 and 250 mg, Sponsored by Asklepion Pharmaceuticals, LLC, Baltimore, MD

At the request of the Division of Gastroenterology and Inborn Errors, Office of Drug Evaluation III, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted an inspection of the analytical portion of the following efficacy study:

**Study Number**: CAC-91-10-10 (including sub-study CAC-92-8-19)
**Study Title**: "Investigation in the Pathogenesis of Liver Disease in Patients with Inborn Errors of Bile Acid Metabolism."

FDA investigators [redacted] (b) (4) (OSI) conducted the inspection at [redacted] (b) (4) (b) (4) (b) (4) The audit included a thorough review of the study records, case report forms, examination of facilities and test

article accountability, as well as interviews and discussions with the lab's management and staff.

The lab used the following procedure to determine atypical bile

(b) (4)

(b) (4)
(b) (4)
(b) (4) Their inspection findings prompted me to question (b) (4)
(b) (4)

(b) (4)
(b) (4) The results were listed in attachment 1. After comparing them with the data submitted to the Agency under NDA 205-750, I found the following issues:

1. (b) (4)
2.
3.

I compared (b) (4)
(b) (4)
(b) (4) Some typical examples are listed in Attachment 4.

(b) (4)

In addition, we found the following issues:

1. (b) (4)

**2.** [redacted] (b) (4)

This DBGLPC scientist is of opinion that [redacted] (b) (4) (b) (4)

This DBGLPC scientist answers the reviewer's questions as follows:

1. **If the signal of abnormal bile acid can be detected in urine samples.**

   Yes, the lab successfully characterized and identified different bile acid synthesis defects through their respective unique FAB-MS spectra. For example, if a patient is deficient in 3β-hydroxyl-Δ5-C27-steroid oxidoreductase, the spectra of his/her urine sample will show molecular ion peaks at m/z 469 and 485 (representing sulfate conjugates of unsaturated dihydroxy- and trihydroxy-cholenoic acids, respectively) and m/z 526 and 542 (representing glycol-sulfate conjugates of unsaturated dihydroxy- and trihydroxy-cholenoic acids, respectively).

[redacted] (b) (4)

**Conclusion:**

Following the above inspection, this DBGLPC scientist concludes [redacted] (b) (4) are NOT acceptable for further Agency review. The rest of the data may only be useful from a qualitative perspective.

Hansong Chen, Ph.D., Pharm.D.
Pharmacologist

**Final Classification:**

[redacted] (b) (4)

cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Bonapace/Skelly/Choi/Dasgupta/Chen
OSI/DBGLPC/Dejernett/Fenty-Stewart/Nkah/Johnson
OSI/DGCP/Leibenhaut/Jamali
CDE D/OD ao/Davis-Williams
ORA [redacted] (b) (4) -DO/ [redacted] (b) (4)

Draft: HC 7/24/2014
Edit: YMC 9/2/2014; SHH 09/04/2014
File: BE6667
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Inspections/BE Program/clinical Sites/ [redacted] (b) (4)
FACTS: 8745501

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/s/

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HANSONG CHEN
09/10/2014

WILLIAM H TAYLOR
09/10/2014

M E M O R A N D U M

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

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# CLINICAL INSPECTION SUMMARY

DATE: July 25, 2014

TO: Brian Strongin, R.Ph., M.B.A, Chief Regulatory Project Manager
Wen-Yi Gao, M.D., Medical Officer
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205750

APPLICANT: Asklepion Pharmaceuticals, LLC.

DRUG: Cholic acid
NME: Yes
THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of (b) (4)

CONSULTATION REQUEST DATE: February 11, 2014
INSPECTION SUMMARY GOAL DATE: September 5, 2014
DIVISION ACTION GOAL DATE: October 21, 2014
PDUFA DATE: October 21, 2014

## I. BACKGROUND:

Asklepion Pharmaceuticals, LLC (Asklepion) submitted this NDA for cholic acid, 50 mg and 250 mg for the treatment of [redacted] (b) (4) The cholic acid research program began as an academic project initiated by James E. Heubi, MD, and Kenneth D. R. Setchell, PhD, at the Cincinnati Children's Hospital Medical Center (CCHMC), [redacted] (b) (4) . There was no expectation at that time of developing cholic acid as a commercially available drug. Drs. Heubi and Setchell submitted IND # 45,470 in June, 1994 with Dr. Heubi as the sponsor investigator.

In 2007 the IND was transferred to Asklepion Pharmaceuticals, LLC, and FDA granted Orphan Product designation for this extremely rare condition. Drs. Heubi and Setchell continue to treat patients under this IND under Protocol CAC-002-01 entitled, "An Open-Label, Single Center, Non-Randomized Continuation Study of Cholic Acid Capsules in Subjects with Inborn Errors of Bile Acid Synthesis".

Protocol CAC-91-10-10 entitled "Investigation in the Pathogenesis of Liver Disease in Patients with Inborn Errors of Bile Acid Metabolism" was initiated as an academic research study in 1992. On 27 Jan 1992, James E. Heubi sent a request to the IRB to include patients with peroxisomal disorders in study 91-10-10. The IRB requested an addendum to Protocol 91-10-10 for these patients. In response, a full study Protocol CAC-92-8-19 entitled "Investigations of the Potential Benefit of Bile Acid Therapy for Patients with Peroxisomal Disorders Affecting Bile Acid Metabolism" was submitted on 22 Jul 1992. The protocol was almost identical to Protocol 91-10-10, except the population included subjects with peroxisomal disorders and omitted the third clinical visit, and was considered a sub-study to protocol CAC-91-10-10.

According to the clinical study report (CSR) Dr. Heubi and Setchell recruited subjects through referrals in the bile acid metabolism community and were able to recruit a total of 85 subjects with either bile acid metabolism defects. Subjects were infants < age 3 months and children presenting for evaluation of cholestasis defined as a conjugated bilirubin > 2mg/dl or increased serum bile acids for age (cholylglycine conjugates, Abbott Laboratories, No. Chicago, IL). Patients were to have thorough evaluation to define the etiology of cholestasis using conventional screening studies (urine culture and clinitest, alpha-1-antitrypsin phenotype, STORCH titers, thyroid function tests, liver ultrasound, liver "function" tests and percutaneous liver biopsy). Patients with other organ dysfunction were not to be included. Older subjects of any age with cholestatic liver disease would be candidates if urine screens suggested that they had inborn errors of bile acid metabolism.

Asklepion submitted a marketing application to the European Medicines Agency (EMA) and CCHMC was inspected by Medicines and Healthcare Products Regulatory Agency (MHRA) from October 22 to 25, 2012. The inspection report is dated November 16, 2012. Numerous GCP issues were identified during the inspection. Specifically, the clinical study report did not accurately reflect the nature of the data quality, issues with product manufacture, distribution and accountability, and compliance with treatment. The sponsor attempted to address these issues in the response to the EMA and also revised the study report to address the EMA concerns. This revised study report was submitted to the current marketing application to the U.S; FDA. On January 23, 2014, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the granting of a marketing authorization for cholic acid for the indication of treatment of inborn errors in primary bile acid synthesis due to Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or a-) methylacyl-CoA racemase (AMACR) deficiency or Cholesterol 7a-hydroxylase (CYP7A1)) deficiency in infants, children and adolescents aged 1 month to 18 years and adults.

The OND review division chose CCMC for inspection because the records for all subjects enrolled into the study are at this location. A sponsor inspection was also conducted because this is a new molecular entity (NME).

## II. RESULTS (by Site):

| **Inspected Entity (Type) Name and Address** | **Protocol # and # of Subjects** | **Inspection Date** | **Final Classification*** |
|---|---|---|---|
| Sponsor (1992 to 2007) and Clinical Investigator (2007 to present): James Heubi, M.D. Cincinnati Children's Hospital Medical Center 3333 Burnet Avenue Cincinnati, OH 45229 | Protocol 91-10-10: 59 subjects<br><br>Protocol 92-8-19: 26 subjects | April 2 to May 7, 2014 | VAI |
| Sponsor (2007 to present): Asklepion Pharmaceuticals, LLC 729 E. Pratt Street Baltimore, MD 21202 | Protocol 91-10-10: 59 subjects<br><br>Protocol 92-8-19: 26 subjects | June 17, 2014 | NAI |

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.

1. **James Heubi, M.D., Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229**

   a. **What was inspected:** The study was inspected under CPGM 7348.811 for clinical investigators and also inspected using the relevant elements of CPGM 7348.810 for sponsors for the time period 1994 to 2007 when Dr. Heubi assumed the role of both sponsor and investigator. The FDA investigators reviewed 53 subject records; 49 of the subjects with single enzyme defects and 4 subjects with peroxisomal enzyme defects. In addition, 16 subjects with peroxisomal defects were reviewed for informed consent and subject deaths. The records reviewed for both protocols included: IND and orphan drug status documentation, Form FDA 1571 and Form FDA 1572, informed consents, original source documents and copies of documents from local treating physicians, case report forms, laboratory data, drug accountability and shipping records, IRB correspondence and approvals, and correspondence between the study site and the current sponsor Asklepion.

   b. **General Observations/Commentary:** The sponsor initiated the protocol as a treatment protocol in which subjects with a history of bile acid disorder were identified at CCHMC by urine screening. The subjects were seen either at CCHMC or at the location of the referring physician. Cholic acid was compounded by the sponsor and was supplied by shipment to the referring physician or the subject's family. Standard laboratory tests and clinical evaluations were conducted at the local sites. Once identified, subjects were followed either locally or at CHCMC. From the screening and enrollment logs, it was determined that 53 subjects were enrolled in Protocol 91-10-10 according to the enrollment log and that Subjects 14, 176 and 194 were not included on the enrollment log but were listed as enrolled in the screening log. Additional documents in the CSR do not have these three subjects. There were a total of 26 subjects enrolled in 92-8-19. The protocol specified visits every six months, but did not appear to be closely followed. There was no evidence of under-reporting of AEs. The liver function tests were considered important efficacy endpoints and the FDA investigators focused on verification of these endpoints. A Form FDA 483 was issued and Dr. Heubi responded adequately on May 22, 2014. He acknowledged that considerations concerning commercialization of the drug were not foremost at the time of initiation of the study in 1997 and that the regulatory environment was rudimentary. He described the changes that have been implemented since 2007 (b) (4)

   The following observations were cited on the Form FDA 483 for Sponsor responsibilities:

   1. Failure to select qualified investigators, ensure proper monitoring of the study and ensure that the study is conducted in accordance with the protocol and investigational plan. Specifically, source documents indicate that subjects were enrolled and followed off-site by numerous investigators. This included

investigators in approximately 15 U.S. cities as well as Canada, England, France, Italy, Argentina, Pakistan, Saudi Arabia, Argentina, Chile, Columbia, and Uruguay. There were no Forms FDA 1572, curriculum vitae, or medical licensure available for review for clinical investigators.

**Dr. Heubi's response:**

Dr. Heubi noted that a referring physician chose the study by virtue of having an affected subject, rather than by being recruited as an investigator, so the referring physician should not have been considered as a CI at a study site, but had a role that was more congruent with a local treating physician. He notes in his response that the underlying conditions are "ultra-rare" disease and the referring physicians may not have had expertise in this area, so it was his intention to provide treatment via consultation to the 85 patients enrolled through the referring physicians.

When the protocol was developed in 1991, there were never plans for any investigators other than those at CCHMC to serve as investigators on this project. Physicians from around the world contacted CCHMC to assist in diagnosis. If the diagnosis was confirmed, then in all circumstances, the actual management of the administration of cholic acid to patients was done by Dr. Heubi in consultation with Dr. Setchell. Initiation of cholic acid therapy and changes in dose were ordered by Dr. Heubi in response to changes in liver chemistries or urine FAB-MS analyses. Physicians treating patients at locations outside CCHMC did not make independent decisions regarding cholic acid administration but rather acted only after consulting CCHMC regarding dosing of cholic acid and/or any adverse events related or unrelated to study drug.

Documentation regarding the routine periodic discussions between Dr. Heubi, Dr. Setchell, and the treating physicians regarding dosing of cholic acid were found in the urine FAB-MS reports. The site has continued to maintain the communication process with the local physicians; however, these communications are now documented in the patients' files.

*Reviewer comment: Dr. Heubi's reply is a reasonable assessment of the situation at the time the IND was in effect. This situation is described in the clinical study report. The findings at the inspection do not contradict the study report.*

2. Lack of adequate records covering shipment to investigators and disposition of investigational drug. Specifically, there are no drug accountability records to show which subjects were receiving which batches of investigational drug product for the period 1993 to 1995.

**Dr. Heubi's response:**

Prior to, and up to April 1993, when an order for cholic acid was requested, the laboratory staff preparing the drug order recorded this action in their Laboratory Notebook with the following information; (1) the date that cholic acid was prepared, (2) the name of the patient, and (3) the number of capsules or volume of liquid that was shipped. This information is documented in the copies of hand-written pages from the Laboratory Notebooks that were provided in the Cholic Acid Supply documents binder. It has been normal/routine practice that shipment

took place immediately upon completion of the order. Patients were shipped drug by overnight Courier (Federal Express) or by normal mail service (only in the case of capsules and when non-urgent). In this period, it was not the normal practice to retain Federal Express airway bill receipts. This practice has changed so that now all shipping receipts are retained in the patient records. In most cases, the drug was shipped directly to the patient, but in some cases it was shipped to the patient's primary physician's office with instructions for the patient to collect it from that office.

