CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203858Orig1s023

Trade Name:	JUXTAPID
Generic or Proper Name:	lomitapide mesylate
Sponsor:	Amryt Pharmaceuticals, Inc
Approval Date:	February 1, 2022
Indication:	JUXTAPID is a microsomal triglyceride transfer protein inhibitor indicated 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-highdensity lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

CENTER FOR DRUG EVALUATION AND RESEARCH

203858Orig1s023

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

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
02/01/2022 10:25:47 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203858Orig1s023

REMS DOCUMENTS

Risk Evaluation and Mitigation Strategy (REMS) Document
JUXTAPID (lomitapide) REMS Program

I. Administrative Information

Application Number:	NDA 203858
Application Holder:	Amryt Pharmaceuticals DAC
Initial REMS Approval:	12/2012
Most Recent REMS Update:	02/2022

II. REMS Goal

The goal of the JUXTAPID REMS is to mitigate the risk of hepatotoxicity associated with the use of JUXTAPID by ensuring that:

- Prescribers are educated about the approved indication for JUXTAPID, the risk of hepatotoxicity associated with the use of JUXTAPID; and the need to monitor patients during treatment with JUXTAPID as per product labeling.
- JUXTAPID is dispensed only to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia (HoFH).
- Patients are informed about the risk of hepatotoxicity associated with the use of JUXTAPID and the need for baseline and periodic monitoring.

III. REMS Requirements

Amryt Pharmaceuticals DAC must ensure that healthcare providers, patients, pharmacies, and wholesalers-distributors comply with the following requirements:

1. Healthcare Providers who prescribe JUXTAPID must:

To become certified to prescribe	1. Review the drug's Prescribing Information. 2. Review the following: Fact Sheet, Prescriber Training Module. 3. Successfully complete the Knowledge Assessment and submit it to the REMS Program. 4. Enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS Program.
Before treatment initiation (first dose)	5. Counsel the patient about the appropriate use, risks associated with JUXTAPID, and need for periodic liver function monitoring using the Patient Guide. Provide a copy of the material to the patient. 6. Assess the patient to confirm a clinical or laboratory diagnosis consistent with the approved indication. 7. Assess the patient's liver function. 8. Enroll the patient by completing and submitting the Patient-Prescriber Acknowledgement Form to the REMS Program.

1. Healthcare Providers who prescribe JUXTAPID must:	
	9. Order the prescription using the Prescription Authorization Form.
During treatment, at least monthly for the first year and every 3 months thereafter	10. Assess the patient's liver function.
During treatment, before dose increases	11. Assess the patient's liver function.
During treatment; before each prescription	12. Order the prescription using the Prescription Authorization Form.
2. Patients who are prescribed JUXTAPID:	
Before treatment initiation	1. Receive counseling from the prescriber on the appropriate use, risks of JUXTAPID, and need for periodic liver function monitoring using the Patient Guide. 2. Enroll in the REMS Program by completing the Patient-Prescriber Acknowledgement Form with the prescriber. Enrollment information will be provided to the REMS Program. 3. Get blood tests to check your liver.
During treatment	4. Get blood tests as directed by your prescriber to check your liver so your prescriber can modify your JUXTAPID treatment, if needed.
At all times	5. Inform the prescriber of signs and/or symptoms of liver injury.
3. Pharmacies that dispense JUXTAPID must:	
To become certified to dispense	1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy. 2. Have the authorized representative review the Prescribing Information, Fact Sheet and Pharmacy Training Module. 3. Have the authorized representative successfully complete the Knowledge Assessment and submit it to the REMS Program. 4. Have the authorized representative enroll in the REMS Program by completing the Pharmacy Enrollment Form and submitting it to the REMS Program.

3. Pharmacies that dispense JUXTAPID must:	
	5. Establish processes and procedures to verify the prescriber is certified, the patient is enrolled, and a completed Prescription Authorization Form is received for each prescription. 6. Train all relevant staff involved in dispensing of JUXTAPID on the REMS Program requirements.
Before dispensing	7. Verify that the prescriber is certified, the patient is enrolled, and a completed Prescription Authorization Form for the patient is received for each prescription through the processes and procedures established as a requirement of the REMS Program.
To maintain certification to dispense	8. Have a new authorized representative enroll by completing and submitting the Pharmacy Enrollment Form, if the authorized representative changes.
At all times	9. Not distribute, transfer, loan, or sell JUXTAPID. 10. Maintain records documenting staff's completion of REMS training. 11. Maintain and submit records of prescription data to the REMS Program. 12. Maintain records that all REMS processes and procedures are in place and are being followed. 13. Comply with audits carried out by Amryt Pharmaceuticals DAC or a third-party acting on behalf of Amryt Pharmaceuticals DAC, to ensure that all processes and procedures are in place and are being followed.

4. Wholesalers-distributors that distribute JUXTAPID must:	
To be able to distribute	1. Establish processes and procedures to ensure the drug is distributed only to certified pharmacies. 2. Train all relevant staff involved in distribution on the REMS requirements.
At all times	3. Distribute only to certified pharmacies. 4. Maintain records of all drug distribution. 5. Maintain records that all REMS processes and procedures are in place and are being followed. 6. Comply with audits carried out by Amryt Pharmaceuticals DAC or a third-party acting on behalf of Amryt Pharmaceuticals DAC, to ensure that all processes and procedures are in place and are being followed.

Amryt Pharmaceuticals DAC must provide training to healthcare providers who prescribe JUXTAPID.

The training includes the following educational materials: Fact Sheet, Prescriber Training Module and Knowledge Assessment. The training must be available online or by contacting the REMS Program call center.

Amryt Pharmaceuticals DAC must provide training to pharmacies that dispense JUXTAPID.

The training includes the following educational materials: Fact Sheet, Pharmacy Training Module and Knowledge Assessment. The training must be available online or by contacting the REMS Program call center.

To support REMS Program operations, Amryt Pharmaceuticals DAC must:

1. Establish and maintain a REMS Program website, www.JUXTAPIDREMSProgram.com. The REMS Program website must include the option to print the Prescribing Information, Medication Guide, and REMS materials. All product websites for consumers and health care providers must include prominent REMS-specific links to the REMS Program website. The REMS Program website must not link back to the promotional product website(s).
2. Make the REMS Program website fully operational and all REMS materials available through www.JUXTAPIDREMSProgram.com and the REMS Program call center.
3. Establish and maintain a REMS Program call center for REMS participants at 1-85-JUXTAPID (1-855-898-2743).
4. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the JUXTAPID REMS Program.
5. Ensure prescribers and pharmacies are able to complete the certification process by email and fax.
6. Ensure prescribers are able to enroll patients and submit completed Prescription Authorization Forms to the call center by fax and email.
7. Ensure pharmacies are able to verify the prescriber is certified, the patient is enrolled, and a completed Prescription Authorization Form is received before dispensing each prescription by phone and online.
8. Provide the Prescriber Training Module and Knowledge Assessment, Prescriber Enrollment Form, Fact Sheet, Patient-Prescriber Acknowledgement Form, Prescription Authorization Form, Pharmacy Training Module and Knowledge Assessment, Pharmacy Enrollment Form, Patient Guide, and the Prescribing Information to prescribers or pharmacies who (1) attempt to prescribe/dispense JUXTAPID and are not yet certified or (2) inquire about how to become certified.
9. Notify prescribers and pharmacies within 48 hours after they become certified in the REMS Program.
10. Provide certified pharmacies access to the database of certified prescribers and enrolled patients.
11. Provide authorized wholesalers-distributors access to the database of certified pharmacies.

To ensure REMS participants' compliance with the REMS Program, Amryt Pharmaceuticals DAC must:

1. Verify annually that the authorized representative's name and contact information corresponds to those of the current designated authorized representative for the certified pharmacy. If different, require the pharmacy to re-certify with a new authorized representative.
2. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: Juxtapid distribution and dispensing; certification of prescribers and pharmacies; authorization of wholesalers-distributors, enrollment of patients; and audits of REMS participants. These records must be readily available for FDA inspections.
3. Establish a plan for addressing noncompliance with REMS Program requirements.
4. Monitor wholesalers-distributors, certified prescribers and certified pharmacies on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
5. Audit certified pharmacies no later than 60 days after they become certified, and annually thereafter to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
6. Audit wholesalers-distributors no later than 60 days after they become authorized, and annually thereafter to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
7. Take reasonable steps to improve implementation of and compliance with the requirements of the JUXTAPID REMS Program based on monitoring and evaluation of the JUXTAPID REMS Program.

