

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

Approval Package for:

APPLICATION NUMBER:

203858Orig1s000

Trade Name: Juxtapid

***Generic
Name:*** Lomitapide

Sponsor: Aegerion Pharmaceuticals, Inc

***Approval
Date:*** 12/21/2012

Indications: As an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo-B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

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APPROVAL LETTER



NDA 203858

NDA APPROVAL

Aegerion Pharmaceuticals, Inc.
Attention: Martha J. Carter
Chief Regulatory Officer and Senior Vice President
101 Main Street, Suite 1850
Cambridge, MA 02142

Dear Ms. Carter:

Please refer to your New Drug Application (NDA) dated February 28, 2012, received February 29, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Juxtapid (lomitapide) capsules 5 mg, 10 mg, and 20 mg.

We acknowledge receipt of your amendments dated March 1, April 16 and 19, May 3, 4, 18 (2), 22, 23, and 30, June 15, 18, 21, and 27, July 2, 13, 18, 23, 27, and 30, August 1, 8, 17, 28, and 31, September 7, 14, 21, 27, and 28 (2), November 20 (2), and December 4, 5, and 17, 2012. We also acknowledge receipt of your email dated December 21, 2012, that included the agreed-upon labeling and Risk Evaluation and Mitigation Strategy (REMS).

This new drug application provides for the use of Juxtapid (lomitapide) Capsules as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

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.

Sufficient stability data has been submitted to support a (b) (4) expiration date.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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, Medication Guide). 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.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate-container labels 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 203858.**” Approval of this submission by FDA is not required before the labeling is used.

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

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 indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication 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 assess a known serious risk of hepatic transaminase elevations and hepatic steatosis, or to assess signals of a serious risk of small bowel and hepatic malignancies and teratogenicity, or to identify an unexpected serious

risk of adverse effects on growth and neurological development in children treated with Juxtapid (lomitapide), or to identify an unexpected serious risk of cardiovascular adverse events.

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 this serious risk.

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

- 1974-1:** A juvenile animal toxicology study to evaluate the effects of lomitapide on neurological development (learning, memory, behavior, and coordination), growth, and long bone development with and without vitamin and essential fatty acid supplementation to determine whether any observed effects are due directly to lomitapide or secondarily to the inhibition of absorption of fat soluble vitamins and/or essential fatty acids. This study should be completed before any formal pediatric studies are initiated.

The timetable you submitted on December 6, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: July 15, 2013
Study Completion: December 30, 2013
Final Report Submission: June 15, 2014

- 1974-2:** An assessment and analysis of spontaneous reports of malignancy, teratogenicity, and hepatic abnormalities in patients treated with Juxtapid (lomitapide) for a period of 10 years from the date of approval. Specialized follow-up should be obtained on these cases to collect additional information on the reports.

The timetable you submitted on November 20, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: November 30, 2013
Interim Report Submissions: December 31, 2014
December 31, 2015
December 31, 2016
December 31, 2017
December 31, 2018
December 31, 2019
December 31, 2020
December 31, 2021
December 31, 2022
Study Completion: December 31, 2023
Final Report Submission: June 1, 2024

1974-3: A long-term prospective observational study (product exposure registry) of patients with homozygous familial hypercholesterolemia (HoFH) treated with Juxtapid (lomitapide) to evaluate known and potential serious risks related to the use of Juxtapid (lomitapide), including hepatic transaminase elevations, hepatic steatosis, small bowel and hepatic malignancies, teratogenicity, death (including cause of death), and major adverse cardiovascular events (including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, and revascularization procedures). The registry will continue for 10 years from the date of last patient enrollment.

The timetable you submitted on December 2, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	November 30, 2013
Interim Report Submission:	January 31, 2015
	January 31, 2016
	January 31, 2017
	January 31, 2018
	January 31, 2019
	January 31, 2020
	January 31, 2021
	January 31, 2022
	January 31, 2023
	January 31, 2024
	January 31, 2025
	January 31, 2026
	January 31, 2027
	January 31, 2028
Study Completion:	March 1, 2028
Final Report Submission:	September 1, 2028

Submit the protocols to your IND 50820, with a cross-reference letter to this NDA. Submit all final reports 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Juxtapid (lomitapide) to ensure the benefits of the drug outweigh the potential risk of hepatotoxicity.

