DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203858/S-013, S-016

**SUPPLEMENT APPROVAL**
**REMS ASSESSMENT PLAN REVISION**

Aegerion Pharmaceuticals
Attention: Sheryl Raukete
Global Regulatory Lead, Regulatory Affairs
One Main Street, 8th Floor
Cambridge, MA 02142

Dear Ms. Raukete:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received October 5, 2015 (S-013) and July 7, 2016 (S-016), and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Juxtapid (lomitapide) capsules, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg.

Supplement -013, submitted as a Prior Approval supplemental new drug application, proposes modifications of the REMS to expand the number of certified pharmacies.

Supplement -016, submitted as a Prior Approval supplemental new drug application, was submitted in response to and proposes modifications described in our Safety Labeling Change Notification/REMS Modification Notification letter dated March 11, 2016. The labeling changes to comply with this notification were approved in supplement-015 on May 23, 2016.

We also refer to our REMS Assessment Acknowledgement letter dated June 17, 2016.

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Juxtapid (lomitapide) was originally approved on December 21, 2012, and the most recent modification was approved on August 13, 2013. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. In order to ensure that the benefits of Juxtapid (lomitapide) outweigh its risks, we determined that you were required to modify the REMS for Juxtpaid. The required modifications were outlined in our Safety Labeling Change Notification/REMS Modification Notification letter issued on March 11, 2016, and included modifications to the REMS document, changes to the existing REMS materials, and the following new REMS materials: Patient Guide and Patient-Prescriber Acknowledgement Form.

Your proposed modified REMS, submitted on October 5, 2015 (S-013), and July 7, 2016 (S-016), as amended and appended to this letter, is approved.

You must implement the modifications to the REMS program within 60 calendar days from the date of this letter. Prescribers and pharmacies have 180 calendar days from the date of this letter to complete the recertification process.

The timetable for submission of assessments of the REMS remains the same as that approved on December 21, 2012.

In order to align with the modified REMS, the REMS assessment plan is being revised. The revised REMS assessment plan must include, but is not limited to, the following:

1. **Knowledge, Attitudes, and Behavior (KAB) Surveys of Prescribers**

   A KAB Survey will be conducted with a random sample of certified prescribers to assess their awareness and understanding of the indication for use, the risk of hepatotoxicity, including appropriate evaluation, monitoring and counseling to minimize this risk, as described in the Prescribing Information (PI), Fact Sheet, and the Prescriber Training Module. The survey will also assess prescribers' awareness of the JUXTAPID REMS Program materials and knowledge of requirements of the JUXTAPID REMS Program. In the event of substantive changes to the methodology and protocol for the KAB Survey, or the survey instrument, these documents will be provided to the FDA at least 90 days before the survey is administered.

   The protocol will include:

   a. the target sample size and precision estimates associated with that sample size

   b. a description of the methodology for recruitment and selection of the prescriber sample

   c. the specific criteria that will be used to select participants in the survey

   d. a description of how and when the surveys will be administered

   e. an explanation of the design features and controls that will be included to minimize bias and compensate for limitations in the methodology

   f. a copy of the survey questionnaire

   The KAB assessment will be included in your next assessment report and will be repeated annually thereafter. Survey results will be provided in each annual REMS Assessment Report.

2. **Survey to Evaluate Patient Knowledge**

   A survey to evaluate the understanding of patients on their understanding of the REMS goal about the risk of hepatotoxicity and the need for baseline and periodic monitoring will be performed and the data included in the second assessment report following the approval of the modification to the JUXTAPID REMS Program, due to be submitted on or before 12/21/2018. The protocol or survey instrument will be provided to the FDA at least 90 days before the survey is implemented.