IV. REMS Assessment Timetable

Amryt Pharmaceuticals DAC must submit REMS Assessments every two years beginning with the 11-year REMS assessment due 12/21/2023. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Amryt Pharmaceuticals DAC must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the JUXTAPID REMS:

Enrollment Forms

Prescriber:

1. Prescriber Enrollment Form

Patient:

2. Patient-Prescriber Acknowledgement Form

Pharmacy:

3. Pharmacy Enrollment Form

Training and Educational Materials

Prescriber:

4. Prescriber Training Module and Knowledge Assessment
5. Fact Sheet

Patient:

6. Patient Guide

Pharmacy:

7. Pharmacy Training Module and Knowledge Assessment
8. Fact Sheet

Patient Care Forms

9. Prescription Authorization Form

Other Materials

10. REMS Program Website (www.juxtapidREMSprogram.com)

Prescriber Enrollment Form

Juxtapid (lomitapide) capsules

REMS Program

THERE ARE 2 PAGES TO THIS FORM | ALL FIELDS ARE REQUIRED | PLEASE PRINT

JUXTAPID is only available through the JUXTAPID Risk Evaluation and Mitigation Strategy (REMS)

All prescribers of JUXTAPID must become certified in the JUXTAPID REMS.
The 3-step process for prescriber certification is outlined below.

1. **REVIEW** the JUXTAPID Prescribing Information and Fact Sheet
2. **COMPLETE** the online Prescriber Training Module and Prescriber Enrollment Form
3. **AGREE** to counsel each patient using the Patient Guide, and to complete a Patient-Prescriber Acknowledgement Form with each patient

PRESCRIBER INFORMATION

First Name: _____ Middle Initial: _____ Last Name: _____

Credentials: ☐ MD ☐ DO ☐ NP ☐ PA ☐ Other (specify): _____

Physician Specialty: ☐ Cardiology ☐ Endocrinology ☐ Internal Medicine ☐ Other (specify): _____

Practice Type (check all that apply): ☐ Individual Practice ☐ Group Practice ☐ Hospital ☐ University (Academic) Center

Practice/Facility Name: _____ Department: _____

Address: _____

City: _____ State: _____ Zip: _____

Phone: _____ Fax: _____

Email: _____ NPI #: _____

OFFICE CONTACT

First Name: _____ Last Name: _____

Phone (if different from above): _____ Fax (if different from above): _____

Email: _____

CONTINUED ON NEXT PAGE

If you have any questions, please contact the JUXTAPID REMS Coordinating Center.
Phone: 1-85-JUXTAPID (1-855-898-2743) | Fax: 1-855-898-2498 | www.juxtapidREMSprogram.com

Reference ID: 4930852

PRESCRIBER ATTESTATION

By signing this form, I attest that:

- JUXTAPID® (lomitapide) capsules are only available through the JUXTAPID REMS and that I must comply with the program requirements in order to prescribe JUXTAPID.
- I have reviewed the **Prescribing Information**, **Fact Sheet** and **Prescriber Training Module**.
- Successfully completed the **Prescriber Knowledge Assessment** and submitted it to the JUXTAPID REMS.

Use:

- I understand that JUXTAPID is only indicated 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).
- I understand that the safety and effectiveness of JUXTAPID has not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).

Hepatotoxicity Risk:

- I understand that there is a risk of hepatotoxicity associated with JUXTAPID.
- I understand the Recommendations for Monitoring of Transaminases with JUXTAPID treatment:

Before treatment initiation (first dose), I must:

- Counsel patients on the approved indication for use in patients with HoFH, the risk of hepatotoxicity with JUXTAPID and the need for regular monitoring using the **Patient Guide**.
- Provide the patient a copy of the **Patient Guide**.
- Enroll the patient by completing and submitting the **Patient-Prescriber Acknowledgement Form** to the JUXTAPID REMS.
- Assess the patient to confirm a clinical or laboratory diagnosis consistent with the approved indication.
- Assess the patient's liver function.
- Order the prescription using the **Prescription Authorization Form**.

Lab Requirements:

- I must assess liver-related tests for this patient as recommended in the JUXTAPID Prescribing Information and in the chart below.

Monitoring of Transaminases

Before Initiating therapy

– Measure ALT, AST, alkaline phosphatase, and total bilirubin

During the first year

– Measure liver-related tests (ALT and AST, at a minimum) **monthly** or prior to each increase in dose, whichever occurs first.

After the first year

– Measure liver-related tests (ALT and AST, at a minimum) at least **every 3 months** and before any increase in dose.

During Treatment:

- I agree to complete and sign the **Prescription Authorization Form** for each prescription.
- I agree that personnel from the JUXTAPID REMS may contact me to gather further information or resolve discrepancies or to provide other information related to JUXTAPID or the JUXTAPID REMS.
- I agree that Amryt, its agents and contractors such as the pharmacy providers may contact me via phone, mail, or email to survey me on the effectiveness of the program requirements for the JUXTAPID REMS.

Prescriber Signature:_____ Date: _____

Prescriber Name:_____ Phone: _____

IMPORTANT

REVIEW TO ENSURE ALL FIELDS ARE COMPLETED | RETURN BOTH PAGES

Fax this form to 1-855-898-2498 or scan and email it to REMS@amrytpharma.com

If you have any questions, please contact the JUXTAPID REMS Coordinating Center.
Phone: 1-85-JUXTAPID (1-855-898-2743) | Fax: 1-855-898-2498 | www.juxtapidREMSprogram.com

What is JUXTAPID?

JUXTAPID is a prescription medicine used along with a low-fat diet and other cholesterol-lowering treatments, including low-density lipoprotein apheresis where available, to lower different forms of cholesterol in people with homozygous familial hypercholesterolemia (HoFH).

Because of the risk of liver problems, JUXTAPID should only be taken by people with HoFH.

It is not known if JUXTAPID is safe and effective in people with high cholesterol who do not have HoFH, including in people who have heterozygous familial hypercholesterolemia (HeFH).

Risk of liver problems with JUXTAPID

JUXTAPID can cause liver problems such as increased liver enzymes or increased fat in the liver.

Your doctor will order blood tests to regularly check your liver:

- before you start JUXTAPID
- if your dose is increased
- monthly during the first year
- every 3 months after the first year

Regular blood test results will tell your doctor if certain liver enzyme levels are higher than normal. Enzyme levels higher than normal can be an early sign of liver problems. If your tests show signs of liver problems, your doctor may reduce your dose or stop JUXTAPID altogether.

There are other side effects associated with the use of JUXTAPID. Talk to your doctor about the other risks associated with JUXTAPID.

What do I need to do?

Before you start treatment with JUXTAPID, tell your doctor if you have had liver problems, including liver problems while taking other medicines.

While you are taking JUXTAPID, tell your doctor right away if you have any of the following symptoms, as these may be signs of liver problems:

- nausea, vomiting, or stomach pain that gets worse, changes, or does not go away
- fever
- yellowing of your eyes or skin
- feeling more tired than usual
- flu-like symptoms

JUXTAPID can cause nausea, vomiting, and stomach pain, especially if you do not eat a low-fat diet. These side effects can also be symptoms of liver problems.

Limit the amount of alcohol you drink (no more than 1 drink per day). One drink can be either a 12-ounce beer, a 5-ounce glass of wine, or 1.5 ounces of liquor.

Keep track of all the medications you are taking, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Make sure to keep your doctor and your pharmacist informed. Some medications, when taken together, can overwork the liver and cause problems.

What is the JUXTAPID Risk Evaluation and Mitigation Strategy (REMS)?

Because of the risk of liver damage with JUXTAPID, the Food and Drug Administration (FDA) has required a special program called a Risk Evaluation and Mitigation Strategy (REMS) for JUXTAPID. The JUXTAPID REMS is designed to educate patients and healthcare providers about the appropriate use of JUXTAPID, the risk of liver damage when taking JUXTAPID, and the need for regular monitoring of your liver.

As part of the REMS, your doctor will discuss the risks of JUXTAPID with you and give you this Patient Guide.

Both you and your prescriber must sign the attached Patient-Prescriber Acknowledgement Form for you to receive JUXTAPID. Your prescriber will provide a copy of the signed form to the JUXTAPID REMS.