*Reviewer comment: Between April 1993 and 1995, there was a transition from a manual style of recording in Laboratory Notebooks to an electronic recording of drug shipments. The site has been unable to find records of drug shipments in this 2 year period. Dr. Heubi's response describes the unsuccessful due diligence efforts to obtain the records. This issue is discussed in the clinical study report. (See response to Item 3.)*

3. Shipment of an investigational new drug to someone not an investigator participating in an investigation. Specifically, James E. Heubi, M.D. (b) (4) . are identified on the FDA 1572 dated 6/7/94 as Investigator and Subinvestigator, respectively, for study protocols #91-10-10 and #92-8-19. No other person is identified as being an investigator or subinvestigator. However, for every subject that was seen outside of CCHMC the investigational drug product was sent directly to either: a) the subjects' local treating physicians, none of whom were listed on the FDA 1572 as a subinvestigator, or b) the subjects' family members, with no assurance or documentation of receipt of the product/shipment.

**Dr. Heubi's response:**

As discussed above, Dr. Heubi stated that he did not intend for the treating physicians to become investigators. Usually, the investigational drug was dispensed directly to the subject/parent, but in some cases it was determined that dispensing the investigational drug to the subject/parent through their treating physician was a more reliable means of ensuring that the subject/patient received the investigational drug, particularly during the early years of the study.

*Reviewer comment: Observations 2 and 3 that are cited on the Form FDA 483 concerning lack of documentation of drug manufacturing and drug shipping are described in detail in the Clinical Study Report Sections 9.4.2 "Identity of Investigational Products(s)" and Section 9.4.8 "Treatment Compliance" and Section 9.8.1 "Changes in the Revised CSR." The findings are consistent with the "non-commercial" nature of the IND that was originally filed. The significance of this finding is deferred to the review division.*

The following observations were cited on the Form FDA 483 for Clinical Investigator responsibilities:

4. Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation. Specifically,

   a. Section IV of Protocol #91-10-10 (dated 3 Jan 1992), titled "Research Plan," Subsection 5, titled "Data Analysis" states: "Serial changes in liver function tests (total and direct bilirubin, SGOT, SGPT) will be evaluated by ANOVA using methods for repeated measures." In a comparison of source documents to case report forms for subjects, 21 of 54 reviewed subjects had unreported bilirubin (total and/or direct) efficacy values. The EIR specifically notes ten of these subjects, specifically Subjects 9, 18, 33, 34, 47, 55, 56, 61, 86, 133.

| Subject # | # of bilirubin values in source documents | # of bilirubin values reported in CRF | Percentage of bilirubin values not reported in CRF | Date range of missing values |
|---|---|---|---|---|
| 9 | 51 | 13 | 75% | 01/1993 – 08/2009 |
| 18* | 5 | 1 | 80% | 10/2000 – 03/2003 |
| 33 | 41 | 0 | 100% | 03/1989 – 08/2006 |
| 34 | 9 | 0 | 100% | 02-1995 – 08/2001 |
| 47* | 31 | 0 | 100% | 08/1988 – 02/2006 |
| 55 | 11 | 0 | 100% | 11/1986 – 06/1993 |
| 56 | 7 | 0 | 100% | 07/1989 – 12/1992 |
| 57 | 3 | 2 | 33% | 12/1999 – 03/2007 |
| 61 | 10 | 0 | 100% | 07/1999 – 04/2001 |
| 73* | 33 | 21 | 36% | 01/1999 – 10/2008 |
| 74 | 8 | 2 | 75% | 07/1999 – 07/2003 |
| 79* | 38 | 31 | 18% | 09/1996 – 07/2009 |
| 86 | 20 | 3 | 85% | 04/2000 – 02/2009 |
| 95 | 14 | 5 | 64% | 12/2003 – 04/2006 |
| 100 | 6 | 5 | 17% | 12/2005 – 10/2009 |
| 133 | 12 | 2 | 83% | 06/2007 – 09/2009 |
| 138 | 5 | 1 | 80% | 06/2007 – 06/2009 |

The asterisks concern presence of exhibits in the Establishment Inspection Report (EIR).

**Dr. Heubi's response:**
Dr. Heubi acknowledged that this information was included in the subject's file for all of the subjects noted in this observation (i.e., 9, 18, 33, 34, 47, 55, 56, 61, 86, 133). He noted that bilirubin was not considered to be a primary efficacy endpoint and the case report forms did not include a space specifically for bilirubin value. He explained that it was not included in the case report forms for several reasons. When the case report forms were completed and monitored, the efforts were focused on the primary safety and efficacy data (i.e., serum AST and ALT values, FAB-MS, adverse events, patient disposition, and study medication). In other cases, some of the information was added to the files after the case report forms were completed.
*Reviewer comment: The significance of this finding depends on the assessment by review division as to whether the bilirubin is an important measure of efficacy. It was communicated to the review division that the EIR has a sampling some of the non-reported values, and is not meant to substitute for the complete reporting by the sponsor. This issue was communicated with the review division and the values were requested from the sponsor.*

b. Three reviewed subjects had errors in transcribing source data to the case report forms. Specifically,

   i. Subject 33: The ALT (SGPT) value reported for 03/23/1990 is reported as 73 U/L per a data sheet in the subject records, but is reported as 63 U/L in the subject's case report form.

   ii. Subject 150: Three of the four bilirubin values reported on the subject's case report forms reported the date wrong. The month and day for each entry were switched on these dates. The lab reports in the subject's source documents state the correct dates.

   iii. Subject 79: Bilirubin values reported as occurring on 03/02/1998 on the case report forms were obtained on 02/03/1998 per the subject's lab report for this visit date.

**Dr. Heubi's response:**
For Subject 33 Dr. Heubi agreed that an error was made in transcribing the serum ALT from the source document to the CRF and the correct entry for 3/22/1990 should be 63 U/L. An additional document in the subject file includes an ALT of 73 U/L for 3/23/90 which was likely the source for this error.
For Subject 150, he noted that the reference in the observation to Subject 150 is incorrect since there was no Subject 150 enrolled in the study (it is more likely a reference to Subject 153).For Subjects 79 and 153, these date errors likely stem from the differences in how dates are expressed in international vs. U.S. locations. For the U.S., the date is always listed as month/day/year but in many international locations it is listed as day/month/year. Most of the time, this transposition error did not occur.

*Reviewer comment: Transcription errors for transaminases appears to have occurred in only a small number of values collected over the years and does not significantly impact the overall the integrity of the data . This response is acceptable.*

5. Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration. Specifically,

   a. Five subjects had no informed consent forms in their subject records under protocol #91-10-10 but began study drug treatment.

**Dr. Heubi's response:**
No investigational drug was ever dispensed without the subject or parent/legal guardian providing informed consent after a verbal explanation of the study followed by signing an ICF. Regrettably the files do not contain ICF for Subjects 9, 47, 100, 156 and 157 and for each of these subjects there is a note to file explaining the circumstances of why such documents are not available and efforts made to obtain the ICFs. As examples, exhaustive efforts were undertaken to find the ICF for Subject #9 who was consented in Pittsburgh and subsequently returned to his home in Saudi Arabia. The clinician managing the patient attests to having a signed ICF but it could not be found despite extensive efforts. Likewise, Subject #100, was consented using the CCHMC ICF at Philadelphia and the ICF could not be found by the treating physician on site. For subject #157 from Argentina, they have an ICF on file that was developed by the clinician caring for the patient which was completed prior to administration of any investigational drug.

   b. Three subjects were consented using a local informed consent form for cholic acid treatment at King Faisal Hospital located in Riyadh, Saudi Arabia. This informed consent form was not approved by CCHMC's IRB.

**Dr. Heubi's response:**
The Saudi physicians treating these three subjects (i.e., 134, 142, and153) used an ICF that they had created for this study.

   c. Subject 27 was consented on 04/07/2003 to participate in protocol #91-10-10 with the ICF used for protocol #92-8-19, a study which was closed by CCHMC's IRB on 08/27/2002. According to the drug accountability log, this subject was dispensed test article on 04/08/2003.

**Dr. Heubi's response:**
For Subject 27, there was an administrative error in consenting him to study 92-8-19 instead of study 91-10-10. The protocols are essentially identical except that study 92-8-19 was specifically designed for patients with peroxisomal disorders. Subject 27 had CTX, a defect due to enzyme deficiency and not a peroxisomal disorder. The relevant substantive information in the consent forms is otherwise the same.

   d. Four subjects were consented with the wrong version of the informed consent form, because newer IRB-approved informed consent form was

available at the time of consent.

**Dr. Heubi's response:**

For Subjects 149, 159, 175, and 177, the ICF used for consenting was not the currently approved ICF at the time of consent. It was the practice of the IRB during the time when these subjects were consented to have the consent document "expire" and re-approve the same version of the consent with each continuing review cycle. As such, while the CI acknowledges that these subjects signed an expired consent, the content of the consent was the same as the content of the consent that was currently approved at that time. The versions of the ICF were identical between the dates with the exception of approval dates.

e. Seven subjects (#12, #20, #21, #46, #51, #64, and #92) were originally consented for and enrolled in protocol #92-8-19 (the peroxisomal disorder protocol), which closed on 08/27/2002. These subjects were not re-consented with the consent form for protocol #91-10-10 when they were moved into this study after the closure of protocol #92-8-19.

**Dr. Heubi's response:**

Regarding these subjects (i.e., 12, 20, 21, 46, 51, 64, and 92), Protocol 92-8-19 was originally proposed as a sub-study to enroll a specific sub-set (peroxisomal disorders) of all patients with bile acid defects diagnosed. However, because FDA Orphan Drug Grant funding was obtained for this sub-study, the 92-8-19 sub-study was opened as a separate protocol in order to ensure that the grant funds were spent correctly. The grant funding ended in 2002 and the 92-8-19 protocol was closed. Because of the 92-8-19 protocol was considered a sub-study of the original 91-10-10 protocol; the IRB did not require a re-consent to move the subjects from protocol 92-8-19 to protocol 91-10-10 when the 92-8-19 protocol was closed.

*Reviewer comment: Observation 5 is considered to have insignificant impact on data reliability. The issues with lack of consent forms were submitted in the final study report as Appendix 16.1.3. This response is acceptable.*

6. Investigational drug disposition records are not adequate with respect to quantity. Specifically, for Subjects 12, 33, 57, 86, 90, 95, and 149, discrepancies existed between source documents and sponsor-provided data with respect to the declared quantity of shipped investigational drug product. For Subject 12, there are 11 instances noted in which 300mL bottles were noted in the source documents and sponsor declared amount was 350mL. For Subject 86, this 300/350mL discrepancy occurs in 6 instances, and for Subject 90, this discrepancy occurs in 4 instances. For Subject 33, there are 3 instances of discrepancy in pill count. Subjects 57 and 95 have only one instance of a discrepancy.

**Dr. Heubi's response:**

For Subjects #12, #57, #86, #90 and #95 The "Sponsor Declared Amount" noted in the observation refers to the actual amount of drug that was sent/given to the patient and this is documented in the Excel Summary File called "Cholic Acid Shipment Log." The "Source Document Amount" referred to forms filled out

requesting drug, and these forms are located within the patient charts. The recipe for preparing cholic acid in solution shows that liquid formula was prepared in exactly a 350 mL quantity, a 750 mL quantity, or a 1000 mL quantity.
The bottles used to ship the liquid formulation were of standard 300 mL/12 oz. size (Exhibit 2), but these did in fact hold up to a maximum volume of 375mL. When patients were shipped 1000 mL of liquid, the entire quantity was transferred into 3 of these bottles, for a 750 mL order 2 bottles were used, and for a 350 mL order 1 bottle was used. This explains the discrepancy between the 'Sponsor Declared Amount" and the "Source Document Amount," the latter referring to the manufacturer's size of bottle shipped and not the exact volume shipped. This applies to, on all dates for which the liquid formulations are listed in the Inspection report.

Patient #33, dated 09/29/05: "Source Document Amount" states 70 capsules which is correct, and "Sponsor Declared Amount" states 150 capsules – this is a clerical error in the summary cholic acid.
Patient #149, dated 02/09/09: The patient was shipped 200 capsules, as indicated by the CCHMC Investigational Pharmacy Drug Inventory Log (see Exhibit 4). This represents a clerical error in the Cholic Acid Shipment Log summary.

*Reviewer comment: The discrepancies in the drug disposition records involved 7 subjects out of the 50 subjects reviewed. Most of the discrepancies cited in the EIR occurred due to the technicality noted above in the CI response and do not represent significance volume of product. For Subjects 33, 86 and 149, the discrepancies are a result of clerical errors. In this study, shipment of drug may be an imperfect measure of subject compliance with drug administration and the significance of this finding is deferred to the review division. The review division can request for analysis the "Sponsor Declared Amount" that was actually shipped to the subject if the difference between the "Sponsor Declared Amount" and the "Source Document Amount" is considered significant.*

7. An investigation was not conducted in accordance with the investigational plan. Section IV (B) of protocol #91-10-10 (dated 3 Jan 1992), under the title "The Study" the first paragraph states: "On admission, the patient will have studies to assess liver function (bilirubin, SGOT, SGPT, alkaline phosphatase, cholesterol, albumin, prothrombin time, and MEG-X). A review of subjects' source data revealed there were no baseline serum laboratory data at enrollment for the following:
    a. Subject # 27 was consented to participate in the study on 04/07/2003.
    b. Subject # 52 was consented to participate in the study on 05/06/2006.
    c. Subject # 86 was consented to participate in the study on 04/04/2000.

