



BLA 125390/S-014

SUPPLEMENT APPROVAL

Aegerion Pharmaceuticals, Inc.
Attention: Cathy L. Walker
Associate Director Regulatory Affairs
One Main Street, Suite 800
Cambridge, MA 02142

Dear Ms. Walker:

Please refer to your Supplemental Biologics License Application (sBLA), dated June 26, 2018, received June 26, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for Myalept (metreleptin) for injection.

This Prior Approval supplemental biologics application provides for proposed modifications to the approved Myalept risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Myalept was originally approved on February 24, 2014, and the most recent REMS modification was approved on December 11, 2017. The REMS consists of elements to assure safe use, a communication plan, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consists of clarification to the process for supplying Myalept for hospitalized patients. In addition to the above-mentioned REMS modification, the following, changes to the REMS documents/materials have been proposed:

- REMS Introduction Sheet - updated to make the format consistent with the rest of the REMS materials
- Prescriber Training module – removed the requirement to send a copy of the completed consent for NAb testing to Aegerion.

REMS document – updated to the current format which includes describing the wholesalers-distributors' requirements.

Your proposed modified REMS, submitted on June 26, 2018, amended and appended to this letter, is approved. The modified REMS consists of a communication plan, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on February 24, 2014.

The revised REMS assessment plan must include, but is not limited to, the following items:

1. REMS Program Operation and Performance Data (per reporting period and cumulatively)
 - a. Number of unique visits to the MYALEPT REMS website.
 - b. The number of REMS Letters for Healthcare Providers (Infections) sent via standard mail, the date(s) the letters were sent, and the number of letters returned from healthcare providers as undeliverable. Include the number of letters sent via email because the mailed letter was undeliverable. For letters sent via email, include the number of letters successfully delivered, and number of email letters opened by the recipients.
 - i. Number of REMS letter distributed by field-based sales and medical representatives upon request during the 12 months after approval of the REMS modification
 - c. REMS Program Call Center Report
 - i. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, wholesaler/distributors, other)
 - ii. Summary of frequently asked questions (FAQ) by stakeholder type
 - iii. Summary program problems reported and corrective actions resulting from issues identified
2. REMS Utilization Data (per reporting period and cumulatively)
 - a. Prescriber Utilization
 - i. Number and specialties of certified prescribers, type of practice setting, and method of enrollment
 - ii. Volume of prescriptions stratified by prescriber and specialty
 - iii. Summary and analysis of neutralizing antibody testing requested by prescribers

The summary and analysis should be consistent with the scope of the data available and should include but is not limited to:

- a. the unique number of patients tested;
- b. the total number of tests performed (and stratified by patient);
- c. the number of prescribers submitting samples;
- d. reason for testing;
- e. the results of the testing; and if available:
 - background patient information (e.g., demographic, disease state, metreleptin treatment information (duration of treatment))
 - any follow-up information (if not being followed through the immunogenicity program)

If any tests are ordered and subsequently cancelled, the reasons for cancellation and whether the patient was continued on MYALEPT.

b. Pharmacy Utilization

- i. Number of certified pharmacies
- ii. Total number of prescriptions dispensed by each certified pharmacy
- iii. Total number of shipments provided to in-patient pharmacies for dispensing

c. Patient Utilization

- i. Number of patients who have received at least one prescription for MYALEPT
- ii. Number of patients with a completed *Prescription Authorization Form* who have not received a dispensed prescription for MYALEPT
- iii. Time between receipt of *Prescription Authorization Form* and prescription dispensing (mean, median, range) and an analysis summarizing any reasons for delays that are related to the MYALEPT REMS Program requirements. Include how many shipment delays resulted in late dispensing. Explain if any of the shipment delays or late dispensing resulted in any treatment interruption and if any adverse events occurred due to the shipment delays or late dispenses.
- iv. For i. and ii, provide demographics of patients including age and gender
- v. Duration of MYALEPT therapy for patients (mean, median, range)
- vi. Number of patients who discontinued treatment and duration of treatment (mean, median, range)

3. REMS Compliance (per reporting period and cumulatively)
 - a. Number of prescriptions written by non-certified prescribers
 - b. Number of prescriptions dispensed by non-certified pharmacies, excluding authorized prescriptions dispensed by hospital pharmacies.
 - c. Number of prescriptions dispensed to patients without a completed *Prescription Authorization Form*.
 - d. Number of prescribers inactivated for noncompliance with the MYALEPT REMS Program requirements. Include summary of reasons for inactivation.
 - e. Number of pharmacies inactivated for noncompliance with the MYALEPT REMS Program requirements. Include summary of reasons for inactivation.
 - f. A summary report of serious or critical deviations found, and corrective actions taken for any certified pharmacy audits conducted during the reporting period.
 - g. A summary report of serious or critical deviations found, and corrective actions taken for any distributor audits conducted during the reporting period.

4. Assessment of prescribers understanding of the following:

Aegerion will conduct healthcare provider surveys at four years, five years, and six years after initial approval of the REMS. Thereafter, conduct prescriber surveys every two years. The surveys will evaluate understanding of the following:

- a. The risks of metreleptin
 - i. Serious adverse events resulting from the development anti-drug antibodies with neutralizing activity
 - ii. Lymphoma
- b. The appropriate use of metreleptin
- c. The metreleptin REMS program requirements

5. 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 1 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 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.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

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:

BLA 125390 REMS ASSESSMENT METHODOLOGY

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

BLA 125390 REMS ASSESSMENT

or

**NEW SUPPLEMENT FOR BLA 125390/ S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR BLA 125390/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR BLA 125390/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125390/ S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR BLA 125390

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Martin White, M.S., Regulatory Project Manager, at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

William Chong, M.D.
Deputy Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM H CHONG
12/21/2018