The JUXTAPID REMS also requires JUXTAPID to be dispensed by a REMS-certified specialty pharmacy. Your doctor will send your prescription to the certified specialty pharmacy.

Where can I get more information about the JUXTAPID REMS?

If you would like more information, talk to your doctor or visit **www.juxtapidREMSprogram.com**

Notes:

Patient-Prescriber Acknowledgement Form

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REMS Program

Instructions for Prescribers

The form must be signed by both the prescriber and patient. If the patient is under the age of 18 years, the form must be signed by the parent or legal guardian.* Provide a copy of the form to patient.

PATIENT ACKNOWLEDGEMENT

Patient First Name: _____ Middle Initial: ____ Last Name: _____

City: _____ State: _____ Zip: _____

Phone: _____ Email: _____

Date of Birth: _____ Gender: ☐ Male ☐ Female ☐ Decline to Identify

I have received, read, and understand the **Patient Guide** with my prescriber. I understand that:

- JUXTAPID is used along with diet and other lipid-lowering treatments in people with homozygous familial hypercholesterolemia (HoFH) to reduce:
  - **LDL ("bad") cholesterol**
  - **A protein that carries "bad" cholesterol in the blood (apolipoprotein B)**
  - **Total cholesterol**
  - **Non-high-density lipoprotein cholesterol (non-HDL-C)**
- JUXTAPID may cause serious side effects including liver problems such as increased liver enzymes or increased fat in the liver.
- Because of these side effects, JUXTAPID is only for people with homozygous familial hypercholesterolemia (HoFH).
- I will enroll in the JUXTAPID REMS by completing the Patient-Prescriber Acknowledgement Form.
- I will need to have blood tests to check my liver:
  - before I start JUXTAPID
  - if my dose is increased
  - monthly during the first year
  - every three months after the first year
- If my tests show liver problems, my doctor may lower my dose of JUXTAPID or stop it.
- I will tell my doctor if I have any of the following symptoms:
  - nausea, vomiting, or stomach pain that gets worse, changes, or does not go away
  - fever
  - yellowing of my eyes or skin
  - feeling more tired than usual
  - flu-like symptoms

Patient Signature: _____ Date: _____

***Parent or Guardian Signature:** _____ Date: _____

Parent or Guardian Name: _____

PRESCRIBER ACKNOWLEDGEMENT

Prescriber First Name: _____ Middle Initial: ____ Last Name: _____

Address: _____

City: _____ State: _____ Zip: _____

Office Phone: _____ NPI #: _____

- I have counseled the patient (parent/guardian when appropriate) on the indication and risks of JUXTAPID, including the risk of liver problems, and the need for periodic liver monitoring.
- I have reviewed the **Patient Guide** with the patient (and parent/guardian when appropriate) and provided a signed copy of this form to the patient.
- I discussed all concerns and answered all questions the patient had about treatment with JUXTAPID.

Prescriber Signature: _____ Date: _____

IMPORTANT

REVIEW TO ENSURE ALL FIELDS ARE COMPLETED | FAX TO 1-855-898-2498

If you have any questions, please contact the JUXTAPID REMS Coordinating Center.
Phone: 1-85-JUXTAPID (1-855-898-2743) | Fax: 1-855-898-2498 | www.juxtapidREMSprogram.com

Reference ID: 4930852

Prescription Authorization Form

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REMS Program

THERE ARE 2 PAGES TO THIS FORM | ALL FIELDS ARE REQUIRED | PLEASE PRINT

This form must be completed and signed for each JUXTAPID prescription.

PATIENT INFORMATION

First Name: _____ Middle Initial: _____ Last Name: _____

Address: _____ Phone: _____

City: _____ Email: _____

State: _____ Zip: _____ Date of Birth: _____

JUXTAPID PRESCRIPTION

Dose: _____ *mg po q hs* (recommended starting dosage is 5 mg daily). Quantity to dispense: _____ Refills: _____

Additional Instructions: _____

PRESCRIBER INFORMATION

First Name: _____ Middle Initial: _____ Last Name: _____

Practice/Facility Name: _____

Office Contact: _____ Office Phone: _____

Address: _____ Office Fax: _____

City: _____ State License #: _____

State: _____ Zip: _____ NPI #: _____

CONTINUED ON NEXT PAGE

If you have any questions, please contact the JUXTAPID REMS Coordinating Center.
Phone: 1-85-JUXTAPID (1-855-898-2743) | Fax: 1-855-898-2498 | www.juxtapidREMSprogram.com

Reference ID: 4930852

PRESCRIBER ATTESTATION OF REMS REQUIREMENTS

- I understand that JUXTAPID is indicated only 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).
- I affirm that my patient has a clinical or laboratory diagnosis consistent with HoFH.
- I have obtained and will continue to obtain the liver-related tests for this patient as directed in the JUXTAPID Prescribing Information.

Lab Testing Recommendations	
Prior to initiating therapy	– Measure ALT, AST, alkaline phosphatase, and total bilirubin.
During the first year	– Measure liver-related tests (ALT and AST, at a minimum) **monthly** or prior to each increase in dose whichever occurs first.
After the first year	– Measure liver-related tests (ALT and AST, at a minimum) at least **every 3 months** and before any increase in dose.

- I authorize the JUXTAPID REMS to act on my behalf for the limited purposes of transmitting this prescription to the appropriate pharmacy designated by the patient utilizing their benefit plan.

Prescriber Signature: _____ _____ _____

Substitution Permitted | Dispense as Written | Date

IMPORTANT

REVIEW TO ENSURE ALL FIELDS ARE COMPLETED | RETURN BOTH PAGES

Fax this form to 1-855-898-2498 or scan and email it to REMS@amrytpharma.com.

If you have any questions, please contact the JUXTAPID REMS Coordinating Center.
Phone: 1-85-JUXTAPID (1-855-898-2743) | Fax: 1-855-898-2498 | www.juxtapidREMSprogram.com

Pharmacy Enrollment Form

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REMS Program

THERE ARE 2 PAGES TO THIS FORM | ALL FIELDS ARE REQUIRED | PLEASE PRINT

JUXTAPID is only available through the JUXTAPID Risk Evaluation and Mitigation Strategy (REMS)

PHARMACY

Pharmacy Name:_____ License #:_____

Address: _____

City:_____ State:_____ Zip:_____

Phone: _____ Fax: _____

AUTHORIZED PHARMACY REPRESENTATIVE

To become enrolled as a certified pharmacy under the JUXTAPID REMS, pharmacies must designate an authorized representative for the pharmacy. The authorized representative must complete the remainder of the form.

Name:_____ Title: _____

Email: _____

Phone: _____ Fax: _____

Authorized Pharmacy Representative Attestation

As the Authorized Pharmacy Representative, I must:

- Review the JUXTAPID Prescribing Information, **Fact Sheet** and **Pharmacy Training Module**
- Successfully complete the **Knowledge Assessment** and submit it to the JUXTAPID REMS
- Establish processes and procedures to verify the prescriber is certified, the patient is enrolled, and a completed **Prescription Authorization Form** is received for each prescription.
- Train all pharmacy staff involved in dispensing JUXTAPID in the requirements of the JUXTAPID REMS

Before dispensing, my pharmacy must verify that:

- The prescriber is certified
- The patient is enrolled
- A completed **Prescription Authorization Form** for the patient is received for each prescription

CONTINUED ON NEXT PAGE

Reference ID: 4930852

At all times, my pharmacy must:

- Not distribute, transfer, loan, or sell JUXTAPID
- Maintain records documenting staff's completion of the JUXTAPID REMS training
- Maintain and submit records of prescription data to the JUXTAPID REMS
- Maintain records that all REMS processes and procedures are in place and are being followed
- Comply with audits carried out by Amryt Pharmaceuticals DAC or a third party acting on behalf of Amryt Pharmaceuticals to ensure that all processes and procedures are in place and are being followed
- Have a new authorized representative enroll by completing and submitting the **Pharmacy Enrollment Form**, if the authorized representative changes

Signature: _____ Date: _____

This form must be completed for initial pharmacy enrollment, re-certification and within 30 days after any changes to the authorized representative.