**Dr. Heubi's response:**

a. For Subject 27, baseline liver chemistries and related laboratories were present in the form of an Excel spreadsheet or correspondence with the treating physician in

patient files but were not transcribed to the CRF. Please refer to the explanation provided in response to Observation No. 4.

b. For Subject 86, baseline liver chemistries were recorded in the CRF on 5Jan2000 and 3Apr2000.
c. There is no Subject 52 enrolled in 91-10-10. This may be a transcription error.

*Reviewer comment: For Subject 86, the line listings contain the values for the dates above for ALT/SGPT only and not for AST/SGOT. It is not clear from Dr. Heubi's response whether this is a transcription error or that this laboratory value was not obtained. It would be unusual that one liver value is determined and another is not determined. This error may be similar to the omission of transcription that occurred for subject. Dr. Heubi's response is inadequate in that he should have provided the values in his response. It is advised that the review division request these values if they are important to the review.*

8. Failure to assure that an IRB was responsible for the initial and continuing review and approval of a clinical study. There were two instances of lapse of approval. Specifically, during the time period of 05/19/2004 to 06/08/2004, protocol 90-10-10 operated without IRB approval due to a lapse in submission of continuing review criteria to the Cincinnati Children's Medical Hospital Center IRB. Shipments of the investigational drug article were shipped out to subjects #20, 21, 57, and 74 during this lapse in IRB approval. There was another lapse in IRB approval from March 24, 2009 through May 26, 2009. Drug Accountability Logs indicate approximately 21 subjects received test article from during this time-frame (Subjects #12, 18, 20, 21, 27, 30, 33, 46, 57, 86, 92, 93, 106, 128, 130, 134, 142, 153, 156, 157, and 159).

**Dr. Heubi's response:**

Two lapses in IRB approval were noted by the inspectors over the 20+ year duration of this study. These were lapses because of failure to file timely continuing review reports.

The first, May 19 to June 8, 2004, was due to late submission of the continuing review and failure of the IRB to review prior to the end of the approval period. In this case, official termination was sent from the IRB on June 1, 2004 and three subjects were sent investigational drug on that date (before receipt of the termination notice). No other investigational drug was shipped before renewal of the study. Although the observation lists four subjects, one subject, #57, was shipped study drug on June 20, 2004 which was prior to the receipt of the termination notice.

The second, March 24 to May 26, 2009, occurred because of the conversion of the IRB management system to Click Commerce. The change in procedures resulted in inadvertent lapse of the protocol. It was not realized by the investigators that the study had expired until May 13, 2009 at which time an electronic version of the protocol and a continuing review survey were submitted to the IRB with final

approval obtained on May 29, 2009. During this time, the IRB Chair verbally agreed that investigational drug could continue to be supplied investigational drug but not enroll new subjects until the protocol was formally reapproved. During this period (March 24 to May 26, 2009) there were no identified adverse event reports.

*Reviewer comment: This does not impact data reliability.*

c. **Assessment of data integrity:** The conduct of the study and the data as described in the clinical study report were able to be verified during the FDA inspection. The Form FDA 483 cites violations of our regulations, administrative violations as well as clinical conduct that would not be considered "good clinical practice". Because many subjects were seen off-site, much of the documentation of data for this study is present in the form of copies of originals sent from treating physicians at far flung locations and cannot be verified with source documentation. However, the availability of other documents that indicate the existence of subjects and their clinical course are accurately described in a study report that was revised after the EMA inspection. Issues noted above concerning lack of documentation of batch records and drug shipment is described in the study report. There was no evidence of falsification of records noted during the inspection. The review division can rely on the data submitted and the study report in review of the submission. Because this study is for an orphan indication and was initiated many years ago, the determination of acceptability of the quality of the data is deferred to the review division. These issues were discussed with the medical team at the midcycle meeting and throughout the review.

## 2. Asklepion Pharmaceuticals, LLC, Baltimore, MD 21202

a. **What was inspected:** As noted in the background section of this report, Asklepion assumed sponsor responsibilities in 2007. Study documents concerning Protocols 91-10-10 and 92-8-19 from 2007 to the present are located at the sponsor. The complete study and regulatory files including monitoring reports, Investigator agreements, financial disclosure forms, retest article accountability records, IRB approvals, case report forms, and correspondence as well as the firm's SOPs training records, adverse event records, statistical analysis plans and safety reports were reviewed by the FDA investigator.

b. **General observations/commentary:** The sponsor currently maintains three INDs: IND 45470 for cholic acid, IND [redacted] (b) (4), and IND [redacted] (b) (4).

Asklepion [redacted] (b) (6) to ensure that cholic acid, would be approved by FDA for treatment of specific disorders. Asklepion is a privately owned company held by Samaritan Health and Well-Being of Australia which in turn is owned by the Seventh Day Adventist Church of

Australia and New Zealand. (b) (6) signed financial disclosures statements on June 17, 2013 and these were submitted to the NDA. (b) (6) . No other COI forms were collected from treating physicians. The sponsor considered (b) (6) in the study (b) (6) The Conflict of Interest (COI) management plan dated March 15, 2010 included independent monitoring by "CCHMC or another independent Clinical Research Organization." The NDA submission contains the audit certificate from an audit conducted November 30, 2010 to February 3, 2011 by (b) (4). During the FDA inspection, (b) (4) is also noted as the legal consultant to the sponsor.

When Asklepion assumed sponsor responsibilities in 2007, the clinical data at the site was transcribed onto case report forms (CRFs). Monitoring of the study by Asklepion focused on verifying study data for liver function tests (LFTs), urine FAB-MS, subject disposition, deaths, adverse events, and test article administration and accountability. Protocol deviations were documented. In response to a question related to Observation 4a at Dr. Heubi's site posed during the inspection of the sponsor, the Clinical Research Director stated that the bilirubin values were not all captured because the focus was on other laboratroy values such as transaminases and urine FAB-MS that were considered a more useful measure of the response to cholic acid therapy. Asklepion obtained all the test article shipping records from Dr. Heubi for the period from 1996 to 2012 and clinical investigator inventory logs for 2008 through 2012.

No regulatory violations were cited and no Form FDA 483 was issued. There was one discussion item concerning lack of documentation of training of study monitors.

c. **Assessment of data integrity:** The discussion item concerning lack of documentation of training of study monitors is considered an isolated item and does not impact data reliability or subject safety. The findings at the sponsor site, including the financial disclosure, are documented in the NDA submission. The data submitted to the FDA are consistent with the findings in the inspection. The review division can rely on the data submitted and the study report in review of the submission.

## III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For this application, inspections were conducted at Drl. Heubi's site, the clinical study site where the study was conducted as a sponsor investigator study from 1994 to 2007 and an inspection was conducted at Asklepion Pharmaceuticals, LLC, the sponsor/applicant site. The classification of Dr. Heubi's site is Voluntary Action Indicated (VAI) because of violations concerning obtaining and

documenting informed consent of study subjects, failure to follow the protocol and inadequate drug disposition records. None of these deficiencies are determined to have significantly impacted data integrity. Deficiencies concerning GCP are described in the clinical study report. The data is accurately reported in the clinical study report and datasets submitted in support of the application. The inspection did not uncover any new information or significant findings that would appear to contradict the study report. The study report and the data generated by the site may be used in evaluation for the efficacy of the product.

***{See appended electronic signature page}***

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

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/s/

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SUSAN LEIBENHAUT
09/03/2014

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**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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# Pediatric and Maternal Health Staff – Maternal Health Review

**Date:** June 20, 2014

**From:** Tamara Johnson, MD, MS, Medical Officer
Pediatric and Maternal Health Staff

**Through:** Jeanine Best, MSN, RN, PNP, Team Leader- Maternal Health
Pediatric and Maternal Health Staff

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff

**To:** Division of Gastroenterology and Inborn Errors Products (DGIEP)

**NDA:** 205750

**Drug:** Cholbam (cholic acid)

**Applicant:** Asklepion Pharmaceuticals, LLC.

**Proposed Indication:** Treatment of [redacted] (b) (4)

**Consult Request:** "The reason for this consult is to invite the Maternal Health team to attend meetings and assist in the labeling review pertaining to this NDA and offer any assistance as necessary."

**Consult Due Date:** July 9, 2014

**Materials Reviewed:** (labeling, reviews)

- Original NDA 205750, Cholic Acid, received November 21, 2013
- Draft Cholic Acid Labeling, received November 21, 2013

## INTRODUCTION

This original NDA for the new molecular entity Cholbam (cholic acid) is submitted as the proposed (b) (4) An orphan designation for this rare condition was granted in 2007.

This marketing application is presented to the Agency with clinical evidence from two single-arm clinical trials for efficacy and safety and one pharmacokinetic study in healthy adult male volunteers. A waiver for required nonclinical studies was granted in 2004. The waiver decision was based upon the abundant nonclinical data available in published literature and because cholic acid is a natural component of the human body. Additional justification for waiver of juvenile toxicology studies is presented in the submitted NDA.

DGIEP requests meeting attendance and input from the Pediatric and Maternal Health Staff - Maternal Health Team (PMHS-MHT) for the proposed full prescribing information of Cholbam, as well as any additional assistance as necessary. This review, therefore, provides recommended revisions and structuring of existing information related to the Pregnancy (b) (4) labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

## BACKGROUND

### *Inborn Errors of Bile Acid Synthesis*

Patients born with inborn errors of bile acid synthesis lack the liver enzymes necessary to produce the primary bile acids (cholic acid and chenodeoxycholic acid) from cholesterol. The final step in the bile acid synthesis process does not occur and patients experience an accumulation of atypical bile acids and bile acid intermediates. This subsequently leads to reduction of bile flow, positive feedback to the liver to produce more bile acid, and more hepatotoxic intermediates. Clinically, this presents as a progressive cholestasis that leads to cirrhosis and liver failure, giant cell hepatitis in infancy, steatorrhea, fat-soluble vitamin deficiencies, low cholesterol, failure to thrive, pruritus, signs of upper motor neuron damage (i.e. spastic paraparesis) with progressive neurological disease in late childhood or adulthood.[1] The bile acid synthesis disorders present during the first few months of life and may be responsible for up to 2% of persistent cholestasis in infants.[2] Time to liver failure and length of survival varies by enzyme deficiency. The main enzyme deficiencies associated with primary bile acid synthesis disorders, include the following:

- 3β-hydroxy-C27-steroid dehydrogenase/isomerase (3β-HSD) deficiency, *most common*
- Δ4-3-Oxosteroid (Δ4-3-oxo-R) 5β-reductase deficiency
- Sterol 27-hydroxylase deficiency (or cerebrotendinous xanthomatosis, CTX)
- 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency

[1] Clayton PT. Disorders of Bile Acid Synthesis. J Inherit Metab Dis (2011) 34:593-604.
[2] Bove KE, Heubi JE, Balistreri WF, Setchell KDR. Bile Acid Synthetic Defects and Liver Disease: A Comprehensive Review. Pediatric and Developmental Pathology 7, 315–334, 2004.



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- Oxysterol 7α-hydroxylase deficiency
- C25-hydroxylase deficiency
- Cholesterol 7α-hydroxylase deficiency
- Peroxisomal disorders (i.e. Zellweger syndrome, infantile Refsum disease, neonatal adrenoleukodystrophy, hyperpipecolicacidemia)
- Bile acid-CoA ligase and bile acid-CoA amino acid N-acytransferase deficiency

For this original NDA, the majority of patients participating in the key retrospective efficacy study (Study CAC-91-10-10) represent 3β-HSD deficiency, Δ4-3-oxo-R deficiency, and Zellweger syndrome.

***Drug description***
Cholbam (cholic acid)

- Chemical Formula: $C_{24}H_{40}O_5$
- Molecular Weight: 408.57
- Formulation: Capsules containing 50 mg or 250 mg of cholic acid
- Dosing Regimen: 10-15 mg/kg once daily by mouth

Cholic acid is one of two major bile acids synthesized by the liver from cholesterol. It is intended to be used as replacement therapy to patients with (b) (4) . Administration of exogenous cholic acid is intended to limit production and accumulation of hepatotoxic bile acid intermediates, stimulate normal bile flow and secretion, and facilitate fat absorption.

In November 2013, the European Medicines Agency granted marketing authorization of this drug product for treatment of inborn errors of primary bile acid synthesis, specifying the single enzyme defects of:

- Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency
- 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency
- Cholesterol 7 α-hydroxylase (CYP7A1) deficiency

## LABELING

***Applicant's Proposed Labeling***
****
(Highlights)
(b) (4)



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## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

(b) (4)

## 17 PATIENT COUNSELING INFORMATION

(b) (4)

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**DISCUSSION**

PMHS-MHT has been working to develop a more consistent and clinically useful approach to the Pregnancy (b) (4) subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (PLLR) (published on May 29, 2008). As part of the labeling review, the PMHS-MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the Pregnancy (b) (4) labeling subsections. In addition, the PMHS-MHT works with the pharmacology/toxicology reviewers to present animal data, in the Pregnancy (b) (4) subsections, to make it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, animal dose including human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. The first paragraph in the pregnancy subsection of labeling summarizes available data



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from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. (b) (4) [redacted] The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

***Pregnancy Data and Literature Review***

No animal reproduction studies have been conducted for cholic aci (b) (4) [redacted] The DGIEP Pharmacology/Toxicology team concluded that this information is not appropriate for labeling (b) (4) [redacted]

There are no adequate and well-controlled trials of Cholbam treatment in pregnant women with inborn errors of bile acid synthesis, and the main clinical study (CAC-91-10-10) from this NDA did not include pregnant or lactating women. Children who have been treated with cholic acid under the IND are now entering reproductive years. This is demonstrated by the report on long-term outcomes (median treatment duration of 12 years) by Gonzales E, *et al.*[3] In this report, two female patients with 3β-HSD deficiency were stated to have had four pregnancies with healthy infants. For patients with inborn errors of bile acid synthesis, pregnancy may require use of additional reserves on an already compromised liver. Gonzales E, *et al.*, however, state that long-term cholic acid treatment normalized the patients' liver histology and size. These two pregnant patients continued on cholic acid therapy and maintained consistent bile acid metabolism. These two patients' experiences are not considered representative of for the use of cholic acid in this heterogeneous patient group. Therefore, a passive pregnancy surveillance program may be considered to monitor pregnancy outcomes if a drug product registry is established.