3. **Additional REMS Metrics**

   The REMS Assessment will also include evaluation of the following program metrics:

   a. Communications with certified prescribers and certified pharmacies:

      i. The date of mailing and number of recipients of the *REMS Letter for Healthcare Providers* and *REMS Letter for Pharmacists*
      ii. The number of mailings returned; and
      iii. A copy of all documents included in each mailing.
      iv. Summary of issues and complaints received by JUXTAPID REMS Program Call Center; summary of resolution of the issues and complaints.
      v. Summary of the reasons (and numbers per reason) for calls into the JUXTAPID REMS Program Call Center.

   b. Prescriber Certification:

      i. The number of Healthcare Prescribers certified (and the number of prescribers that were certified at the time of a requirement for re-certification was instituted) in the JUXTAPID REMS Program (during the reporting period and cumulatively) and stratified by prescriber degree, practice setting (i.e., type of practice and geographic location) including a full breakdown of prescribing specialties contained in the "other" category.
      ii. Volume of prescriptions for each prescriber and each specialty, including a full breakdown of prescribing specialties contained in the "other" category.
      iii. Specialties of the "high volume" prescribers, i.e., those who write more than 4 prescriptions in an assessment period and cumulatively, including a full breakdown of prescribing specialties contained in the "other" category.
      iv. A summary of the method prescribers used to enroll (fax, email) (during the reporting period and cumulatively).
      v. Number of healthcare providers that had their certification revoked during the reporting period and cumulatively and the reason for the revocation.

c. Wholesaler/Distributor Authorization:

i. The number of wholesalers/distributors that were authorized in the REMS program (during the reporting period and cumulatively).
ii. Number of wholesalers/distributors that had their authorization revoked during the reporting period and cumulatively and the reason for the revocation.
iii. The number of JUXTAPID orders shipped to pharmacies during the reporting period and cumulatively, including number of bottles, bottle size and dosage strength.
iv. Number of JUXTAPID orders shipped to non-certified pharmacies.

d. Pharmacy Enrollment:

i. The number of pharmacies that were certified (and the number of pharmacies that were certified at the time of a requirement for re-certification was instituted that recertified) in the REMS program (during the reporting period and cumulatively).
ii. Number of pharmacies that had their certification revoked during the reporting period and cumulatively and the reason for the revocation.

e. Pharmacy Metrics:

i. The number of new prescriptions received, and the number that were not accompanied by the JUXTAPID REMS Program Prescription Authorization Form.
ii. The number of prescriptions dispensed for JUXTAPID, including quantity of capsules (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 certified vs. non-certified healthcare providers, number of initial prescriptions dispensed without a signed attestation on the JUXTAPID REMS Program Prescription Authorization Form). Dispensing details are to be obtained from the pharmacies.
iii. The number of instances certified pharmacies dispensed JUXTAPID using a prescription that was not accompanied by a JUXTAPID REMS Program Patient-Prescriber Acknowledgement Form.
iv. Information on the number of prescribers who have submitted an altered JUXTAPID REMS Program Prescription Authorization Form (and what alterations were made).
v. Number of instances certified pharmacies dispensed JUXTAPID in response to a prescription received on an altered JUXTAPID REMS Program Prescription Authorization Form.
vi. The number and demographics (e.g., including gender, age, geographic location) of unique patients who received JUXTAPID during the reporting

period and annually. The number is to be calculated by reconciling orders dispensed to unique patients.

vii. Duration of therapy for patients (mean, median, range).
viii. The number of prescriptions pending and canceled, as well as the reason for prescriptions pending and canceled.
ix. Specific criterion used to classify a prescription as canceled.
x. Report of number, length, and reasons for shipment delays to patients and whether or not these reasons were related to the REMS, and any additional information from insurance payers as to what they are stating as the reason for delay/non-payment.
xi. Percentage of fill delays that involve new prescriptions versus refills.
xii. Detailed description of root cause of noncompliance with REMS program-required dispensing and any corrective and/or preventive actions taken to address noncompliance during the reporting period and cumulatively.

f. With regard to the risk of hepatotoxicity associated with JUXTAPID, provide an analysis of the post-marketing cases of specific hepatic adverse events reported in association with JUXTAPID to Aegerion (during the reporting period and cumulatively), including outcome.

g. Specification of measures that would be taken to increase awareness if prescriber surveys indicate that prescriber awareness of the risks associated to JUXTAPID is not adequate.

4. 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 REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

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