IMPORTANT

REVIEW TO ENSURE ALL FIELDS ARE COMPLETED | RETURN BOTH PAGES

Fax this form to 1-855-898-2498 or scan and email it to REMS@amrytpharma.com

If you have any questions, please contact the JUXTAPID REMS Coordinating Center.
Phone: 1-85-JUXTAPID (1-855-898-2743) | Fax: 1-855-898-2498 | www.juxtapidREMSprogram.com

Note to Reviewer:

The JUXTAPID REMS Prescriber Training and Knowledge Assessment can be accessed online by clicking the link on the website. The participant will need to register to enter the Prescriber Training Module and Knowledge Assessment.

Participants will be required to enter their name, practice name, city, state and zip code and NPI number. The participant's email address will be requested, if this is not provided the participant will still be able to continue.

JUXTAPID Risk Evaluation and Mitigation Strategy (REMS)

Prescriber Training Module and Knowledge Assessment

This interactive tool:

- Provides an overview of the JUXTAPID REMS
- Discusses the risk of hepatotoxicity with JUXTAPID and the recommended hepatic monitoring requirements and dose adjustments
- Provides an overview of the prescriber, patient and pharmacy requirements for the JUXTAPID REMS

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Reference ID: 4930852

User Guide

To become certified to prescribe JUXTAPID all prescribers must:

- **Successfully complete** this Prescriber Training Module and Knowledge Assessment
- **Submit** the **signed** *Prescriber Enrollment Form* and Certificate of Training Completion to the JUXTAPID REMS Coordinating Center, by fax: 1-855-898-2498, or by email: REMS@amrytpharma.com

At the end of the Prescriber Training Module, there is a Knowledge Assessment with interactive questions that you must pass. If your answer is incorrect, you will be directed back to the relevant page in the materials and required to re-answer the question.

This Prescriber Training Module and Knowledge Assessment is intended to be read in conjunction with the *Fact Sheet* and the JUXTAPID Prescribing Information (PI).

This program is expected to take **15-20** minutes.

Click here to begin

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Overview

As there is a risk of hepatotoxicity with the use of JUXTAPID, it is only available through a restricted program called the "JUXTAPID Risk Evaluation and Mitigation Strategy (REMS)."

The purpose of this training module is to educate healthcare professionals about the JUXTAPID REMS.

A Risk Evaluation and Mitigation Strategy is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some products to ensure that the benefits of the drug outweigh its risks.

JUXTAPID REMS Goals

The aim of the JUXTAPID REMS is **to mitigate the risk of hepatotoxicity associated with the use of JUXTAPID** by ensuring that**:**

❶ **Prescribers are educated** about:

- the approved indication for JUXTAPID
- the risk of hepatotoxicity associated with the use of JUXTAPID
- the need to monitor patients during treatment with JUXTAPID as per the product labeling

❷ JUXTAPID is **dispensed only to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia** (HoFH)

❸ **Patients are informed about the risk of hepatotoxicity** associated with the use of JUXTAPID and the need for baseline and periodic liver monitoring

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Reference ID: 4930852

Indication

JUXTAPID is indicated 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).

Limitations of use related to the REMS:

- The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).

Please see JUXTAPID full Prescribing Information for the limitations to use, and the **BOXED WARNING** on hepatotoxicity as included on www.juxtapidREMSprogram.com

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Appropriate Patient Selection

JUXTAPID is only indicated for use in patients with HoFH.

- Patients must have a clinical or laboratory diagnosis consistent with HoFH.

Contraindications related to the REMS:

- **Moderate** or **severe hepatic impairment** or **active liver disease** including unexplained persistent abnormal liver function tests.

Please see JUXTAPID full Prescribing Information as included on www.juxtapidREMSprogram.com for the full contraindications.

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Boxed Warning – Risk of Hepatotoxicity

JUXTAPID can cause elevations in transaminases. In the JUXTAPID clinical trial, 10 (34%) of the 29 patients treated with JUXTAPID had at least one elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3x upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), or alkaline phosphatase.

JUXTAPID also increases hepatic fat, with or without concomitant increases in transaminases. The median absolute increase in hepatic fat was 6% after both 26 and 78 weeks of treatment, from 1% baseline, measured by magnetic resonance spectroscopy. Hepatic steatosis associated with JUXTAPID treatment may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis.

Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT and AST regularly as recommended. During treatment adjust dose of JUXTAPID if the ALT or AST are ≥3x ULN. Discontinue JUXTAPID for clinically significant liver toxicity.

Please see JUXTAPID full Prescribing Information including the full **BOXED WARNING** as included on www.juxtapidREMSprogram.com

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ℝisk of Hepatotoxicity: JUXTAPID Can Cause Elevations in Transaminases

Elevations in transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) are associated with JUXTAPID. In the clinical trial, 10 (34%) of the 29 patients with HoFH had at least one elevation in ALT or AST ≥3x ULN, and 4 (14%) of the patients had at least one elevation in ALT or AST ≥5x ULN. There were no concomitant or subsequent clinically meaningful elevations in bilirubin, INR, or alkaline phosphatase.

Although cases of hepatic failure have not been reported, there is concern that JUXTAPID could induce steatohepatitis, which can progress to cirrhosis over several years.

If transaminase elevations are accompanied by clinical symptoms of liver injury, such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms, increases in bilirubin ≥2x ULN, or active liver disease, discontinue treatment with JUXTAPID and identify the probable cause.

Continued next slide

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Risk of Hepatotoxicity: JUXTAPID Increases Hepatic Fat *(continued from previous slide)*

JUXTAPID increases hepatic fat, with or without concomitant increases in transaminases.

The median absolute increase in hepatic fat was 6% after both 26 and 78 weeks of treatment, from 1% baseline, measured by magnetic resonance spectroscopy. Hepatic steatosis associated with JUXTAPID treatment may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis.

Clinical data suggest that hepatic fat accumulation is reversible after stopping treatment with JUXTAPID, but whether histological sequelae remain is unknown.

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Dosage & Administration

The recommended starting dose of JUXTAPID is 5 mg taken once daily (QD).

The dose should be escalated gradually based on acceptable safety and tolerability.

- After two weeks, increase the dose based on acceptable safety and tolerability to 10 mg, taken once daily.
- Then, at a minimum of 4-week intervals, increase dose to 20 mg, 40 mg, or 60 mg daily.

QD Dose	Duration of Administration Before Considering Dose Increase
5 mg	At least two weeks
10 mg	At least four weeks
20 mg	
40 mg	
60 mg	Maximum recommended dose

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MONITORING OF TRANSAMINASES	
Timing	**Liver Monitoring Recommendations**
Prior to initiating JUXTAPID	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin
If abnormal, consider initiating JUXTAPID only after an appropriate workup and the baseline abnormalities have been explained or resolved.	
During the first year of treatment	ALT and AST (at a minimum) **monthly**, or prior to each increase in dose, whichever occurs first
After the first year of treatment	ALT and AST (at a minimum) at least every 3 months and prior to any increase in dose

At any time during treatment

If transaminases are abnormal, reduce or withhold dosing of JUXTAPID and monitor as recommended in the Prescribing Information. Discontinue JUXTAPID for persistent or clinically significant elevations.

If transaminase elevations are accompanied by accompanied by clinical symptoms of liver injury (such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin ≥2x ULN, or active liver disease, discontinue treatment with JUXTAPID and identify the probable cause.

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Hepatic Monitoring Recommendations

ALT or AST	Treatment and Monitoring Recommendations*
≥3x and <5x ULN	• Confirm elevation with a repeat measurement within one week. • If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). • Repeat tests weekly and withhold dosing if there are signs of abnormal liver function (increase in bilirubin or INR), if transaminase levels rise above 5x ULN, or if transaminase levels do not fall below 3x ULN within approximately 4 weeks. In these cases of persistent or worsening abnormalities, also investigate to identify the probable cause. • If resuming JUXTAPID after transaminases resolve to <3x ULN, consider reducing the dose and monitor liver-related tests more frequently.
≥5x ULN	• Withhold dosing, obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR), and investigate to identify the probable cause. • If resuming JUXTAPID after transaminases resolve to <3x ULN, reduce the dose and monitor liver-related tests more frequently.

If transaminase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin ≥2x ULN, or active liver disease, discontinue treatment with JUXTAPID and investigate to identify the probable cause.