In summary, there is insufficient evidence to conclude any risk to the mother or fetus, or to provide a recommendation about the use of Cholbam during pregnancy. (b) (4) [redacted]

***Lactation Data and Literature Review***

There are no formal studies of Cholbam or cholic acid in lactating women. However, there is limited published information on the secretion of the endogenous bile salt, cholate, into breastmilk. Forsyth JS, *et al.*, while exploring the presence of biologically active substances in breastmilk and their contribution to the neonate's digestion, studied

[3] Gonzales E, Gerhardt M, Fabre M, Setchell K et al. Oral Cholic Acid for Hereditary Defects of Primary Bile Acid Synthesis: A Safe and Effective Long - term Therapy. Gastroenterology 2009; 137:1310-1320.



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breastmilk samples for the presence of bile salts.[4] Samples of breastmilk and maternal serum were collected from 28 healthy nursing mothers during the first week postpartum. Both bile salts were present in transitional milk and colostrum, with a predominance of cholate over chenodeoxycholate approximately 3:1. The mean concentrations of endogenous cholate were similar in transitional milk and maternal serum, 0.89 μM and 0.93 μM, respectively, with much less in colostrum at 0.24 μM. The mean concentrations of endogenous chenodeoxycholate were lower in transitional milk compared to maternal serum, 0.26 μM and 0.89 μM, respectively, and again much lower in colostrum at 0.09 μM. The transport mechanism, passive or active, for bile salts across breast alveolar cells has not been determined. The results of Forsyth JS, *et al.*, go against the general understanding that passive diffusion is markedly increased during the colostrum milk phase compared with that of the mature milk phase. The authors hypothesized that bile salt transfer was not likely via passive diffusion across breast alveolar cells but possibly via active transportation. This is suggested by the lower concentration of the bile salts into colostrum than in transitional milk and the greater transfer of cholate than chenodeoxycholate into breastmilk. If bile salts were transported by passive diffusion in transitional milk, then the non-polar chenodeoxycholate would be present in greater concentration than the polar cholate. Although not further explained, the authors conclude the concentration of bile salts transferred to the neonate through breastmilk is unlikely to make a significant contribution to the bile salt concentration in the infant's duodenum. The authors did not collect data on the concentration of bile salts in the infants.

Many, but not all, drugs transfer to breast milk. The transport of a drug into breast milk is largely a function of the drug's physicochemical properties and its concentration in maternal plasma. All of the following factors influence the amount of drug transfer into human milk: plasma and milk protein binding, molecular weight, mechanism of transport, degree of ionization, and clearance pathways. Factors that tend to produce higher human milk levels of drugs include: higher maternal plasma concentration, higher lipid solubility, higher pKa, lower protein binding, and lower molecular weight. The mean pH of human milk is 7.2, about 0.2 units lower than that of plasma. This difference influences the transfer of drugs into milk, more so for drugs that are weak bases with pKa values in that range. Drugs that are more lipid soluble may accumulate in the lipid fraction of the milk, leading to higher concentrations of drug in human milk than in maternal plasma. Most drugs move between maternal serum and human milk based on equilibrium forces. Drugs with higher molecular weights, especially those with weights greater than 800 Daltons, must generally be actively transported or dissolved in the cells lipid membranes. Protein drugs with very high molecular weights (e.g., Insulin, Heparin) are usually excluded from breast milk. [5]

Based on the information from Forsyth, *et al*., the Applicant rationalizes that no adverse effects are anticipated for the infant because the systemic exposure of the nursing mother to cholic acid are "negligible given the low serum levels". The LactMed database contains no information on cholic acid, but does provide a statement similar to the

[4] Forsyth JS, Ross PE, Bouchier IAD. Bile salts in breast milk. Eur J Pediatr 1983: 140: 126-127.
[5] Hale T. Medications and Mothers' Milk, 12th ed, 2012.



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Applicant's regarding use of ursodiol in nursing mothers. Ursodiol, or ursodeoxycholic acid, is an endogenous human bile salt that is present in small quantities. It is approved in the U.S. for the treatment of primary biliary cirrhosis, primary sclerosing cholangitis, nonalcoholic steatohepatitis, and the treatment and prevention of gallstones. Clinically, it has been used for the treatment of intrahepatic cholestasis of pregnancy.[6] LactMed states that "because of the low levels of ursodiol in breastmilk, amounts ingested by the infant are small and are not expected to cause any adverse effects in breastfed infants." The LactMed database provides information for FDA-approved drugs when available on maternal levels in breastmilk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered, and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

***Medical Officer's Comment***

***The mother's serum concentration of Cholbam is expected to be low because the Cholbam distribution is mostly limited to the enterohepatic circulation; less than 5% may reach the mother's systemic circulation. A small amount of cholate may transfer via breastmilk; however, the bile salt would be absorbed into the infant's enterohepatic circulation and would not reach the infant's systemic circulation. Therefore, the cholate concentration in an infant's serum will reflect the infant's endogenous cholate level and not exposure to cholate transferred via breastmilk.***

From the safety data available in the single-arm clinical trials (n=95) submitted with this NDA and the article by Gonzales E, *et al.,* on long term treatment outcomes, patients treated with Cholbam experienced no serious adverse events that would support a decision to discontinue Cholbam treatment in a nursing mother or to advise the mother to stop nursing while taking Cholbam. Serious adverse events reported in the clinical trials were deaths attributed to underlying disease (n=13), unknown cause (n=6), convulsion (n=1), and coagulopathy (n=1). The most frequent treatment emergent adverse events included disease progression, diarrhea, abdominal pain, jaundice, dehydration, and vomiting. Gonzales E, *et al.,* reported no serious adverse events in the more than 180 patient-years observed, but reported cases of cholic acid overdose in four children. These children presented with pruritus, diarrhea, and elevated liver function biomarkers; all of which resolved with dose reduction. There have been no reports of clinically adverse effects in a breastfed infant whose mother was being treated with Cholbam. Prescribers should use caution when administering Cholbam to a nursing mother.

In summary, the limited information available on endogenous cholic acid transfer into breastmilk demonstrates that cholic acid is present in breastmilk. With Cholbam's predominant distribution in the enterohepatic circulation, the maternal serum concentration of Cholbam is expected to be low and a small amount of Cholbam transferred via breastmilk. The small amount of Cholbam in breastmilk would not be systemically absorbed by the infant and may not be clinically relevant for the infant.

[6] Weiner CP, Buhimschi C. Drugs for pregnant and lactating women. Philadelphia, PA: Saunders/Elsevier, c2009. pp.1143-44.



Reference ID: 3528500

Lastly, because the inborn errors of bile acid synthesis are rare and the anticipated use of Cholbam during pregnancy infrequent, a formal lactation study in patients with inborn errors of bile acid synthesis is not recommended at this time.

## CONCLUSIONS

While there is some published literature, there is insufficient evidence to clearly determine the effect of Cholbam on reproduction, labor or delivery, and lactation in patients with inborn errors of bile acid synthesis. The limited report of four normal pregnancies in two patients does not provide reassurance about the potential risks to the mother or fetus when Cholbam is used during pregnancy. A pregnancy surveillance program is recommended for the postmarketing period to monitor the outcomes of pregnant mothers and infants exposed to Cholbam. Because of the small patient population, PMHS-MHT recommends that a pregnancy surveillance program is best incorporated into a postmarketing product registry rather than a dedicated pregnancy registry for this product.

PMHS-MHT structured the Pregnancy [redacted] (b) (4) subsections of the Cholbam labeling in the spirit of the proposed PLLR, while complying with current labeling regulations.

PMHS-MHT participated in the team and labeling meetings with DGIEP held between January 2014 and July 2014. Final labeling will be negotiated with the Applicant and may not fully reflect changes recommended here.

## RECOMMENDATIONS

1. A Pregnancy Surveillance Program to monitor outcomes of women and infants who are exposed to Cholbam during pregnancy. (See Appendix A – Data Elements for Collecting Pregnancy Exposure Data.) PMHS-MHT has suggested language for this program to be included in Sections 8.1. See below.

2. PMHS-MHT recommends revisions to the Applicant's proposed labeling. These labeling revisions are shown below; deleted text has a strikethrough, while new text is underlined. Recommendations made by the Pharmacology/Toxicology Review team, Dr. K. Zhang and Dr. D. Joseph, are included in this version of the labeling.

(Highlights)

[redacted] (b) (4)

- [redacted] (b) (4)
- [redacted]



Reference ID: 3528500

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy (b) (4)

(b) (4)

(b) (4)

*Risk Summary*

(b) (4)

(b) (4)

(b) (4)

(b) (4)

# 17 PATIENT COUNSELING INFORMATION

(b) (4)



Reference ID: 3528500

## APPENDIX A

**PMHS Recommended Data Elements for Collecting Pregnancy Exposure Data**

**A. General**

- Patient identifier
- Name of reporter at initial contact
- Date of initial contact
- Dates of any follow-up contacts
- Telephone number of reporter
- Additional contact names and phone numbers (if reporter is the patient)

**B. Maternal Information**

- Source of information (e.g., obstetrician, pregnant woman, other)
- Birth date
- Race
- Occupation
- Maternal medical history (e.g., hypertension, diabetes, seizure disorder, thyroid disorder, allergic disorders, heart disease, connective disease, autoimmune disease, hepatitis, known risk factors for adverse pregnancy outcomes including environmental or occupational exposures, other)
- Obstetrical History:
    - Number of pregnancies and outcome of each (live birth, spontaneous abortion, elective termination, ectopic pregnancy, molar pregnancy)
    - Previous maternal pregnancy complications
    - Previous fetal/neonatal abnormalities and type
- Current Pregnancy:
    - Date of last menstrual period
    - Complications during pregnancy (including any adverse drug reactions) and dates
    - Number of fetuses
    - Labor/delivery complications
    - Disease course(s) during pregnancy and any complications
    - Medical product exposures (prescription drugs, OTC products & dietary supplements):
        - Name
        - Dosage & route
        - Date of first use & duration
        - Indication
    - Recreational drug use (e.g., tobacco, alcohol, illicit drugs) and amount

- Family History (specify type, maternal/paternal, etc.):
    - Spontaneous Abortions
    - Anomalies/Malformations
    - Multiple fetuses/births



Reference ID: 3528500

**C. Neonatal Information**

Initial:

- Source of information (e.g., obstetrician, pediatrician, mother)
- Date of receipt of information
- Date of birth or termination
- Gestational age at birth or termination
- Gestational outcome (live born, fetal death/stillborn, spontaneous abortion, elective termination)
- Sex
- Pregnancy weight gain of mother
- Obstetric complications ( e.g., pre-eclampsia, premature labor, premature delivery)
- Pregnancy order (singleton, twin, triplet)
- Results of neonatal physical examination including
- Anomalies diagnosed at birth or termination
- Anomalies diagnosed after birth
- Weight at birth indicating whether small, appropriate, or large for gestational age
- Length at birth
- Condition at birth (including when available Apgar scores at 1 and 5 minutes, umbilical cord vessels and gases, need for resuscitation, admission to intensive care nursery)
- Neonatal illnesses, hospitalizations, drug therapies

Follow-up:

- Source of information (e.g., pediatrician, mother)
- Date of receipt of information
- Anomalies diagnosed since initial report
- Developmental assessment
- Infant illnesses, hospitalizations, drug therapies

Note: Infants should be followed for 12 months with assessment times at birth, at 12 months, and some point in between.



Reference ID: 3528500

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/s/

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TAMARA N JOHNSON
06/20/2014

JEANINE A BEST
06/20/2014

LYNNE P YAO
06/30/2014

**M E M O R A N D U M**

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

---

DATE: February 24, 2014

TO: Director, Investigation Branch
Cincinnati District Office
6751 Steger Dr.
Cincinnati, OH 45237

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: Amendment to **FY 2014, CDER High Priority Pre-Approval NDA Data Validation 'For Cause' Inspection,** Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 205-750
DRUG: Cholic acid capsules, 50 and 250 mg
SPONSOR: Asklepion Pharmaceuticals, LLC, Baltimore, MD

This memo requests that you arrange for inspections of the clinical and analytical portions of the following efficacy study.

Once you identify an ORA investigator, please contact the DBGLPC point of contact (POC) listed at the end of this assignment memo to schedule the inspection of the analytical site. A DBGLPC scientist will participate in the inspection of the analytical site to provide scientific and technical expertise.

Background materials will be available in ECMS under the ORA folder. **The inspections should be completed prior to August 21, 2014.**

**<u>Do not</u> reveal the applicant/sponsor, application number, study to be inspected, drug name, or the study investigators to the site prior to the start of the inspections.** The site will receive this information during the inspection opening meeting. The inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

**At the completion of the inspection, please send a scanned copy of the completed section A of this memo to the DBGLPC POC.**

**Study #1**: CAC-91-10-10 (including sub-study CAC-92-8-19)
**Study Title**: "Investigation in the Pathogenesis of Liver Disease in Patients with Inborn Errors of Bile Acid Metabolism."

