



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205750

NDA APPROVAL

Asklepion Pharmaceuticals, LLC
Attention: Gary Pasternack, M.D., Ph.D.
Chief Executive Officer
729 E. Pratt Street
Suite 360
Baltimore, MD 21202

Dear Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for CHOLBAM (cholic acid) Capsules, 50mg and 250mg.

We also refer to our approval letter dated March 17, 2015 which contained an error in the labeling.

This replacement approval letter incorporates the correction of the error in the enclosed labeling. The effective approval date will remain March 17, 2015, the date of the original approval letter.

We acknowledge receipt of your amendments dated November 21, 2013; December 3, 2013; December 4, 2013; December 19, 2013; December 20, 2013; January 24, 2014; January 31, 2014; February 14, 2014; February 18, 2014; February 21, 2014; March 5, 2014; March 21, 2014; March 26, 2014; April 4, 2014; April 9, 2014; April 10, 2014; April 25, 2014; April 30, 2014; May 2, 2014; May 5, 2014; May 6, 2014; May 23, 2014; May 30, 2014; June 5, 2014; June 6, 2014; June 16, 2014; June 20, 2014; June 30, 2014; July 7, 2014; July 11, 2014; August 8, 2014; August 15, 2014; August 20, 2014; September 5, 2014; September 10, 2014; September 12, 2014; October 21, 2014; October 22, 2014; October 24, 2014; November 5, 2014; November 21, 2014; December 9, 2014; December 18, 2014; December 19, 2014; December 23, 2014; January 7, 2015; January 13, 2015; January 27, 2015; February 3, 2015; February 5, 2015; February 13, 2015; February 19, 2015; February 20, 2014; February 25, 2015; March 6, 2015, March 11, 2015, March 17, 2015 and March 23, 2015.

This new drug application provides for the use of CHOLBAM (cholic acid) Capsules for the treatment of bile acid synthesis disorders due to single enzyme defects and as adjunctive treatment of peroxisomal disorders including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea or complications from decreased fat soluble vitamin absorption.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

IMMEDIATE CONTAINER LABELS

Submit final printed immediate container labels that are identical to the immediate container labels submitted on December 23, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 205750.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV NDA 205750. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, “Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.
- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
 - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
 - the estimated demand in the U.S. for the product, and
 - the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program at <http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf> (see Section 908 of FDASIA on pages 1094-1098 which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

Please submit one market package of the drug product when it is available to the following address:

Brian Strongin, R.Ph., MBA
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building #22, Room: 5116
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for cholic acid was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

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

Because this drug product for these indications has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious 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.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2882-1 A prospective, long-term, observational study in a routine clinical setting of patients aged 3 weeks or older with bile acid synthesis disorders due to single enzyme defects and patients with peroxisomal disorders, including Zellweger spectrum disorders, who exhibit manifestations of liver disease, steatorrhea, fat soluble vitamin deficiency, or a neuropathic process related to a vitamin deficiency. The purpose of the study is to assess primarily the long term safety of treatment with Cholbam (cholic acid) capsules with respect to incidence rates of worsening cholestasis, steatorrhea leading to poor growth, fat soluble vitamin deficiency, or neuropathic process related to a vitamin deficiency, and the incidence of death and adverse effects on pregnancy, pregnancy outcomes and

infant status. Additional evaluations will include dosing regimens and reasons for any dose modifications, weight gain, length/height and developmental outcomes. Specify concise case definitions and validation algorithms for all outcomes. Enroll at least 55 patients (25 receiving cholic acid and 30 not receiving cholic acid) including at least 20 peroxisomal disorder patients with liver dysfunction, steatorrhea, fat soluble vitamin deficiency or a neuropathic process related to the latter. Enroll over an initial 3-year period and follow for a minimum of 10 years from the time of enrollment or until death, whichever comes first.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2015
Study Completion:	September 2028
Final Report Submission:	March 2029

Submit the protocol(s) to your IND 045470, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2882-2 Develop a quantitative urinary bile acid analysis assay method along with standards for bile acid synthesis disorders.

The timetable you submitted on February 25, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2017

Submit clinical protocols to your IND 045470 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Brian Strongin, R.Ph., MBA, Chief, Regulatory Project Management Staff, at (301) 796-1008.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling

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

/s/

JULIE G BEITZ
03/17/2015