*Recommendations based on an ULN of approximately 30-40 international units/L

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Contents

Reference ID: 4930852

JUXTAPID REMS Goals

The aim of the JUXTAPID REMS is **to mitigate the risk of hepatotoxicity associated with the use of JUXTAPID** by ensuring that**:**

❶ **Prescribers are educated** about:

- the approved indication for JUXTAPID
- the risk of hepatotoxicity associated with the use of JUXTAPID
- the need to monitor patients during treatment with JUXTAPID as per the product labeling

❷ JUXTAPID is **dispensed only to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia** (HoFH)

❸ **Patients are informed about the risk of hepatotoxicity** associated with the use of JUXTAPID and the need for baseline and periodic liver monitoring

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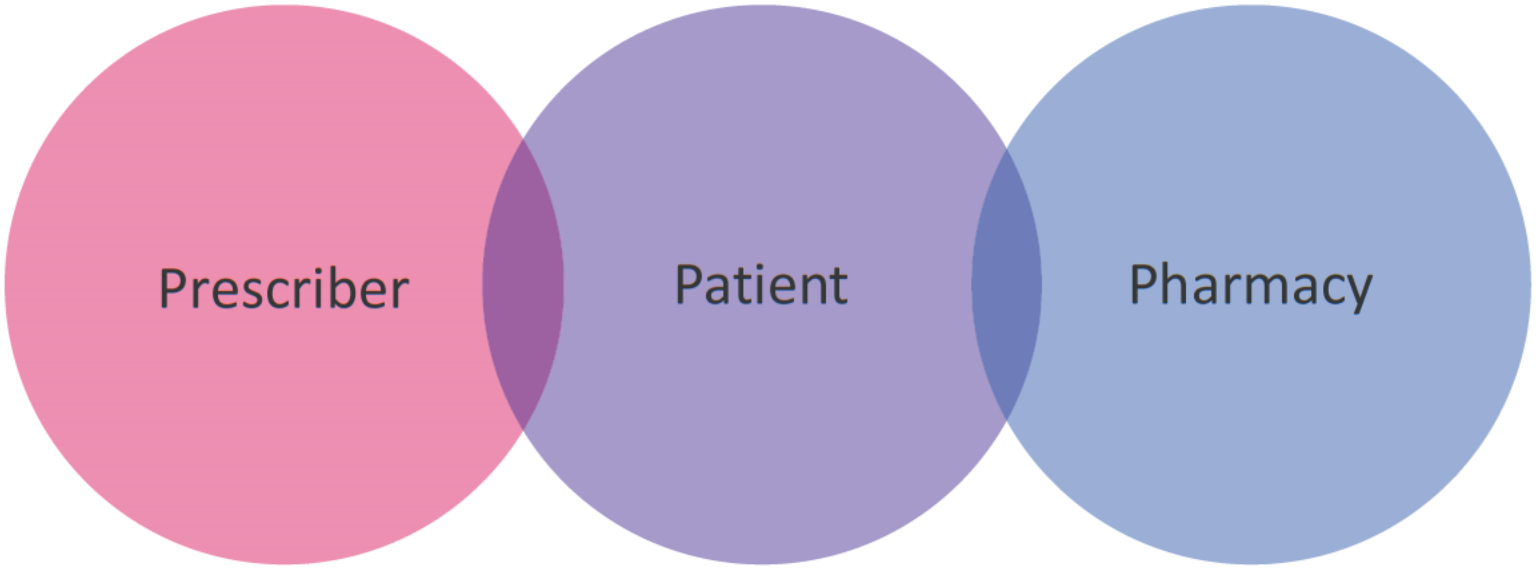
JUXTAPID REMS Key Elements



Prescribers must be certified to prescribe JUXTAPID

Patients must undergo education about the approved indication for use (HoFH), the risk of hepatotoxicity with JUXTAPID and the need for regular monitoring as part of the REMS

Pharmacies must be certified to distribute and dispense JUXTAPID

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Prescriber Certification Process

❶ **Review** the:

- JUXTAPID Prescribing Information
- *Fact Sheet*

❷ **Complete** the JUXTAPID REMS:

- Prescriber Training Module and Knowledge Assessment

❸ **Agree** to:

- **Counsel** patients using the *Patient Guide*
- **Complete, sign and submit** the *Patient-Prescriber Acknowledgement Form* with the patient
- **Submit** a *Prescription Authorization Form* for each prescription

❹ **Submit** to the REMS Coordinating Center the:

- **Completed** *Prescriber Enrollment Form*
- Certificate of Training Completion

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JUXTAPID Prescription Process

1

- **Certify** as a Prescriber in the JUXTAPID REMS*

2

- **Review** *Patient Guide* with Patient
- **Complete and Sign** *Patient-Prescriber Acknowledgement Form (PPAF),* give copy of *Patient Guide* to Patient
- **Submit** the PPAF to JUXTAPID REMS

3

- **Complete and Sign** the *Prescription Authorization Form (PAF)* for each prescription
- **Fax** the PAF to the JUXTAPID REMS

*prescribers are only required to certify one time

JUXTAPID REMS :
Email: REMS@amrytpharma.com
☎ 1-855-898-2743 fax: 1-855-898-2498

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Where do I find the REMS Materials?

All JUXTAPID REMS materials can be found on the **JUXTAPID REMS website:**

www.juxtapidREMSprogram.com

REMS materials can also be requested by contacting the **JUXTAPID REMS Coordinating Center at:**

1- 855-898-2743

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Knowledge Assessment

Reference ID: 4930852

Question 1

The goals of the JUXTAPID REMS are:
(check the answer that is the most inclusive)

- ☐ To educate prescribers about the risk of hepatotoxicity with the use of JUXTAPID.
- ☐ To restrict the use of JUXTAPID to only those patients with a clinical and laboratory diagnosis of HoFH.
- ☐ To ensure both prescribers and patients understand the risk of hepatotoxicity with JUXTAPID and the need for monitoring of liver function.
- ☐ All of the above.

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Question 1

The goals of the JUXTAPID REMS are:
(check the answer that is the most inclusive)

- ☐ **To educate prescribers about the risk of hepatotoxicity with the use of JUXTAPID.**
- ☐ To restrict the use of JUXTAPID to only those patients with a clinical and laboratory diagnosis of HoFH.
- ☐ To ensure both prescribers and patients understand the risk of hepatotoxicity with JUXTAPID and the need for monitoring of liver function.
- ☐ All of the above.

Partly correct

The education of prescribers about the risk of hepatotoxicity with the use of JUXTAPID is a key part of the JUXTAPID REMS. However, there are other goals too. Review the REMS goals and try again.

Question 1

The goals of the JUXTAPID REMS are:
(check the answer that is the most inclusive)

- ☐ To educate prescribers about the risk of hepatotoxicity with the use of JUXTAPID.
- ☐ **To restrict the use of JUXTAPID to only those patients with a clinical and laboratory diagnosis of HoFH.**
- ☐ To ensure both prescribers and patients understand the risk of hepatotoxicity with JUXTAPID and the need for monitoring of liver function.
- ☐ All of the above.

Partly correct

The restriction of the use of JUXTAPID to patients with a clinical or laboratory diagnosis of HoFH is a key part of the JUXTAPID REMS. However, there are other goals too. Review the REMS goals and try again.

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Question 1

The goals of the JUXTAPID REMS are:
(check the answer that is the most inclusive)

- ☐ To educate prescribers about the risk of hepatotoxicity with the use of JUXTAPID.
- ☐ To restrict the use of JUXTAPID to only those patients with a clinical and laboratory diagnosis of HoFH.
- ☐ **To ensure both prescribers and patients understand the risk of hepatotoxicity with JUXTAPID and the need for monitoring of liver function.**
- ☐ All of the above.

Partly correct

The education of both prescribers and patients about the risk of hepatotoxicity with JUXTAPID and the need for monitoring is an important part of the JUXTAPID REMS. However, there are other goals. Review the REMS goals and try again.

Question 1

The goals of the JUXTAPID REMS are:
(check the answer that is the most inclusive)

- ☐ To educate prescribers about the risk of hepatotoxicity with the use of JUXTAPID.
- ☐ To restrict the use of JUXTAPID to only those patients with a clinical and laboratory diagnosis of HoFH.
- ☐ To ensure both prescribers and patients understand the risk of hepatotoxicity with JUXTAPID and the need for monitoring of liver function.
- ☐ **All of the above.**

Correct!

All three are goals of the JUXTAPID REMS.

Click here to advance

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Question 2

Which conditions are appropriate for the use of JUXTAPID?

- ☐ Mixed dyslipidemia.
- ☐ Homozygous familial hypercholesterolemia (HoFH).
- ☐ Heterozygous familial hypercholesterolemia (HeFH).
- ☐ All of the above.