**Clinical Site**: Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue,
Cincinnati, OH 45229
TEL: (513)636-8046
FAX: (513)803-1039

**Investigator**: James Heubi, MD

## SECTION A – CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

**During the clinical site inspection, please**:

☐ Confirm the informed consent forms and study records for 100% of subjects enrolled at the site.

☐ Compare the study report in the NDA submission to the original documents at the site.

☐ Check for under-reporting of adverse events (AEs).

☐ Check for evidence of inaccuracy in the electronic data capture system.

☐ Check reports for the subjects audited.

- Number of subject records reviewed during the inspection:_____
- Number of subjects screened at the site:_____
- Number of subjects enrolled at the site:_____
- Number of subjects completing the study:_____

- ☐ Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- ☐ Confirm that site personnel followed SOPs during study conduct.
- ☐ Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- ☐ Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- ☐ Other comments:

_____

_____

_____

## SECTION B – AUDIT OF ANALYTICAL DATA

**Analytical Site**: (b) (4)

**Investigator:** (b) (4)

**Methodology**: Fast atom bombardment mass spectrometry

**Please be advised that this is a "For Cause" inspection requested by the review division. During the analytical site inspection , please focus on the following items during the inspection:**

1. If the signal of abnormal bile acid can be detected in urine

(b) (4)

(b) (4)

**In addition to the above items, also address the following during the analytical site inspection:**

- ☐ Examine all pertinent items related to the analytical method used for the measurement of analytes (atypical bile acids) concentrations in human urine.
- ☐ Compare the accuracy of the analytical data in the NDA submission against the original documents at the site.
- ☐ Determine if the site employed a validated analytical method to analyze the subject samples.
- ☐ Determine if the subject samples were analyzed within the conditions and times of demonstrated stability.
- ☐ Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.
- ☐ Scrutinize the number of repeat assays of the subject urine samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria sufficiently covered the stability of reanalyzed subject samples.
- ☐ Examine correspondence files between the analytical site and the Applicant for their content.

**Additional instructions to the ORA Investigator:**

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

**If you issue Form FDA 483, please forward a copy to the DBGLPC POC. If it appears that the observations may warrant an OAI classification, notify the DBGLPC POC as soon as possible.**

**Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received and EIR to the DBGLPC POC.**

DBGLPC POC: Hansong Chen, Ph.D., Pharm.D.
Pharmacologist
Office of Scientific Investigations
Tel: (240)-402-4143
FAX: (301)-847-8748
Email: Hansong.Chen@fda.hhs.gov

DARRTS cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Bonapace/Haidar/Choi/Chen/Dejernett
CDER/OND/ODEIII/DGIEP/GAO/Davis-Williams

Emai c:
ORA (b) (4) -DO/ORA (b) (4) BIMO

Draft: HC 02/13/2014
Edit: GB 02/25/2014; SHH 02/25/2014
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Labora
tes/ (b) (4)

MS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/ Clinical Sites/Cincinnati Children’s Hospital Medical Center, Cincinnati, OH

OSI file #: BE 6667, bio205750.ammend
**FACTS: 8745501**

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/s/

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HANSONG CHEN
02/25/2014

SAM H HAIDAR
02/27/2014

**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

| | |
|---|---|
| **Date of This Review:** | February 14, 2014 |
| **Requesting Office or Division:** | Division of Gastroenterology and Inborn Errors Products (DGIEP) |
| **Application Type and Number:** | NDA 0205750 |
| **Product Name and Strength:** | Cholbam (Cholic Acid) Capsules, 50 mg and 250 mg |
| **Product Type:** | Single Ingredient Product |
| **Rx or OTC:** | Rx |
| **Applicant/Sponsor Name:** | Asklepion Pharmaceuticals, LLC |
| **Submission Date:** | November 21, 2013 and December 4, 2013 |
| **OSE RCM #:** | 2013-2752 |
| **DMEPA Primary Reviewer:** | Terri Wood-Cummings, MD |
| **DMEPA Team Leader:** | Lubna Merchant, M.S., Pharm.D |



Reference ID: 3454793

## 1. REASON FOR REVIEW

This review responds to a consult from DGIEP to evaluate the proposed [redacted] (b) (4) Full Prescribing Information (FPI) for Cholbam (Cholic Acid) for areas of vulnerability that could lead to medication errors. DGIEP requested this review as part of their evaluation for NDA 205750.

## 2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

**Table 1. Materials Considered for this Label and Labeling Review**

| Material Reviewed | Appendix Section (for Methods and Results) |
|---|---|
| Product Information/Prescribing Information | A |
| FDA Adverse Event Reporting System (FAERS) | N/A |
| Previous DMEPA Reviews | N/A |
| Human Factors Study | N/A |
| ISMP Newsletters | N/A |
| Other | N/A |
| [redacted] (b) (4) Labeling | G |

N/A=not applicable for this review

## 3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Cholbam (Cholic Acid) is a new molecular entity. The Applicant is proposing two strengths (50 mg and 250 mg) for the capsules. Cholbam will be dosed as 10 to 15 mg/kg once daily. [redacted] (b) (4) . DMEPA performed a risk assessment of the proposed Full Prescribing Information (FPI) to identify deficiencies that may lead to medication errors. We note that the instructions for administrations in pediatric (and other) patients who are unable to swallow capsules are unclear and may cause confusion.

DMEPA reviewed the [redacted] (b) (4) and noted that [redacted] (b) (4)

## 4. CONCLUSION & RECOMMENDATIONS

We conclude that the [redacted] (b) (4) Full Prescribing Information can be improved to mitigate confusion [redacted] (b) (4)
We provide recommendations below to help promote the safe use of the product.



Reference ID: 3454793

## 4.1 COMMENTS TO THE DIVISION

We provide recommendations (as track changes) to Section 2 Dosage and Administration of the FPI in Appendix G for consideration by the Review Division.

## 4.2 COMMENTS TO THE APPLICANT

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA.

(b) (4)

[redacted]

If you have further questions or need clarifications, please contact Phong Do, OSE Regulatory Project Manager, at 301-796-4795.

## 4.1 APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Cholbam that Asklepion Pharmaceuticals, LLC submitted on November 21, 2013 and December 4, 2013.

| Table 2. Relevant Product Information for Cholbam | |
|---|---|
| **Active Ingredient** | Cholic Acid |
| **Indication** | Treatment of [redacted] (b) (4) |
| **Route of Administration** | Oral |
| **Dosage Form** | Capsules |
| **Strength** | 50 mg, 250 mg |
| **Dose and Frequency** | The recommended pediatric [redacted] (b) (4) and adult starting dose is 10 to 15 mg/kg orally with food once daily. [redacted] (b) (4) . |
| **How Supplied** | Bottles of 90 capsules |
| **Storage** | Store at room temperature 20°C to 25°C ( [redacted] (b) (4) °C to 77°F). Excursions are permitted between 15°C to 30°C (59°F to 86°F). |
| **Container Closure** | White HDPE Bottles with a nominal capacity of 185 mL closed with an [redacted] (b) (4) HDPE grooved screw cap. |



Reference ID: 3454793

## APPENDIX G. (b) (4) LABELING

### G.1 List of (b) (4) Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Cholbam (b) (4) labeling submitted by Asklepion Pharmaceuticals, LLC on November 21, 2013 and December 4, 2013.

(b) (4)

- Full Prescribing Information

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.



Reference ID: 3454793

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/s/

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TERRI WOOD-CUMMINGS
02/14/2014

LUBNA A MERCHANT
02/16/2014

**M E M O R A N D U M**

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

---

DATE: January 27, 2014

TO: Director, Investigation Branch
New Jersey District Office
10 Waterview Blvd.
Third Floor
Waterview Corp. Center
Parsippany, NJ 07054

Director, Investigation Branch
Philadelphia District Office
U.S. Customhouse
Room 900
2nd & Chestnut Streets
Philadelphia, PA 19106

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2014, CDER High Priority Pre-Approval NDA Data Validation Inspection,** Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 205-750
DRUG: Cholic acid capsules, 50 and 250 mg
SPONSOR: Asklepion Pharmaceuticals, LLC, Baltimore, MD

This memo requests that you arrange for inspections of the clinical and analytical portions of the following in vivo bioequivalence (BE)/pharmacokinetic study.

Once you identify an ORA investigator, please contact the DBGLPC point of contact (POC) listed at the end of this assignment memo to schedule the inspection of the analytical site. A DBGLPC scientist will participate in the inspection of the analytical site to provide scientific and technical expertise.

Background materials will be available in ECMS under the ORA folder. **The inspections should be completed prior to May 21, 2014.**

**Do not reveal the applicant/sponsor, application number, study to be inspected, drug name, or the study investigators to the sites prior to the start of the inspections.** The sites will receive this information during the inspection opening meeting. The inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

**At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to the DBGLPC POC.**

**Study #1**: CAC-003-01
**Study Title**: "Comparative bioavailability of three formulations of cholic acid in healthy male subjects using a multiple dose repeated measures approach."

**Clinical Site**: Frontage Clinical Services
241 Main Street, 3rd Floor
Hackensack, NJ 07601
TEL: (201)678-0288
FAX: (201)678-0349

**Investigator**: Benno G. Roesch, MD

**SECTION A - (b) (4)**

the bioequivalence study is subject to 21 CFR (b) (4) (b) (4) the site conducting the study (i.e., investigator site) is responsible for (b) (4) (b) (4) (b) (4)

The final rule for (b) (4) (b) (4) (b) (4) specifically addresses the (b) (4).

Please refer to CDER's "Guidance for Industry, (b) (4) (b) (4), which clarifies (b) (4) (b) (4).

**During the clinical site inspection, please**:

(b) (4)

[redacted]

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: 1-314-539-2135

## SECTION B – CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

**During the clinical site inspection, please**:

☐ Confirm the informed consent forms and study records for 100% of subjects enrolled at the site.

☐ Compare the study report in the NDA submission to the original documents at the site.

☐ Check for under-reporting of adverse events (AEs).

☐ Check for evidence of inaccuracy in the electronic data capture system.

☐ Check reports for the subjects audited.

- o Number of subject records reviewed during the inspection:_____
- o Number of subjects screened at the site:_____
- o Number of subjects enrolled at the site:_____
- o Number of subjects completing the study:_____

☐ Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.

☐ Confirm that site personnel followed SOPs during study conduct.

☐ Examine correspondence files for any applicant or monitor-requested changes to study data or reports.

☐ Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.

☐ Other comments:

_____

_____

_____

## SECTION C – AUDIT OF ANALYTICAL DATA

**Analytical Site**: (b) (4)

[redacted] (b) (4)

**Note:** Please note that [redacted] (b) (4) in [redacted] (b) (4) has changed. [redacted] (b) (4) location where study samples were analyzed [redacted] (b) (4) (b) (4)

**Investigator:** [redacted] (b) (4)

**Methodology:** LC-MS/MS

**During the analytical site inspection, please:**

- ☐ Examine all pertinent items related to the analytical method used for the measurement of analytes (cholic acid, glycocholic acid and taurocholic acid) concentrations in human plasma.
- ☐ Compare the accuracy of the analytical data in the NDA submission against the original documents at the site.
- ☐ Determine if the site employed a validated analytical method to analyze the subject samples.
- ☐ Compare the assay parameters (such as variability between and within runs, accuracy and precision, etc.) observed during the study sample analysis with those obtained during method validation.
- ☐ Confirm that the accuracy and precision in matrix were determined using standards and QCs prepared from separate stock solutions.
- ☐ Determine if the subject samples were analyzed within the conditions and times of demonstrated stability.
- ☐ Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.
- ☐ Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria (e.g., number of freeze-thaw cycles) sufficiently covered the stability of reanalyzed subject samples.

☐ Examine correspondence files between the analytical site and the Applicant for their content.