Pursuant to 505-1(f)(1), we have also determined that Juxtapid (lomitapide) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risk of elevated liver transaminases and hepatic steatosis, a risk factor for advanced liver disease including steatohepatitis and cirrhosis, that are listed in the labeling. The elements to assure safe use will educate prescribers about the risk of hepatotoxicity associated with the use of Juxtapid (lomitapide), the need to monitor patients during treatment with Juxtapid (lomitapide) as per product labeling, and to restrict access to therapy with Juxtapid (lomitapide) to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia (HoFH).

We remind you that section 505-1(f)(8) of the FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on December 21, 2012, and appended to this letter, is approved. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Juxtapid (lomitapide) into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. A survey study to evaluate healthcare providers' knowledge of the risk of hepatotoxicity associated with the use of Juxtapid (lomitapide), the need to monitor liver-related laboratory tests before and during treatment with Juxtapid (lomitapide) as described in product labeling, and prescribers' knowledge that FDA's determination of the safety and efficacy of Juxtapid (lomitapide) is limited to patients diagnosed with homozygous familial hypercholesterolemia.

- a. The target level of healthcare provider knowledge for each educational goal of the REMS.
 - b. If the target levels for healthcare provider knowledge are not met, provide possible causes for the deficiencies and proposed measures to improve knowledge.
1. An assessment of enrollment in the Juxtapid REMS Program, including the following:
 - a. Number of healthcare providers certified during the reporting period and cumulatively.
 - i. Prescriber information, including degree, specialty, and practice setting (i.e., type of practice, geographic location)
 - ii. Volume of prescriptions for each prescriber and each specialty
 - b. Number of pharmacies certified during the reporting period and cumulatively.
 - c. Number of healthcare providers and pharmacies that had their certification revoked during the reporting period and cumulatively and the reason for the revocation.
 2. Metrics regarding Juxtapid (lomitapide) distribution and dispensing to assess pharmacy compliance with the Juxtapid REMS:
 - a. The number of Juxtapid (lomitapide) orders shipped to pharmacies during the reporting period and cumulatively, including number of bottles, bottle size, and dosage strength.
 - b. Pharmacy compliance with Juxtapid REMS Program requirements (e.g., shipped to a Juxtapid REMS certified pharmacy versus a non-certified pharmacy).
 - c. The number of prescriptions dispensed for Juxtapid (lomitapide), including quantity of tablets (mean, minimum, maximum) and dosage strength during the reporting period and cumulatively, overall and subset by compliance with the Juxtapid REMS Program requirements (e.g., received from Juxtapid REMS certified versus non-certified healthcare providers, number of initial prescriptions dispensed without a signed attestation on the Juxtapid Prescription Authorization Form). Dispensing details are to be obtained from the pharmacies.
 - d. The number and demographics (e.g., gender, age, geographic location) of patients who received Juxtapid (lomitapide) during the reporting period and annually. The number is to be calculated by reconciling orders dispensed to unique patients.
 - e. Duration of therapy for patients (mean, median, range).

- f. Report of number, length, and reasons for shipment delays to patients.
 - g. Detailed description of root cause of noncompliance with Juxtapid REMS Program-required dispensing and any corrective and/or preventive actions taken to address noncompliance during the reporting period and cumulatively.
3. Summary of issues and complaints received by Juxtapid REMS call center; summary of resolution of the issues and complaints.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 203858 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 203858 REMS ASSESSMENT
NEW SUPPLEMENT FOR NDA 203858

**PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 203858
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (*if included*)**

If you do not submit electronically, please send five copies of REMS-related submissions.

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. For instruction on completing the Form FDA 2253, see page 2 of the Form. 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-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action 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.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, M.D.
Acting Deputy Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling
Medication Guide
Carton and Container Labeling
 5 mg-28 capsules
 10 mg-28 capsules
 20 mg-28 capsules
REMS
 Prescriber Training Module
 Prescriber Enrollment Form
 Dear Healthcare Provider letter
 Dear Professional Society letter
 Prescription Authorization Form
 Web site screen shot

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

/s/

CHRISTINE P NGUYEN
12/21/2012