Question 2

Which conditions are appropriate for the use of JUXTAPID?

- ☐ **Mixed dyslipidemia.**
- ☐ Homozygous familial hypercholesterolemia (HoFH).
- ☐ Heterozygous familial hypercholesterolemia (HeFH).
- ☐ All of the above.

Incorrect

JUXTAPID is indicated for use in patients with homozygous familial hypercholesterolemia (HoFH).

Review the Indication for JUXTAPID and try again.

Question 2

Which conditions are appropriate for the use of JUXTAPID?

- ☐ Mixed dyslipidemia.
- ☐ **Homozygous familial hypercholesterolemia (HoFH).**
- ☐ Heterozygous familial hypercholesterolemia (HeFH).
- ☐ All of the above.

Correct!

JUXTAPID is indicated for use 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).

Click here to advance

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Question 2

Which conditions are appropriate for the use of JUXTAPID?

- ☐ Mixed dyslipidemia.
- ☐ Homozygous familial hypercholesterolemia (HoFH).
- ☐ **Heterozygous familial hypercholesterolemia (HeFH).**
- ☐ All of the above.

Incorrect

JUXTAPID is indicated for use in patients with homozygous familial hypercholesterolemia (HoFH).

Review the Indication for JUXTAPID and try again.

Question 2

Which conditions are appropriate for the use of JUXTAPID?

- ☐ Mixed dyslipidemia.
- ☐ Homozygous familial hypercholesterolemia (HoFH).
- ☐ Heterozygous familial hypercholesterolemia (HeFH).
- ☐ **All of the above.**

Incorrect

JUXTAPID is indicated for use in patients with homozygous familial hypercholesterolemia (HoFH).

Review the Indication for JUXTAPID and try again.

Question 3

What are the hepatic monitoring recommendations during the first year of treatment with JUXTAPID?

- ☐ Check transaminases only if the patient experiences signs and symptoms of liver injury.
- ☐ Monitor transaminase levels every 3 months.
- ☐ Monitor ALT and AST (at a minimum) monthly or prior to each increase of dose, whichever occurs first.

Question 3

What are the hepatic monitoring recommendations during the first year of treatment with JUXTAPID?

- ☐ **Check transaminases only if the patient experiences signs and symptoms of liver injury.**
- ☐ Monitor transaminase levels every 3 months.
- ☐ Monitor ALT and AST (at a minimum) prior to each increase of dose or monthly, whichever occurs first.

Incorrect

During the first year of therapy transaminases should be monitored every 30 days or prior to each increase in dose.

At a minimum ALT and AST should be checked every 30 days.

Review the Hepatic Monitoring Recommendations for JUXTAPID and try again.

Question 3

What are the hepatic monitoring recommendations during the first year of treatment with JUXTAPID?

- ☐ Check transaminases only if the patient experiences signs and symptoms of liver injury.
- ☐ **Monitor transaminase levels every 3 months.**
- ☐ Monitor ALT and AST (at a minimum) prior to each increase of dose or monthly, whichever occurs first.

Incorrect

During the first year of therapy transaminases should be monitored every 30 days or prior to each increase in dose.

At a minimum ALT and AST should be checked every 30 days.

Review the Hepatic Monitoring Recommendations for JUXTAPID and try again.

Question 3

What are the hepatic monitoring recommendations during the first year of treatment with JUXTAPID?

- ☐ Check transaminases only if the patient experiences signs and symptoms of liver injury.
- ☐ Monitor transaminase levels every 3 months.
- ☐ **Monitor ALT and AST (at a minimum) prior to each increase of dose or monthly, whichever occurs first.**

Correct!

During the first year of therapy transaminases should be monitored every 30 days or prior to each increase in dose.

At a minimum ALT and AST should be checked every 30 days.

Click here to advance

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Question 4

Jane Smith is 24 years old and has a clinical and laboratory diagnosis of HoFH.

She has been on JUXTAPID for 13 months, appears to be compliant with her medication. You want to increase the dose, what should you do before you increase the dose?

- ☐ Measure AST, ALT, alkaline phosphatase and total bilirubin after the increase in dose.
- ☐ Increase her dose, see her back in a month.
- ☐ Measure AST, ALT, alkaline phosphatase and total bilirubin if not performed in the last 30 days and only adjust the dose if normal.

Question 4

Jane Smith is 24 years old and has a clinical and laboratory diagnosis of HoFH.

She has been on JUXTAPID for 13 months, appears to be compliant with her medication. You want to increase the dose, what should you do before you increase the dose?

- ☐ **Measure AST, ALT, alkaline phosphatase and total bilirubin after the increase in dose.**
- ☐ Increase her dose, see her back in a month.
- ☐ Measure AST, ALT, alkaline phosphatase and total bilirubin if not performed in the last 30 days and only adjust the dose if normal.

Incorrect

Before you increase Ms. Smith's dose minimally AST and ALT should be measured and confirmed to be within acceptable ranges. Review the options and consider another approach.

Review the Hepatic Monitoring Recommendations for JUXTAPID and try again.

Question 4

Jane Smith is 24 years old and has a clinical and laboratory diagnosis of HoFH.

She has been on JUXTAPID for 13 months, appears to be compliant with her medication. You want to increase the dose, what should you do before you increase the dose?

- ☐ Measure AST, ALT, alkaline phosphatase and total bilirubin after the increase in dose.
- ☐ **Increase her dose, see her back in a month.**
- ☐ Measure AST, ALT, alkaline phosphatase and total bilirubin if not performed in the last 30 days and only adjust the dose if normal.

Incorrect

Before you increase Ms. Smith's dose minimally AST and ALT should be measured and confirmed to be within acceptable ranges. Review the options and consider another approach.

Review the Hepatic Monitoring Recommendations for JUXTAPID and try again.

Question 4

Jane Smith is 24 years old and has a clinical and laboratory diagnosis of HoFH.

She has been on JUXTAPID for 13 months, appears to be compliant with her medication. You want to increase the dose, what should you do before you increase the dose?

- ☐ Measure AST, ALT, alkaline phosphatase and total bilirubin after the increase in dose.
- ☐ Increase her dose, see her back in a month.
- ☐ **Measure AST, ALT, alkaline phosphatase and total bilirubin if not performed in the last 30 days and only adjust the dose if normal.**

Correct!

Before you increase Ms. Smith's dose minimally AST and ALT should be measured and confirmed to be within acceptable ranges.

Click here to advance

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Question 5

Your patient Thomas Jones, who has a clinical and laboratory diagnosis of HoFH, presents to your clinic after being on JUXTAPID for 6 months. His ALT is ≥5x the ULN.

Your next step should be:

- ☐ Withhold dosing, obtain additional liver related labs and investigate the potential cause.
- ☐ Repeat the ALT in one week, if still elevated reduce the dose, repeat ALT tests weekly until it is less than 3x ULN.
- ☐ Decrease the dose of JUXTAPID.
- ☐ Continue the JUXTAPID for another month and re-measure the ALT.

Question 5

Your patient Thomas Jones, who has a clinical and laboratory diagnosis of HoFH, presents to your clinic after being on JUXTAPID for 6 months. His ALT is ≥5x the ULN.

Your next step should be:

- ☐ **Withhold dosing, obtain additional liver related labs and investigate the potential cause.**
- ☐ Repeat the ALT in one week, if still elevated reduce the dose, repeat ALT tests weekly until it is less than 3x ULN.
- ☐ Decrease the dose of JUXTAPID.
- ☐ Continue the JUXTAPID for another month and re-measure the ALT.

Correct!

If AST and/or ALT is ≥5x ULN the dose of JUXTAPID should be withheld, obtain additional liver related laboratories if not already obtained and investigate the potential cause. Withhold dosing until transaminase levels drop below 3x ULN.

Click here to advance

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Question 5

Your patient Thomas Jones, who has a clinical and laboratory diagnosis of HoFH, presents to your clinic after being on JUXTAPID for 6 months. His ALT is ≥5x the ULN.

Your next step should be:

- ☐ Withhold dosing, obtain additional liver related labs and investigate the potential cause.
- ☐ **Repeat the ALT in one week, if still elevated reduce the dose, repeat ALT tests weekly until it is less than 3x ULN.**
- ☐ Decrease the dose of JUXTAPID.
- ☐ Continue the JUXTAPID for another month and re-measure the ALT.