**Additional instructions to the ORA Investigator:**

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

**If you issue Form FDA 483, please forward a copy to the DBGLPC POC. If it appears that the observations may warrant an OAI classification, notify the DBGLPC POC as soon as possible.**

**Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received and EIR to the DBGLPC POC.**

DBGLPC POC: Hansong Chen, Ph.D., Pharm.D.
Pharmacologist
Office of Scientific Investigations
Tel: (240)-402-4143
FAX: (301)-847-8748
Email: Hansong.Chen@fda.hhs.gov

DARRTS cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Bonapace/Haidar/Choi/Chen/Dejernett
CDER/OPS/ONDQA/Ghosh/Riviere/
CDER/OND/ODEIII/DGIEP/Davis-Williams

Email cc:
ORA -DO/ORA BIMO
ORA (b) (4) -DO/ORA (b) (4) BIMO

Draft: HC 01/23/2014
Edit: YMC 01/24/2014; SHH 1/24/14
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laborat E Program/Analytical Sites/ (b) (4)

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/ Clinical Sites/Frontage Clinical Services, Hackensack, NJ

OSI file #: BE 6667, bio205750
**FACTS: 8745501**

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/s/

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HANSONG CHEN
01/27/2014

SAM H HAIDAR
01/30/2014

| OSI Consult<br>Request for Biopharmaceutical Inspections | |
|---|---|
| Date | January 21, 2014 |
| Subject | Request for Biopharmaceutical Inspections (BE) |
| Addressed to | William H. Taylor, PhD<br>Director, Division of BE and GLP Compliance<br>Office of Scientific Investigations<br>william.taylor1@fda.hhs.gov |
| Consulting Office/Division | CDER/Division of Gastroenterology/Inborn Errors Products |
| Project Manager | CDR Anissa Davis-Williams |
| Application Type | PEPFAR? ☐ Yes ☒ No |
| | ☒ NDA ☐ BLA ☐ ANDA |
| Application Number | 205750 |
| Drug Product | Cholic acid |
| Sponsor Name | Asklepion Pharmaceuticals, LLC |
| Sponsor Address | 729 E. Pratt Street<br>Suite 360<br>Baltimore, MD 21202 |
| US Agent (if applicable) | n/a |
| US Agent Address | n/a |
| Electronic Submission | ☒ Yes ☐ No |
| PDUFA/BsUFA Due Date | July 21, 2014 |
| Action Goal Date | July 21, 2014 |
| OSI Review Requested By | Kareen Riviere, Ph.D. |

| **Inspection Request Detail** (All fields should be fill out completely) | | | | |
|---|---|---|---|---|
| Study #1 | | | | |
| Study Number | CAC-003-01 | | | |
| Study Title | Comparative Bioavailability of Three Formulations of Cholic Acid in Healthy Male Subjects Using a Multiple Dose Repeated Measures Approach | | | |
| Study Type | ☒ In vivo BE | ☐ In vitro BE | ☐ Permeability | ☐ Others (specify) |

| ☐ Inspection Request - Clinical Site | ☐ Inspection Request - Analytical Site |
|---|---|
| Facility #1 Name: **Frontage Clinical Services**<br>Address: **241 Main Street, 3rd Floor Hackensack, NJ 07601**<br>(Tel) **201.678.0288**<br>(Fax) **201.678.0349** | Facility #1 Name: [redacted] (b) (4)<br>Address: [redacted] (b) (4)<br>(Tel) [redacted] (b) (4)<br>(Fax) |
| Clinical Investigator: **Benno G. Roesch, MD**<br>(email) **ben.roesch@abr-clinical.com** | Principal Analytical Investigator: [redacted] (b) (4)<br>(email) [redacted] (b) (4) |

OSI 08/1/12

| | |
|---|---|
| Facility #2 Name: (if applicable)<br>Address:<br>(Tel)<br>(Fax) | Facility #2 Name: (if applicable)<br>Address:<br>(Tel)<br>(Fax) |
| Clinical Investigator:<br>(email) | Principal Analytical Investigator:<br>(email) |
| Check one: ☒ Routine inspection<br>☐ For cause | Check one: ☐ Routine inspection<br>☐ For cause |
| *(please include specific review concerns or items to be addressed during the inspection in the appendix below)* | |
| ☐ Study Report: (location, eg., 5.3.1.2) | ☐ Validation Report: (eg., 5.3.1.2)<br>☒ Bioanalytical Report: (eg., 5.3.1.4)<br><br>**Determination Of Cholic Acid, Glycocholic Acid And Taurocholic Acid In Human ($K_2EDTA$) Plasma By LC/MS/MS**<br><br>**Method No: BTM-1365-RO** |

| Study #2 | | | | |
|---|---|---|---|---|
| Study Number | | | | |
| Study Title | | | | |
| Study Type | ☐ In vivo BE | ☐ In vitro BE | ☐ Permeability | ☐ Others (specify) |
| ☐ Inspection Request - Clinical Site | | ☐ Inspection Request - Analytical Site | | |
| Facility Name: (or indicate if same as above)<br>Address:<br>(Tel)<br>(Fax) | | Facility Name: (or indicate if same as above)<br>Address:<br>(Tel)<br>(Fax) | | |
| Clinical Investigator:<br>(email) | | Principal Analytical Investigator:<br>(email) | | |
| Check one: ☐ Routine inspection<br>☐ For cause | | Check one: ☐ Routine inspection<br>☐ For cause | | |
| *(please include specific review concerns or items to be addressed during the inspection in the appendix below)* | | | | |
| ☐ Study Report: (location, eg., 5.3.1.2) | | ☐ Validation Report: (eg., 5.3.1.2)<br>☐ Bioanalytical Report: (eg., 5.3.1.4) | | |

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, OSI.**

## *I. Appendix*

| **Specific Items To be Addressed During the Inspection** |
|---|

1. Evaluate whether the study was conducted as per approved protocol (*i.e., the study subject recruitment followed the specified inclusion/exclusion criteria and dropouts followed the protocol's criteria and were properly documented*).
2. Evaluate whether protocol deviations were properly documented and justified.
3. Evaluate whether the blood/plasma samples were taken, stored, transported, and analyzed as per approved SOPs and the analytical and PK data analysis results were properly documented.
4. Evaluate whether the data excluded from the bioequivalence data analysis is justified.

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

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/s/

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KAREEN RIVIERE
01/21/2014

# RPM FILING REVIEW

**(Including Memo of Filing Meeting)**

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]**

| Application Information | | |
|---|---|---|
| NDA # 205750<br>BLA# N/A | NDA Supplement #:S- N/A<br>BLA Supplement # N/A | Efficacy Supplement Type SE- N/A |
| Proprietary Name: Cholbam<br>Established/Proper Name: cholic acid<br>Dosage Form: capsules<br>Strengths: 50 mg and 250 mg | | |
| Applicant: Asklepion Pharmaceuticals, LLC<br>Agent for Applicant (if applicable): N/A | | |
| Date of Application: November 21, 2013<br>Date of Receipt: November 21, 2013<br>Date clock started after UN: N/A | | |
| PDUFA Goal Date: July 21, 2014 | Action Goal Date (if different): N/A | |
| Filing Date: January 20, 2014 | Date of Filing Meeting: January 8, 2014 | |
| Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1 | | |
| Proposed indication(s)/Proposed change(s): Treatment of [redacted] (b) (4) | | |

| | |
|---|---|
| Type of Original NDA:<br>AND (if applicable)<br>Type of NDA Supplement:<br><br>***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:***<br>***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499***<br>***and refer to Appendix A for further information.*** | ☐ 505(b)(1)<br>☒ 505(b)(2)<br>☐ 505(b)(1)<br>☐ 505(b)(2) |
| Review Classification:<br><br>***If the application includes a complete response to pediatric WR, review classification is Priority.***<br><br>***If a tropical disease priority review voucher was submitted, review classification is Priority.*** | ☐ Standard<br>☒ Priority<br><br>☐ Tropical Disease Priority Review Voucher submitted |
| Resubmission after withdrawal? ☐ | Resubmission after refuse to file? ☐ |
| Part 3 Combination Product? ☐<br><br>***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults*** | ☐ Convenience kit/Co-package<br>☐ Pre-filled drug delivery device/system (syringe, patch, etc.)<br>☐ Pre-filled biologic delivery device/system (syringe, patch, etc.)<br>☐ Device coated/impregnated/combined with drug<br>☐ Device coated/impregnated/combined with biologic<br>☐ Separate products requiring cross-labeling<br>☐ Drug/Biologic<br>☐ Possible combination based on cross-labeling of separate products<br>☐ Other (drug/device/biological product) |



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| | |
|---|---|
| ☐ Fast Track Designation<br>☐ Breakthrough Therapy Designation<br>☐ Rolling Review<br>☒ Orphan Designation<br><br>☐ Rx-to-OTC switch, Full<br>☐ Rx-to-OTC switch, Partial<br>☐ Direct-to-OTC<br><br>Other: | ☐ PMC response<br>☐ PMR response:<br>☐ FDAAA [505(o)]<br>☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)]<br>☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)<br>☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) |

Collaborative Review Division (*if OTC product*): N/A

List referenced IND Number(s): 045470

| **Goal Dates/Product Names/Classification Properties** | **YES** | **NO** | **NA** | **Comment** |
|---|---|---|---|---|
| PDUFA and Action Goal dates correct in tracking system?<br><br>***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.*** | ☒ | ☐ | | |
| Are the proprietary, established/proper, and applicant names correct in tracking system?<br><br>***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.*** | ☒ | ☐ | | |
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm***<br><br>***If no, ask the document room staff to make the appropriate entries.*** | ☒ | ☐ | ☐ | |
| **Application Integrity Policy** | **YES** | **NO** | **NA** | **Comment** |
| Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm*** | ☐ | ☒ | | |
| **If yes**, explain in comment column. | | | X | |
| **If affected by AIP**, has OC/OMPQ been notified of the submission? **If yes,** date notified: | ☐ | ☐ | X | |
| **User Fees** | **YES** | **NO** | **NA** | **Comment** |
| Is Form 3397 (User Fee Cover Sheet) included with authorized signature? | ☒ | ☐ | | |



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| User Fee Status | Payment for this application: |
|---|---|
| ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.*** | ☐ Paid<br>☒ Exempt (orphan, government)<br>☐ Waived (e.g., small business, public health)<br>☐ Not required |
| ***If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.*** | Payment of other user fees:<br>☒ Not in arrears<br>☐ In arrears |

| **505(b)(2)**<br>**(NDAs/NDA Efficacy Supplements only)** | **YES** | **NO** | **NA** | **Comment** |
|---|---|---|---|---|
| Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? | ☐ | ☒ | ☐ | |
| Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].** | ☐ | ☒ | ☐ | |
| Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?**<br><br>***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs*** | ☐ | ☒ | ☐ | |
| Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?<br>***Check the Electronic Orange Book at:***<br>***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm***<br><br>**If yes**, please list below: | ☐ | ☒ | ☐ | |

| Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

*If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.*

| **Exclusivity** | **YES** | **NO** | **NA** | **Comment** |
|---|---|---|---|---|
| Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug*** | ☐ | ☒ | | (b) (4) |



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| | | | | |
|---|---|---|---|---|
| ***Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm* | | | | (b) (4) |
| **If another product has orphan exclusivity**, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**?<br><br>***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy*** | ☐ | ☐ | ☒ | |
| Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)***<br><br>**If yes**, # years requested: 7<br><br>***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* | ☒ | ☐ | ☐ | |
| Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)? | ☐ | ☒ | ☐ | |
| **If yes**, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?<br><br>***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.*** | ☐ | ☐ | ☒ | |

| **Format and Content** | | | | |
|---|---|---|---|---|
| ***Do not check mixed submission if the only electronic component is the content of labeling (COL).*** | ☐ All paper (except for COL)<br>☒ All electronic<br>☐ Mixed (paper/electronic)<br><br>☒ CTD<br>☐ Non-CTD<br>☐ Mixed (CTD/non-CTD) | | | |
| **If mixed (paper/electronic) submission**, which parts of the application are submitted in electronic format? | | | | |
| **Overall Format/Content** | **YES** | **NO** | **NA** | **Comment** |
| **If electronic submission,** does it follow the eCTD guidance?[1]<br>**If not,** explain (e.g., waiver granted). | ☒ | ☐ | ☐ | |
| **Index:** Does the submission contain an accurate comprehensive index? | ☒ | ☐ | | |

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf



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| | | | | |
|---|---|---|---|---|
| Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:<br><br>☒ legible<br>☒ English (or translated into English)<br>☒ pagination<br>☒ navigable hyperlinks (electronic submissions only)<br><br>**If no**, explain. | ☒ | ☐ | | |
| **BLAs only**: Companion application received if a shared or divided manufacturing arrangement?<br><br>**If yes**, BLA # | ☐ | ☐ | ☒ | |
| | | | | |
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| | | | | |
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| | | | | |
| **Forms and Certifications** | | | | |
| ***Electronic*** *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* | | | | |
| **Application Form** | **YES** | **NO** | **NA** | **Comment** |
| Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?<br><br>***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].*** | ☒ | ☐ | | Corrected version received on 12/19/13 listing "IND 045470" as a Cross Reference along with DMF information |
| Are all establishments and their registration numbers listed on the form/attached to the form? | ☒ | ☐ | ☐ | |
| **Patent Information (NDAs/NDA efficacy supplements only)** | **YES** | **NO** | **NA** | **Comment** |
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)? | ☒ | ☐ | ☐ | |
| **Financial Disclosure** | **YES** | **NO** | **NA** | **Comment** |
| Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?<br><br>***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].***<br><br>***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* | ☒ | ☐ | | |
| **Clinical Trials Database** | **YES** | **NO** | **NA** | **Comment** |



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| | | | | |
|---|---|---|---|---|
| Is form FDA 3674 included with authorized signature?<br><br>***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***<br><br>***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant*** | ☒ | ☐ | | |
| **Debarment Certification** | **YES** | **NO** | **NA** | **Comment** |
| Is a correctly worded Debarment Certification included with authorized signature?<br><br>***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].***<br><br>***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"* | ☒ | ☐ | ☐ | |
| **Field Copy Certification (NDAs/NDA efficacy supplements only)** | **YES** | **NO** | **NA** | **Comment** |
| **For paper submissions only:** Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?<br><br>***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)***<br><br>***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.*** | ☐ | ☐ | ☒ | However, the Applicant submitted a statement. |
| **Controlled Substance/Product with Abuse Potential** | **YES** | **NO** | **NA** | **Comment** |
| For NMEs:<br>Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?<br><br>***If yes,*** *date consult sent to the Controlled Substance Staff:*<br><br>For non-NMEs:<br>*Date of consult sent to Controlled Substance Staff*: | ☐ | ☐ | ☒ | |
| **Pediatrics** | **YES** | **NO** | **NA** | **Comment** |
| **PREA**<br><br>Does the application trigger PREA?<br><br>***If yes, notify PeRC RPM (PeRC meeting is required)***[2] | ☐ | ☒ | | The indication received Orphan designation 7/18/03 |

