DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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) month 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.

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