Incorrect

If AST and/or ALT is ≥5x ULN the dose of JUXTAPID should be withheld, obtain additional liver related laboratories if not already obtained and investigate the potential cause. Withhold dosing until transaminase levels drop below 3x ULN.

Review the Hepatic Monitoring Recommendations for JUXTAPID and try again.

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Question 5

Your patient Thomas Jones, who has a clinical and laboratory diagnosis of HoFH, presents to your clinic after being on JUXTAPID for 6 months. His ALT is ≥ 5x the ULN.

Your next step should be:

- ☐ Withhold dosing, obtain additional liver related labs and investigate the potential cause.
- ☐ Repeat the ALT in one week, if still elevated reduce the dose, repeat ALT tests weekly until it is less than 3x ULN.
- ☐ **Decrease the dose of JUXTAPID.**
- ☐ Continue the JUXTAPID for another month and re-measure the ALT.

Incorrect

If AST and/or ALT is ≥5x ULN the dose of JUXTAPID should be withheld, obtain additional liver related laboratories if not already obtained and investigate the potential cause. Withhold dosing until transaminase levels drop below 3x ULN.

Review the Hepatic Monitoring Recommendations for JUXTAPID and try again.

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Question 5

Your patient Thomas Jones, who has a clinical and laboratory diagnosis of HoFH, presents to your clinic after being on JUXTAPID for 6 months. His ALT is ≥ 5x the ULN.

Your next step should be:

- ☐ Withhold dosing, obtain additional liver related labs and investigate the potential cause.
- ☐ Repeat the ALT in one week, if still elevated reduce the dose, repeat ALT tests weekly until it is less than 3x ULN.
- ☐ Decrease the dose of JUXTAPID.
- ☐ **Continue the JUXTAPID for another month and re-measure the ALT.**

Incorrect

If AST and/or ALT is ≥5x ULN the dose of JUXTAPID should be withheld, obtain additional liver related laboratories if not already obtained and investigate the potential cause. Withhold dosing until transaminase levels drop below 3x ULN.

Review the Hepatic Monitoring Recommendations for JUXTAPID and try again.

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Question 6

Sandra Brown has been on JUXTAPID for 4 months. She presents to your clinic with nausea, vomiting, abdominal pain, jaundice and is feeling "achy all over."

You check transaminases and the AST is 3x ULN, the ALT is 2x ULN.

What should you do next?

- ☐ Discontinue JUXTAPID treatment.
- ☐ Identify the probable cause.
- ☐ Follow AST, ALT, total bilirubin and alkaline phosphatase until normal.
- ☐ All of the above.

Question 6

Sandra Brown has been on JUXTAPID for 4 months. She presents to your clinic with nausea, vomiting, abdominal pain, jaundice and is feeling "achy all over."

You check transaminases and the AST is 3x ULN, the ALT is 2x ULN.

What should you do next?

- ☐ **Discontinue JUXTAPID treatment.**
- ☐ Identify the probable cause.
- ☐ Follow AST, ALT, total bilirubin and alkaline phosphatase until normal.
- ☐ All of the above.

Partly correct

Although it is recommended that JUXTAPID treatment is discontinued in patients who experience symptoms of liver injury accompanied by elevations in transaminases. However, there are other actions that should be considered.

Review the Hepatic Monitoring Recommendations for JUXTAPID and try again.

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Question 6

Sandra Brown has been on JUXTAPID for 4 months. She presents to your clinic with nausea, vomiting, abdominal pain, jaundice and is feeling "achy all over."

You check transaminases and the AST is 3x ULN, the ALT is 2x ULN.

What should you do next?

- ☐ Discontinue JUXTAPID treatment.
- ☐ **Identify the probable cause.**
- ☐ Follow AST, ALT, total bilirubin and alkaline phosphatase until normal.
- ☐ All of the above.

Partly correct

Although the identification of the possible cause of the elevations in AST and ALT and the symptoms of liver injury is important, there are other actions that should be considered.

Review the Hepatic Monitoring Recommendations for JUXTAPID and try again.

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Question 6

Sandra Brown has been on JUXTAPID for 4 months. She presents to your clinic with nausea, vomiting, abdominal pain, jaundice and is feeling "achy all over."

You check transaminases and the AST is 3x ULN, the ALT is 2x ULN.

What should you do next?

- ☐ Discontinue JUXTAPID treatment.
- ☐ Identify the probable cause.
- ☐ **Follow AST, ALT, total bilirubin and alkaline phosphatase until normal.**
- ☐ All of the above.

Partly correct

Although the AST and ALT are not higher than 3x ULN, the patient is experiencing symptoms accompanied with transaminase elevations. It is also important to follow liver functions until they resolve, however there may be other actions you should take.

Review the Hepatic Monitoring Recommendations for JUXTAPID and try again.

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Question 6

Sandra Brown has been on JUXTAPID for 4 months. She presents to your clinic with nausea, vomiting, abdominal pain, jaundice and is feeling "achy all over."

You check transaminases and the AST is 3x ULN, the ALT is 2x ULN.

What should you do next?

- ☐ Discontinue JUXTAPID treatment.
- ☐ Identify the probable cause.
- ☐ Follow AST, ALT, total bilirubin and alkaline phosphatase until normal.
- ☐ **All of the above.**

Correct!

It is recommended that patients who experience elevations in transaminases accompanied by symptoms of liver injury accompanied by, discontinue treatment with JUXTAPID, LFTs should continue to be followed until they resolve, and further investigation should be instituted to identify the probable cause.

Click here to advance

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Question 7

One of the key points in the REMS is patient education on the risks of hepatotoxicity with JUXTAPID.

- ☐ True
- ☐ False

Reference ID: 4930852

Question 7

One of the key points in the REMS is patient education on the risks of hepatotoxicity with JUXTAPID.

- ☐ **True**
- ☐ False

Correct!

JUXTAPID is associated with a risk of hepatotoxicity and as a result there is a REMS in place to ensure that its benefits outweigh its risks. The REMS requires patients to participate in the treatment decision process. This requires the prescriber to review the *Patient Guide* with the patient. Knowledge of the appropriate indication for use and the risk of hepatotoxicity is expected to allow them to participate effectively in that process.

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Question 7

One of the key points in the REMS is patient education on the risks of hepatotoxicity with JUXTAPID.

- ☐ True
- ☐ **False**

Incorrect

Review the goals of the JUXTAPID REMS and retry this question.

Question 8

How does a prescriber become certified in the JUXTAPID REMS?

- ☐ Complete and submit the *Prescriber Enrollment Form.*
- ☐ Successfully complete the Prescriber Training Module and Knowledge Assessment.
- ☐ Review the JUXTAPID PI and the *Fact Sheet.*
- ☐ All of the above.

Question 8

How does a prescriber become certified in the JUXTAPID REMS?

- ☐ **Complete and submit the *Prescriber Enrollment Form.***
- ☐ Successfully complete the Prescriber Training Module and Knowledge Assessment.
- ☐ Review the JUXTAPID PI and the *Fact Sheet.*
- ☐ All of the above.

Almost

To become a certified prescriber in the JUXTAPID REMS you must sucessfully complete the *Prescriber Enrollment Form*, Training Module and Knowledge Assessment, and review the PI and *Fact Sheet.*

Review the Prescriber Certification Process and try again.

Question 8

How does a prescriber become certified in the JUXTAPID REMS?

- ☐ Complete and submit the *Prescriber Enrollment Form.*
- ☐ **Successfully complete the Prescriber Training Module and Knowledge Assessment.**
- ☐ Review the JUXTAPID PI and the *Fact Sheet.*
- ☐ All of the above.

Almost

To become a certified prescriber in the JUXTAPID REMS you must sucessfully complete the *Prescriber Enrollment Form*, Training Module and Knowledge Assessment, and review the PI and *Fact Sheet*.

Review the Prescriber Certification Process and try again.

Question 8

How does a prescriber become certified in the JUXTAPID REMS?

- ☐ Complete and submit the *Prescriber Enrollment Form.*
- ☐ Successfully complete the Prescriber Training Module and Knowledge Assessment.
- ☐ **Review the JUXTAPID PI and the *Fact Sheet.***
- ☐ All of the above.

Almost

To become a certified prescriber in the JUXTAPID REMS you must sucessfully complete the *Prescriber Enrollment Form*, Training Module and Knowledge Assessment, and review the PI and *Fact Sheet*.