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm



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| | | | | |
|---|---|---|---|---|
| ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* | | | | |
| **If the application triggers PREA**, are the required pediatric assessment studies or a full waiver of pediatric studies included? | ☐ | ☐ | ☒ | |
| **If studies or full waiver not included,** is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?<br><br>***If no, request in 74-day letter*** | ☐ | ☐ | ☒ | |
| **If a request for full waiver/partial waiver/deferral is included**, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?<br><br>***If no, request in 74-day letter*** | ☐ | ☐ | ☒ | |
| **BPCA (NDAs/NDA efficacy supplements only):**<br><br>Is this submission a complete response to a pediatric Written Request?<br><br>***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3] | ☐ | ☒ | | |
| **Proprietary Name** | **YES** | **NO** | **NA** | **Comment** |
| Is a proposed proprietary name submitted?<br><br>***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."*** | ☒ | ☐ | ☐ | Submitted on 12/3/13 |
| **REMS** | **YES** | **NO** | **NA** | **Comment** |
| Is a REMS submitted?<br><br>***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox*** | ☐ | ☒ | ☐ | However, Applicant submitted a REMS waiver request with submission. Information forwarded to OSE RPM, Phone Do, and CDER OSI RMP mailbox on 12/4/13 |
| **Prescription Labeling** | ☐ **Not applicable** | | | |
| Check all types of labeling submitted. | ☒ Package Insert (PI)<br>☐ Patient Package Insert (PPI)<br>☐ Instructions for Use (IFU)<br>☐ Medication Guide (MedGuide)<br>☒ (b) (4)<br>☒ Immediate container labels | | | |

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm



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| | | | | |
|---|---|---|---|---|
| | ☐ Diluent<br>☐ Other (specify) | | | |
| | **YES** | **NO** | **NA** | **Comment** |
| Is Electronic Content of Labeling (COL) submitted in SPL format?<br><br>***If no, request applicant to submit SPL before the filing date.*** | ☒ | ☐ | | |
| Is the PI submitted in PLR format?[4] | ☒ | ☐ | | |
| **If PI not submitted in PLR format**, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request?<br><br>***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.*** | ☐ | ☐ | ☒ | |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP? | ☒ | ☐ | ☐ | Submitted on 12/5/13 |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) | ☐ | ☐ | ☒ | |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)? | ☒ | ☐ | ☐ | Submitted on 12/5/13 |
| **OTC Labeling** | ☒ **Not Applicable** | | | |
| Check all types of labeling submitted. | ☐ Outer carton label<br>☐ Immediate container label<br>☐ Blister card<br>☐ Blister backing label<br>☐ Consumer Information Leaflet (CIL)<br>☐ Physician sample<br>☐ Consumer sample<br>☐ Other (specify) | | | |
| | **YES** | **NO** | **NA** | **Comment** |
| Is electronic content of labeling (COL) submitted?<br><br>***If no, request in 74-day letter.*** | ☐ | ☐ | X | |
| Are annotated specifications submitted for all stock keeping units (SKUs)?<br><br>***If no, request in 74-day letter.*** | ☐ | ☐ | ☒ | |
| If representative labeling is submitted, are all represented SKUs defined?<br><br>***If no, request in 74-day letter.*** | ☐ | ☐ | ☒ | |
| All labeling/packaging, and current approved Rx PI (if | ☐ | ☐ | ☒ | |

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm



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| | | | | |
|---|---|---|---|---|
| switch) sent to OSE/DMEPA? | | | | |
| **Other Consults** | **YES** | **NO** | **NA** | **Comment** |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)<br><br>***If yes, specify consult(s) and date(s) sent: Submitted application to OSE (DRISK, DEPI and DPV)-12/5/13*** | ☒ | ☐ | ☐ | |
| **Meeting Minutes/SPAs** | **YES** | **NO** | **NA** | **Comment** |
| End-of Phase 2 meeting(s)?<br>**Date(s):**<br><br>***If yes, distribute minutes before filing meeting*** | ☐ | ☒ | | |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?<br>**Date(s):** 10/25/2004; 05/31/2005, 01/25/2010, 7/25/2013, and 7/29/2013<br><br>***If yes, distribute minutes before filing meeting*** | ☒ | ☐ | | Meeting minutes forwarded to reviewers on 12/31/13 |
| Any Special Protocol Assessments (SPAs)?<br>**Date(s):**<br><br>***If yes, distribute letter and/or relevant minutes before filing meeting*** | ☐ | ☒ | | |



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ATTACHMENT

# MEMO OF FILING MEETING

**DATE**: January 8, 2014

**BLA/NDA/Supp #**: 205750

**PROPRIETARY NAME**: Cholbam

**ESTABLISHED/PROPER NAME**: cholic acid

**DOSAGE FORM/STRENGTH**: capsules, 50 mg and 250 mg

**APPLICANT**: Asklepion Pharmaceuticals, LLC

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S)**: Treatment of (b) (4)

**BACKGROUND**:
Asklepion Pharmaceuticals, LLC (Asklepion) submitted a new drug application which provides for a new molecular entity, cholic acid, with the following proposed indication: (b) (4) The indication received orphan designation in 2003.

There were three Pre-NDA meetings held regarding this application, most recently on January 25, 2010. However, there was a teleconference held on July 29, 2013 to discuss the PDUFA V Program requirement for a complete application since the Pre-NDA meetings for IND 045470 (referenced IND) occurred before PDUFA V went into effect.

Asklepion has provided natural history data, a bridging study for the formulations (to-be-marketed and compounded formulations of cholic acid capsules used to treat children with inborn errors of bile acid synthesis), nonclinical literature, and other information to support this application.

This is a 505(b)(2), New Molecular Entity (NME) application being reviewed under the PDUVA V Program.

**REVIEW TEAM**:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|---|---|---|---|
| Regulatory Project Management | RPM: | CDR Anissa Davis-Williams | Y |
| | CPMS/TL: | Brian Strongin | N |



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| | | | |
|---|---|---|---|
| Cross-Discipline Team Leader (CDTL) | Lara Dimick-Santos | | Y |
| Clinical | Reviewer: | Wen-Yi Yao | Y |
| | TL: | Lara Dimick-Santos | Y |
| Social Scientist Review (*for OTC products*) | Reviewer: | N/A | N/A |
| | TL: | N/A | N/A |
| OTC Labeling Review (*for OTC products*) | Reviewer: | N/A | N/A |
| | TL: | N/A | N/A |
| Clinical Microbiology (*for antimicrobial products*) | Reviewer: | N/A | N/A |
| | TL: | N/A | N/A |

| | | | |
|---|---|---|---|
| Clinical Pharmacology | Reviewer: | Insook Kim | Y |
| | TL: | Sue Chih Lee | Y |
| Biostatistics | Reviewer: | Behrang Vali | Y |
| | TL: | Freda Cooner | Y |
| Nonclinical (Pharmacology/Toxicology) | Reviewer: | Ke Zhang | Y |
| | TL: | David Joseph | Y |
| Statistics (carcinogenicity) | Reviewer: | N/A | N/A |
| | TL: | N/A | N/A |
| Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)* | Reviewer: | N/A | N/A |
| | TL: | N/A | N/A |
| Product Quality (CMC) | Reviewer: | Gene Holbert | Y |
| | TL: | Marie Kowblansky | Y |
| Quality Microbiology *(for sterile products)* | Reviewer: | Bryan Riley | N |
| | TL: | Stephen Langille | N |
| CMC Labeling Review | Reviewer: | N/A | N/A |
| | TL: | NA | N/A |



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| | | | |
|---|---|---|---|
| Facility Review/Inspection | Reviewer: | Christina Capacci-Daniel | Y |
| | TL: | Mahesh Ramanadham | N |
| OSE/DMEPA (proprietary name) | Reviewer: | Terri Wood-Cummings | Y |
| | TL: | Lubna Merchant | Y |
| OSE/DRISK (REMS) | Reviewer: | George Neyarapally | N |
| | TL: | Kendra Worthy & Reema Mehta | Reema Mehta (Y) |
| OC/OSI/DSC/PMSB (REMS) | Reviewer: | N/A | N/A |
| | TL: | N/A | N/A |

| | | | |
|---|---|---|---|
| Bioresearch Monitoring (OSI) | Reviewer: | Susan Leibenhaut | Y |
| | TL: | N/A | N/A |
| Controlled Substance Staff (CSS) | Reviewer: | N/A | N/A |
| | TL: | N/A | N/A |
| Other reviewers: Biopharmaceutics | Reviewer: Kareen Riviere<br>TL-Tapash Ghosh | | N<br>Y |
| PMHS (Peds): | Reviewer: Ethan Hausman<br>TL-Hari Sachs | | Y<br>Y |
| PMHS(Maternal): | Reviewer: Tamara Johnson<br>TL: Jeanine Best | | Y<br>N |
| OSE/DPV: | Reviewer: Eileen (LingYu) Wu | | N |
| OSE/DEPI: | Reviewer: David Shih (Meeting attendance only) | | N |
| OPDP: | Reviewer: Adewale Adeleye<br>TL: Kathleen Klemm | | Y<br>N |
| Other attendees | Julie Beitz, Hansong Chen, Amy Egan, Yvette Waples, Denise Pica-Branco, Maria Walsh | | |

**FILING MEETING DISCUSSION:**

| **GENERAL** | |
|---|---|
| • 505(b)(2) filing issues: | ☐ Not Applicable |
| ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? | ☐ YES ☒ NO |



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| | |
|---|---|
| ○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?<br><br>Describe the scientific bridge (e.g., BA/BE studies): | ☒ YES ☐ NO<br><br>Cholic acid is an endogenous substance (the most abundant bile acid in humans) for which the target pediatric patient population is severely deficient. The sponsor provided publications which indicate that the proposed dose levels will produce a total body cholic acid content that will not exceed the levels found in normal children. Therefore, no nonclinical studies are needed to support approval. This was the nonclinical recommendation from 2010. |
| • Per reviewers, are all parts in English or English translation?<br><br>**If no**, explain: | ☒ YES<br>☐ NO |
| • Electronic Submission comments<br><br>**List comments**: none | ☐ Not Applicable |
| **CLINICAL**<br><br>**Comments**:<br>1. Provide efficacy data (summary tables and original data) of liver function test (LFT) and bilirubin test (direct, total, and indirect bilirubin) in patients with single enzyme defect.<br><br>2. Provide detailed narratives of the PIDs 0, 16, 103, 127, 143, 152, and 181.<br><br>3. On page 20 of your clinical overview you state that you prepared a revised clinical study report to address the EMA comments. Please provide a copy of the EMA comments and clarify how you revised the study report to address these comments.<br><br>4. Sponsor should be requested to provide the "coding dictionary" consisting of a list of all investigator | ☐ Not Applicable<br>☒ FILE<br>☐ REFUSE TO FILE<br><br>☒ Review issues for 74-day letter |



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|---|---|
| verbatim terms and the preferred terms to which they were mapped. | |
| • Clinical study site(s) inspections(s) needed?<br><br>**If no,** explain: | ☒ YES<br>☐ NO |
| • Advisory Committee Meeting needed?<br><br>**Comments**:<br><br>***If no, for an NME NDA or original BLA , include the reason. For example:***<br>○ ***this drug/biologic is not the first in its class***<br>○ ***the clinical study design was acceptable***<br>○ ***the application did not raise significant safety or efficacy issues***<br>○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease*** | ☐ YES<br>Date if known:<br>☒ NO<br>☐ To be determined<br><br>Reason: |
| • Abuse Liability/Potential<br><br>**Comments**: | ☒ Not Applicable<br>☐ FILE<br>☐ REFUSE TO FILE<br><br>☐ Review issues for 74-day letter |
| • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?<br><br>**Comments**: | ☒ Not Applicable<br>☐ YES<br>☐ NO |
| **CLINICAL MICROBIOLOGY**<br><br>**Comments**: | ☒ Not Applicable<br>☐ FILE<br>☐ REFUSE TO FILE<br><br>☐ Review issues for 74-day letter |
| **CLINICAL PHARMACOLOGY**<br><br>**Comments**: We note that the bioanalytical assay validation for urinary bile acids was done in a qualitative assessment not a quantitative assessment. (b) (4) | ☐ Not Applicable<br>☒ FILE<br>☐ REFUSE TO FILE<br><br>☒ Review issues for 74-day letter |



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|---|---|
| (b) (4) This will be a review issue in the assessment of the suppression of the synthesis of atypical bile acids by cholic acid treatment. | |
| • Clinical pharmacology study site(s) inspections(s) needed? | ☒ YES<br>☐ NO |
| **BIOSTATISTICS**<br><br>**Comments**: For Study CAC-91-10-10, provide a separate subgroup efficacy analyses by gender and by race for the primary efficacy variables. For the subgroup efficacy analysis by race, there should be three subgroups analyzed: Whites, Non-Whites, and Unknown. | ☐ Not Applicable<br>☒ FILE<br>☐ REFUSE TO FILE<br><br>☒ Review issues for 74-day letter |
| **NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)**<br><br>**Comments**: None | ☐ Not Applicable<br>☒ FILE<br>☐ REFUSE TO FILE<br><br>☐ Review issues for 74-day letter |

| | |
|---|---|
| **IMMUNOGENICITY (BLAs/BLA efficacy supplements only)**<br><br>**Comments**: | ☒ Not Applicable<br>☐ FILE<br>☐ REFUSE TO FILE<br><br>☐ Review issues for 74-day letter |
| **PRODUCT QUALITY (CMC)**<br><br>**Comments**: None<br><br>**<u>Biopharmaceutics Comments:</u>**<br>1. Provide solubility data for the drug substance covering the physiological pH range;<br><br>2. Provide data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products (aberrant formulations) that are intentionally manufactured with meaningful variations for the most relevant manufacturing variables (i.e., ± 10-20% | ☐ Not Applicable<br>☒ FILE<br>☐ REFUSE TO FILE<br><br>☒ Review issues for 74-day letter |



