NDA 203858/S-023

SUPPLEMENT APPROVAL

Amryt Pharmaceuticals, Inc.
US Agent for Amryt Pharmaceutical DAC
Attention: Karla Werre
REMS Manager
160 Federal Street, 21st floor
Boston, MA 02110

Dear Ms. Werre:

Please refer to your supplemental new drug application (sNDA) dated and received August 5, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Juxtapid (lomitapide) capsules.

This Prior Approval sNDA provides for proposed modifications to the approved Juxtapid (lomitapide) 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 Juxtapid (lomitapide) was originally approved on December 21, 2012, and the most recent REMS modification was approved on May 27, 2021. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of:

1. Updating the format of the REMS document in line with the recommendations in the *Format and Content of a REMS Document- Guidance for Industry*[1]

2. Changes to program materials secondary to findings of the completed Qualitative Research (QR) around the deficit of prescriber knowledge on program requirements around liver monitoring as demonstrated in recent poor KAB survey scores

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

3. Omitting obsolete materials (2017 Stakeholder letters) and

4. Editorial changes such as added demographic fields to Patient Guide, Patient Prescriber Acknowledgement Form (PPAF) and Prescription Authorization Form (PAF) and other editorial revisions related to punctuation, grammar, spelling, defining acronyms, flow, font, simplification, and consistency to REMS appended materials.

Your proposed modified REMS, submitted on August 5, 2021, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS must be revised. Submit REMS assessments every two years beginning with the 11-year REMS assessment due December 21, 2023.

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

Program Implementation and Operations (per reporting period and cumulatively)

1. REMS Enrollment Statistics
    a. Healthcare Provider Certification
        i. The number of newly certified healthcare providers and the number of active healthcare providers (prescribed at least once during the reporting period) in the Juxtapid REMS Program stratified by healthcare provider credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant) and specialty (cardiology, endocrinology, internal medicine, other (and include a full breakdown of prescribing specialties contained in the "other" category)), and practice type (e.g., individual practice, group practice, hospital, university (academic) center), and geographic region (as defined by US Census).
        ii. Method of certification (i.e. through fax, or email).
    b. Pharmacy Enrollment
        i. The number of pharmacies that were newly certified and the number of pharmacies that were active (dispensed Juxtapid at least once during the reporting period) in the REMS program, stratified by geographic region (as defined by US Census)
        ii. Method of certification (e.g., through fax, or email).
    c. Wholesaler/Distributor Authorization
        i. The number of wholesalers/distributors that were newly authorized in the REMS program and the number that were active (shipped Juxtapid at least once during the reporting period).

2. REMS Compliance

   a. Provide a summary of non-compliance identified, including but not limited to:

      i. Provide a copy of the non-compliance plan used during that reporting period, including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each case, and which events lead to de-certification from the REMS

      ii. 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.

      iii. Provide a copy of the audit plan for each stakeholder (i.e. certified pharmacies, wholesalers/distributors, or other entities) including any auditing surveys or protocols used

      iv. Report of audit findings for each stakeholder

         1. The number of audits expected, and the number of audits conducted

         2. The number and types of deficiencies noted for each group of audited stakeholders

         3. For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) within one month of audit

         4. Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time

   b. Healthcare Provider

      i. Number of healthcare providers who that had their certification revoked during the reporting period and cumulatively and the reason for the revocation

      ii. Information on the number of prescribers who have submitted an altered Juxtapid REMS Program Prescription Authorization Form (and what alterations were made).

   c. Pharmacies

      i. Number of pharmacies that had their certification revoked during the reporting period and cumulatively and the reason for the revocation.

      ii. The number of instances certified pharmacies dispensed Juxtapid using a prescription that was not accompanied by a Juxtapid REMS

Program Patient-Prescriber Acknowledgement Form.

iii. Number of instances certified pharmacies dispensed Juxtapid in response to a prescription received on an altered Juxtapid REMS Program Prescription Authorization Form.

iv. The number of new prescriptions received, and the number that were not accompanied by the Juxtapid REMS Program Prescription Authorization Form.

d. Wholesalers/Distributors

i. Number of wholesalers/distributors that had their authorization revoked during the reporting period and cumulatively and the reason for the revocation.

ii. Number of Juxtapid orders shipped to non-certified pharmacies.

3. REMS Call Center

a. Summary of issues and complaints received by Juxtapid REMS Program Call Center; summary of resolution of the issues and complaints.

b. Summary of the reasons (and numbers per reason) for calls into the Juxtapid REMS Program Call Center.

4. Juxtapid Utilization Data

a. The number of prescriptions dispensed for Juxtapid, including quantity of capsules (mean, minimum, maximum) and dosage strength, 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.

b. Volume of prescriptions for each prescriber stratified by specialty, including a full breakdown of prescribing specialties contained in the “other” category.

c. Specialties of the “high volume” prescribers, i.e., those who write more than four prescriptions in an assessment period and cumulatively, including a full breakdown of prescribing specialties contained in the “other” category.

d. The number of Juxtapid orders shipped to pharmacies during the reporting period and cumulatively, including number of bottles, bottle size and dosage strength.

e. 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.

f. Duration of therapy for patients (mean, median, range).

g. The number of prescriptions pending and canceled, as well as the reason for prescriptions pending and canceled.

h. Specific criterion used to classify a prescription as canceled.

i. 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.

j. Percentage of fill delays that involve new prescriptions versus refills.

Knowledge (per reporting period and cumulatively)

5. Knowledge, Attitudes, and Behavior (KAB) Surveys of Prescribers to assess understanding of:
    a. The approved indication of Juxtapid
    b. The risk of hepatoxicity associated with Juxtapid use
    c. The need to monitor patients during treatment with Juxtapid as per product labeling
6. Survey to Evaluate Patient Knowledge of:
    a. the risk of hepatoxicity
    b. the need for baseline and periodic monitoring
7. Specification of measures that would be taken to increase awareness if surveys indicate that awareness of the risks associated to Juxtapid is not adequate.

Safe Use Conditions (per reporting period and cumulatively)

8. Prescription Authorization Form (PAF)
    a. Number of patients with completed PAFs who have not received a dispensed prescription for Juxtapid.
    b. Time between receipt of PAF and prescription dispensing and analysis and summary of reasons for delays
    c. Proportion of prescriptions that were associated with the updated PAF from the February 2022 REMS modification.
9. Patient-Prescriber Acknowledgement Form (PPAF)
    a. Proportion of dispensed prescriptions associated with an updated PPAF from

the February 2022 REMS modification.

Health Outcomes and/or Surrogates of Health Outcomes (per reporting period and cumulatively)

10. 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, including outcome.

11. 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:

NDA 203858 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

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.

We remind you that section 505-1(f)(8) of 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.

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:

NDA 203858 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 203858/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 203858/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 203858/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 NDA 203858/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 NDA 203858

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 NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ron Picking, Regulatory Project Manager, at 240-402-3211.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:

Juxtapid REMS Document
Juxtapid REMS Materials:

- Prescriber Enrollment Form
- Patient Guide
- Patient-Prescriber Acknowledgement Form
- Prescription Authorization Form
- Pharmacy Enrollment Form
- Prescriber Training Module and Knowledge Assessment
- Pharmacy Training Module and Knowledge Assessment
- Fact Sheet
- Website

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/

MONIKA A HOUSTOUN
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