

BLA 125390/S-029

## SUPPLEMENT APPROVAL

Chiesi Farmaceutici S.p.A  
C/O Chiesi USA, Inc.  
Attention: Karla Werre, MBA, RAC  
Director Regulatory/Head, REMS Programs  
175 Regency Woods Place  
Suite 600  
Cary, NC 27518

Dear Karla Werre:

Please refer to your supplemental biologics license application (sBLA) received March 21, 2025, and your amendments, submitted under section 351(a) of the Public Health Service Act for Myalept (metreleptin) for injection.

This Prior Approval sBLA provides for modifications to the approved Myalept risk evaluation and mitigation strategy (REMS). This supplement is in response to our November 5, 2024, REMS Assessment Acknowledgement letter.

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 March 31, 2023. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modification to the REMS consists of:

- The REMS Assessment Timetable changing from annually to every other year to match survey reporting.
- Updates to the REMS document in accordance with the REMS Document Technical Conformance Guide to add the risks to “Section I. Administrative Information” and to add “Section VI. Statutory Elements.”
- Revisions to the audit requirements for certified pharmacies and wholesalers-distributors in the compliance section of the REMS document.

Your proposed modified REMS, submitted on March 21, 2025, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS must be revised to February 24, 2026, and every 2 years thereafter.

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

For each metric, provide the previous, current, and cumulative reporting periods (if applicable), unless otherwise noted.

## **PROGRAM IMPLEMENTATION AND OPERATIONS**

### 1. REMS Operation and Performance Data (per reporting period and cumulatively)

- a. Number of unique visits to the Myalept REMS website.
- b. REMS Coordinating Center Report
  - i. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, wholesalers/distributors, other)
  - ii. Summary of frequently asked questions (FAQ) by stakeholder type
  - iii. Summary of 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. Number of active prescribers (i.e., prescribed Myalept at least once during the reporting period)
- 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. Provide demographics of patients including age and gender
- iii. Duration of Myalept therapy for patients (mean, median, range)
- iv. Number of patients who discontinued treatment and duration of treatment (mean, median, range)

d. Wholesalers/Distributors

- i. Number of wholesalers/distributors that were newly authorized to distribute.
- ii. Number of wholesalers/distributors that are active (i.e., distributed Myalept at least once during the reporting period).

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.
- c. Number of prescriptions dispensed to patients without a completed Prescription Authorization Form.
- d. Number of prescribers inactivated for noncompliance with the Myalept REMS requirements. Include summary of reasons for inactivation.
- e. Number of patients who received Myalept for an off-label indication. Include actions taken to address the issue, including any subsequent prescriber decertifications.
- f. Summary of outcomes of verifications of disease state interventions at the time of prescribing
  - i. Indicate the number and percentage of new Myalept prescriptions that underwent the strict reason for use verification process prior to dispensing.
  - ii. Indicate how many, if any, strict reason for use verification process attempts failed or were bypassed (e.g., the prescriber could not be

contacted) prior to dispensing a Myalept prescription. Provide an analysis of reasons for failure/bypass.

- g. Number of pharmacies inactivated for noncompliance with the Myalept REMS requirements. Include summary of reasons for inactivation.
- h. A summary report of serious or critical deviations found, and corrective actions taken for any certified pharmacy audits conducted during the reporting period.
- i. A summary report of serious or critical deviations found, and corrective actions taken for any wholesaler-distributor audits conducted during the reporting period.

## **SAFE USE BEHAVIORS**

### **4. Prescription Authorization Form**

- a. Number of patients with a completed *Prescription Authorization Form* who have not received a dispensed prescription for Myalept.
- b. 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 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.

## **KNOWLEDGE**

### **5. Assessment of Prescribers' understanding of the following:**

The Applicant will conduct healthcare provider surveys at 4 years, 5 years, and 6 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 of anti-drug antibodies with neutralizing activity
  - ii. Lymphoma
- b. The appropriate use of metreleptin

- c. The metreleptin REMS requirements

## **HEALTH OUTCOMES AND/OR SURROGATES OF HEALTH OUTCOMES**

### **6. 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:
  - i. background patient information (e.g., demographic, disease state, metreleptin treatment information (duration of treatment))
  - ii. 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

### **7. An analysis of US adverse events in the post-marketing setting, including Myalept use outside of the indication of generalized lipodystrophy.**

- a. Provide a root cause analysis for each case where Myalept was being used outside of the labeled indication.
- b. For each of the patients, provide the following:
  - i. Age of patient
  - ii. Sex of the patient
  - iii. Reason for Myalept use
  - iv. Date of Myalept initiation, if known
  - v. Original source of Myalept (commercial supply versus clinical trial supply)

- vi. Data source utilized to identify patient (e.g., global safety database, name of specific registry or study, other databases—specify)
  - a. If data source is adverse event report, include causality assessment of adverse events reported
- c. For any patients experiencing adverse events and antibody testing was not performed, include the following details:
  - i. Whether or not antibody testing criteria for that adverse event was met (e.g., patient experiencing severe infection). Specify the criteria for each case.
  - ii. An analysis of why antibody testing was not performed if the patient met the testing criteria.

## **OVERALL ASSESSMENT OF REMS EFFECTIVENESS**

8. 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 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**

(insert concise description of content in bold capital letters, e.g.,

**ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

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 LABELING  
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**

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

**U.S. Food and Drug Administration**  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For more information on submitting REMS in SPL format, please email [FDAREMSwebsite@fda.hhs.gov](mailto: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, contact Kalyann Kauv, Regulatory Project Manager, at 301-837-7357 or [kalyann.kauv@fda.hhs.gov](mailto:kalyann.kauv@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Monika Houstoun, Pharm.D., M.P.H.  
Deputy Director for Safety  
Division of Diabetes, Lipid Disorders, and Obesity  
Office of Cardiology, Hematology, Endocrinology,  
and Nephrology  
Office of New Drugs  
Center for Drug Evaluation and Research

ENCLOSURE:

- REMS

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**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.**  
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/s/  
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