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| | |
|---|---|
| change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent;<br><br>3. Provide complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for all components of the proposed product.<br><br>4. To support the Level 2 drug product manufacturing site change, provide *in vitro* comparative dissolution data and f2 similarity values (n=12) for the drug product manufactured at the old and new site in three media (b) (4) and phosphate buffers pH (b) (4) and 6.8.<br><br>**Quality Microbiology Comments:** None | |
| **Environmental Assessment**<br><br>• Categorical exclusion for environmental assessment (EA) requested?<br><br>**If no**, was a complete EA submitted?<br><br>**If EA submitted**, consulted to EA officer (OPS)?<br><br>**Comments**: | <br>☒ YES<br>☐ NO<br><br>☐ YES<br>☐ NO<br><br>☒ YES<br>☐ NO |
| **Quality Microbiology (for sterile products)**<br><br>• Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)<br><br>**Comments**: | ☒ Not Applicable<br><br>☐ YES<br>☐ NO |
| **Facility Inspection**<br><br>• Establishment(s) ready for inspection?<br><br>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?<br><br>**Comments**: No comments for 74-day letter | ☐ Not Applicable<br><br>☒ YES<br>☐ NO<br><br>☒ YES<br>☐ NO |



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| | |
|---|---|
| **Facility/Microbiology Review (BLAs only)**<br><br>**Comments**: | ☒ Not Applicable<br>☐ FILE<br>☐ REFUSE TO FILE<br><br>☐ Review issues for 74-day letter |
| **CMC Labeling Review**<br><br>**Comments**: None | ☐ Review issues for 74-day letter |
| **APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)** | ☐ N/A |
| • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? | ☒ YES<br>☐ NO |
| • If so, were the late submission components all submitted within 30 days? | ☒ YES<br>☐ NO |
| • What late submission components, if any, arrived after 30 days? | N/A |
| • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? | ☒ YES<br>☐ NO |
| • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? | ☒ YES<br>☐ NO |
| • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? | ☒ YES<br>☐ NO |
| **REGULATORY PROJECT MANAGEMENT** | |
| **Signatory Authority:** Julie Beitz, M.D. | |



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**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): February 27, 2014

**21st Century Review Milestones (see attached)** (listing review milestones in this document is optional):

| **GOAL DATES** | |
|---|---|
| Primary Reviews Due | April 21, 2014 |
| Secondary Reviews Due | April 24, 2014 |
| Labeling/REMS/PMR-PMC Comments to Sponsor (REMS w/i 6 wks after MC meeting) | April 21, 2014 |
| CDTL Review Due | June 23, 2014 |
| **PDUFA Date** | **July 21, 2014** |
| **Milestone Meetings** | |
| Filing Meeting | **January 8, 2014 @ 4pm Rm# 5270** |
| Planning Meeting | **January 21, 2014 @ 4pm; Rm# 5270** |
| Mid-Cycle Meeting | **February 27, 2014 @ 9am; Rm# 5270** |
| Post Mid-Cycle Meeting with Applicant (2 wks post Mid-Cycle) | **March 13, 2014 @ 1pm; Rm# 5313** |
| Pre-Meeting for Late Cycle Meeting (5.25 months) | **April 24, 2014 @ 2pm; Rm# 5270** |
| Late Cycle Meeting with Applicant (briefing packet to applicant- (12 days prior)-By May 8, 2014 | **May 20, 2014 @ 11am; Rm# 1309** |
| PeRC<br>***PeRC Paperwork Due: not applicable*** | **N/A; granted Orphan Designation** |
| **Wrap-up Meeting** | **June 16, 2014 @ 1pm; Rm# 5270** |

| **Team Meetings** | |
|---|---|
| **1** | **February 10, 2014 @ 3pm rm# 5270** |
| **2** | **March 6, 2014 @ 1pm rm# 5270** |
| **3** | **April 7, 2014 @ 1pm rm# 5270** |
| **4** | **May 12, 2014 @ 1pm rm# 5270** |

| **Labeling Meetings** | |
|---|---|
| Labeling Planning Mtg | March 13, 2014 @ 11am rm# 5313 |
| 1 | March 20, 2014 @ 1pm rm# 5313 |
| 2 | March 27, 2014 @ 2pm rm# 5313 |
| 3 | April 3, 2014 @ 9am rm# 5313 |
| 4 | April 10, 2014 @ 11am rm# 5313 |
| 5 | April 17, 2014 @ 3pm rm# 5313 |
| 6 | April 24, 2014 @ 10am rm# 5201 |
| 7 | May 1, 2014 @ 1pm rm# 5313 |

**Comments**: None

**REGULATORY CONCLUSIONS/DEFICIENCIES**



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| | |
|---|---|
| ☐ | The application is unsuitable for filing. Explain why: |
| ☒ | The application, on its face, appears to be suitable for filing.<br><br>Review Issues:<br><br>☐ No review issues have been identified for the 74-day letter.<br><br>☒ Review issues have been identified for the 74-day letter. List (optional):<br><br>Review Classification:<br><br>☐ Standard Review<br><br>☒ Priority Review |
| **ACTIONS ITEMS** | |
| ☒ | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug). |
| ☐ | If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). |
| ☐ | If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. |
| ☐ | BLA/BLA supplements: If filed, send 60-day filing letter |
| ☒ | If priority review:<br>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)<br><br>• notify OMPQ (so facility inspections can be scheduled earlier) |
| ☒ | Send review issues/no review issues by day 74 |
| ☒ | Conduct a PLR format labeling review and include labeling issues in the 74-day letter |
| ☒ | Update the PDUFA V DARRTS page (for NME NDAs in the Program) |
| ☐ | BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f ] |
| ☐ | Other |



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APPEARS THIS WAY ON ORIGINAL



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## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely



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for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.



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

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/s/

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ANISSA A DAVIS
01/18/2014

BRIAN K STRONGIN
01/18/2014

# REGULATORY PROJECT MANAGER
# PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
# OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 205750

**Application Type:** New NDA-NME

**Name of Drug/Dosage Form:** cholic acid capsules

**Applicant:** Asklepion Pharmaceuticals, LLC

**Receipt Date: November 21, 2013**

**Goal Date: July 21, 2014**

## 1. Regulatory History and Applicant's Main Proposals

Asklepion Pharmaceuticals, LLC (Asklepion) submitted a new drug application which provides for a new molecular entity, cholic acid, with the following proposed indication: (b) (4) [redacted] The indication received orphan designation in 2003.

There were three Pre-NDA meetings held regarding this application, most recently on January 25, 2010. However, there was a teleconference held on July 29, 2013 to discuss the PDUFA V Program requirement for a complete application since the Pre-NDA meetings for IND 045470 (referenced IND) occurred before PDUFA V went into effect.

Asklepion has provided natural history data, bridging study for the formulations (to-be-marketed and currently used formulation of cholic acid capsules used to that children with inborn errors of bile acid synthesis), and other information to support this application.

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by February 17, 2014. The resubmitted PI will be used for further labeling review.

## Appendix



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The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

---

# Highlights

**See Appendix A for a sample tool illustrating the format for the Highlights.**

**HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI**

**YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

***Comment:***

**NO** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES**" in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

***Comment:*** *Highlight is greater than one-half page. CDTL notified and deficiency will be conveyed to Applicant in the 74-day letter.*

**YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

***Comment:***

**YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

***Comment:***

**NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between



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the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

***Comment:*** *There is no white space before "ADVERSE REACTIONS" heading.*

**NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

***Comment:*** *The first bullet under "USE IN SPECIFIC POPULATIONS" does not have reference.*

**NO** 7. Section headings must be presented in the following order in HL:

| Section | Required/Optional |
|---|---|
| • **Highlights Heading** | Required |
| • **Highlights Limitation Statement** | Required |
| • **Product Title** | Required |
| • **Initial U.S. Approval** | Required |
| • **Boxed Warning** | Required if a BOXED WARNING is in the FPI |
| • **Recent Major Changes** | Required for only certain changes to PI* |
| • **Indications and Usage** | Required |
| • **Dosage and Administration** | Required |
| • **Dosage Forms and Strengths** | Required |
| • **Contraindications** | Required (if no contraindications must state "None.") |
| • **Warnings and Precautions** | Not required by regulation, but should be present |
| • **Adverse Reactions** | Required |
| • **Drug Interactions** | Optional |
| • **Use in Specific Populations** | Optional |
| • **Patient Counseling Information Statement** | Required |
| • **Revision Date** | Required |

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

***Comment:*** *The revision date is missing in HL.*

## HIGHLIGHTS DETAILS

### Highlights Heading

**YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

***Comment:***

### Highlights Limitation Statement

**YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

***Comment:***

### Product Title in Highlights

**YES** 10. Product title must be **bolded**.



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***Comment:***

**Initial U.S. Approval in Highlights**

**YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

***Comment:*** *However, the format is the same as Appendix A example..*

**Boxed Warning (BW) in Highlights**

**N/A** 12. All text in the BW must be **bolded**.

***Comment:***

**N/A** 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

***Comment:***

**N/A** 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

***Comment:***

**N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

***Comment:***

**Recent Major Changes (RMC) in Highlights**

**N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

***Comment:***

**N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

***Comment:***

**N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

***Comment:***

**Indications and Usage in Highlights**

**YES**



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19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

    ***Comment:***

**Dosage Forms and Strengths in Highlights**

**YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

    ***Comment:***

**Contraindications in Highlights**

**YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

    ***Comment:***

**Adverse Reactions in Highlights**

**YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

    ***Comment:***

**Patient Counseling Information Statement in Highlights**

**YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

***Comment:***

**Revision Date in Highlights**

**NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

    ***Comment:*** *The revision date is missing.*



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# Contents: Table of Contents (TOC)

**See Appendix A for a sample tool illustrating the format for the Table of Contents.**

**YES** 25. The TOC should be in a two-column format.

***Comment:***

**YES** 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

***Comment:***

**N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

***Comment:***

**NO** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

***Comment:*** *Entire section is in blue font; therefore, it is unable to determine if bolded are not.*

**NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

***Comment:*** *Entire section is in blue font. Therefore, it is unable to determine if bolded are not.*

**NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

***Comment:*** *Subsection 12.2 Pharmacodynamics located in the FPI is not annotated in TOC.*

**NO** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

***Comment:*** *The statement "*Sections or subsections omitted from the full prescribing information are not listed" is not annotated as required.*



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# Full Prescribing Information (FPI)

## FULL PRESCRIBING INFORMATION: GENERAL FORMAT

**YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

| |
|---|
| **BOXED WARNING** |
| **1 INDICATIONS AND USAGE** |
| **2 DOSAGE AND ADMINISTRATION** |
| **3 DOSAGE FORMS AND STRENGTHS** |
| **4 CONTRAINDICATIONS** |
| **5 WARNINGS AND PRECAUTIONS** |
| **6 ADVERSE REACTIONS** |
| **7 DRUG INTERACTIONS** |
| **8 USE IN SPECIFIC POPULATIONS** |
| **8.1 Pregnancy** |
| **8.2 Labor and Delivery** |
| **8.3 Nursing Mothers** |
| **8.4 Pediatric Use** |
| **8.5 Geriatric Use** |
| **9 DRUG ABUSE AND DEPENDENCE** |
| **9.1 Controlled Substance** |
| **9.2 Abuse** |
| **9.3 Dependence** |
| **10 OVERDOSAGE** |
| **11 DESCRIPTION** |
| **12 CLINICAL PHARMACOLOGY** |
| **12.1 Mechanism of Action** |
| **12.2 Pharmacodynamics** |
| **12.3 Pharmacokinetics** |
| **12.4 Microbiology (by guidance)** |
| **12.5 Pharmacogenomics (by guidance)** |
| **13 NONCLINICAL TOXICOLOGY** |
| **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** |
| **13.2 Animal Toxicology and/or Pharmacology** |
| **14 CLINICAL STUDIES** |
| **15 REFERENCES** |
| **16 HOW SUPPLIED/STORAGE AND HANDLING** |
| **17 PATIENT COUNSELING INFORMATION** |

***Comment:***

**NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"[see Warnings and Precautions (5.2)]"*.

***Comment:*** *The cross-references in the FPI are annotated with section number only.*



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N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

***Comment:***

**FULL PRESCRIBING INFORMATION DETAILS**

**FPI Heading**

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

***Comment:***

**BOXED WARNING Section in the FPI**

N/A 36. In the BW, all text should be **bolded**.

***Comment:***

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

***Comment:***

**CONTRAINDICATIONS Section in the FPI**

YES 38. If no Contraindications are known, this section must state "None."

***Comment:*** *The contraindications are annotated.*

**ADVERSE REACTIONS Section in the FPI**

NO 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

***Comment:*** *The above statement is not annotated.*

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

***Comment:***

**PATIENT COUNSELING INFORMATION Section in the FPI**

N/A 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and



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include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

***Comment:***

**N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

***Comment:***



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## Appendix A: Format of the Highlights and Table of Contents

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].**

**[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]**
**Initial U.S. Approval: [year]**

**WARNING: [SUBJECT OF WARNING]**
*See full prescribing information for complete boxed warning.*
- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

**To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

**See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].**

**Revised: [m/year]**

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**FULL PRESCRIBING INFORMATION: CONTENTS***


WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
1.1 [text]
1.2 [text]
2 DOSAGE AND ADMINISTRATION
2.1 [text]
2.2 [text]
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 [text]
5.2 [text]
6 ADVERSE REACTIONS
6.1 [text]
6.2 [text]
7 DRUG INTERACTIONS
7.1 [text]
7.2 [text]
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
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10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 [text]
14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION


*Sections or subsections omitted from the full prescribing information are not listed.



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

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/s/

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ANISSA A DAVIS
01/10/2014

BRIAN K STRONGIN
01/11/2014