Review the Prescriber Certification Process and try again.

Question 8

How does a prescriber become certified in the JUXTAPID REMS?

- ☐ Complete and submit the *Prescriber Enrollment Form.*
- ☐ Successfully complete the Prescriber Training Module and Knowledge Assessment.
- ☐ Review the JUXTAPID PI and the *Fact Sheet.*
- ☐ **All of the above.**

Correct!

To become a certified prescriber in the JUXTAPID REMS you must sucessfully complete the *Prescriber Enrollment Form*, Training Module and Knowledge Assessment, and review the PI and *Fact Sheet*.

Click here to advance

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Congratulations!

You have successfully completed the Prescriber Training Module and Knowledge Assessment.

Next Steps:

- **Obtain** the *Certificate of Completion* for the Prescriber Training Module and Knowledge Assessment

  Click here for a copy of your *Certificate of Completion*

- **Complete and sign** the *Prescriber Enrollment Form*
- **Submit both documents** to the JUXTAPID REMS Coordinating Center by fax: 1-855-898-2498 or by email to: REMS@amrytpharma.com

If all the certification requirements are met, the JUXTAPID REMS Coordinating center will confirm you are certified as a prescriber in the JUXTAPID REMS. Once you are certified in the JUXTAPID REMS you can counsel patients on the REMS requirements and prescribe JUXTAPID.

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Note to Reviewer:

The following slides are the “refresher” slides that you are directed to after answering a question incorrectly. These slide are duplicates of the original slide with the exception of the hyperlink back to the question. These slides will not be visible in the training, unless the participant answers the questions incorrectly.

JUXTAPID REMS Goals

Redirect from Question 1

The aim of the JUXTAPID REMS is **to mitigate the risk of hepatotoxicity associated with the use of JUXTAPID** by ensuring that**:**

❶ **Prescribers are educated** about:

- the approved indication for JUXTAPID
- the risk of hepatotoxicity associated with the use of JUXTAPID
- the need to monitor patients during treatment with JUXTAPID as per the product labeling

❷ JUXTAPID is **dispensed only to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia** (HoFH)

❸ **Patients are informed about the risk of hepatotoxicity** associated with the use of JUXTAPID and the need for baseline and periodic liver monitoring

To retry Question 1 click here

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Indication

Redirect from Question 2

JUXTAPID is indicated 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).

Limitations of use:

- The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH.

Please see JUXTAPID full Prescribing Information for the limitations to use, and the **BOXED WARNING** on hepatotoxicity as included on www.juxtapidREMSprogram.com

To retry Question 2 click here

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MONITORING OF TRANSAMINASES	
Timing	**Liver Monitoring Recommendations**
Prior to initiating JUXTAPID	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin
If abnormal, consider initiating JUXTAPID only after an appropriate workup and the baseline abnormalities have been explained or resolved.	
During the first year of treatment	ALT and AST (at a minimum) **monthly**, or prior to each increase in dose, whichever occurs first
After the first year of treatment	ALT and AST (at a minimum) at least every 3 months and prior to any increase in dose

At any time during treatment

If transaminases are abnormal, reduce or withhold dosing of JUXTAPID and monitor as recommended in the Prescribing Information. Discontinue JUXTAPID for persistent or clinically significant elevations.

If transaminase elevations are accompanied by accompanied by clinical symptoms of liver injury (such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin ≥2x ULN, or active liver disease, discontinue treatment with JUXTAPID and identify the probable cause.

To retry Question 3
click here

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Hepatic Monitoring Recommendations

Redirect from Question 4

ALT or AST	Treatment and Monitoring Recommendations*
≥3x and <5x ULN	• Confirm elevation with a repeat measurement within one week. • If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). • Repeat tests weekly and withhold dosing if there are signs of abnormal liver function (increase in bilirubin or INR), if transaminase levels rise above 5x ULN, or if transaminase levels do not fall below 3x ULN within approximately 4 weeks. In these cases of persistent or worsening abnormalities, also investigate to identify the probable cause. • If resuming JUXTAPID after transaminases resolve to <3x ULN, consider reducing the dose and monitor liver-related tests more frequently.
≥5x ULN	• Withhold dosing, obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR), and investigate to identify the probable cause. • If resuming JUXTAPID after transaminases resolve to <3x ULN, reduce the dose and monitor liver-related tests more frequently.

If transaminase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin ≥2x ULN, or active liver disease, discontinue treatment with JUXTAPID and investigate to identify the probable cause.

*Recommendations based on an ULN of approximately 30-40 international units/L

To retry Question 4
click here

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Hepatic Monitoring Recommendations

Redirect from Question 5

ALT or AST	Treatment and Monitoring Recommendations*
≥3x and <5x ULN	• Confirm elevation with a repeat measurement within one week. • If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). • Repeat tests weekly and withhold dosing if there are signs of abnormal liver function (increase in bilirubin or INR), if transaminase levels rise above 5x ULN, or if transaminase levels do not fall below 3x ULN within approximately 4 weeks. In these cases of persistent or worsening abnormalities, also investigate to identify the probable cause. • If resuming JUXTAPID after transaminases resolve to <3x ULN, consider reducing the dose and monitor liver-related tests more frequently.
≥5x ULN	• Withhold dosing, obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR), and investigate to identify the probable cause. • If resuming JUXTAPID after transaminases resolve to <3x ULN, reduce the dose and monitor liver-related tests more frequently.

If transaminase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin ≥2x ULN, or active liver disease, discontinue treatment with JUXTAPID and investigate to identify the probable cause.

*Recommendations based on an ULN of approximately 30-40 international units/L

To retry Question 5
click here

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Hepatic Monitoring Recommendations

Redirect from Question 6

ALT or AST	Treatment and Monitoring Recommendations*
≥3x and <5x ULN	• Confirm elevation with a repeat measurement within one week. • If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). • Repeat tests weekly and withhold dosing if there are signs of abnormal liver function (increase in bilirubin or INR), if transaminase levels rise above 5x ULN, or if transaminase levels do not fall below 3x ULN within approximately 4 weeks. In these cases of persistent or worsening abnormalities, also investigate to identify the probable cause. • If resuming JUXTAPID after transaminases resolve to <3x ULN, consider reducing the dose and monitor liver-related tests more frequently.
≥5x ULN	• Withhold dosing, obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR), and investigate to identify the probable cause. • If resuming JUXTAPID after transaminases resolve to <3x ULN, reduce the dose and monitor liver-related tests more frequently.

If transaminase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin ≥2x ULN, or active liver disease, discontinue treatment with JUXTAPID and investigate to identify the probable cause.

*Recommendations based on an ULN of approximately 30-40 international units/L

To retry Question 6
click here

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JUXTAPID REMS Goals

Redirect from Question 7

The aim of the JUXTAPID REMS is **to mitigate the risk of hepatotoxicity associated with the use of JUXTAPID** by ensuring that**:**

❶ **Prescribers are educated** about:

- the approved indication for JUXTAPID
- the risk of hepatotoxicity associated with the use of JUXTAPID
- the need to monitor patients during treatment with JUXTAPID as per the product labeling

❷ JUXTAPID is **dispensed only to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia** (HoFH)

❸ **Patients are informed about the risk of hepatotoxicity** associated with the use of JUXTAPID and the need for baseline and periodic liver monitoring

To retry Question 7 click here

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Prescriber Certification Process

Redirect from Question 8

❶ **Review** the:

- JUXTAPID *Prescribing Information*
- *Fact Sheet*

❷ **Complete** the JUXTAPID REMS:

- Prescriber Training Module and Knowledge Assessment

❸ **Agree** to:

- **Counsel** patients using the *Patient Guide*
- **Complete, sign and submit** the *Patient-Prescriber Acknowledgement Form* with the patient
- **Submit** a *Prescription Authorization Form* for each prescription

❹ **Submit** to the REMS Coordinating Center the:

- Completed *Prescriber Enrollment Form* and Certificate of Training Completion

To retry Question 8 click here

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AMRYT
PHARMA

Reference ID: 4930852

Note to Reviewer:

The JUXTAPID REMS Pharmacy Training Module and Knowledge Assessment can be accessed online by clicking the link on the website. The participant will need to register to enter the Pharmacy Training Module and Knowledge Assessment. The registration page requires the participant to indicate that they are an authorized representative of the pharmacy.

Participants will be required to enter their name, pharmacy name, city, state and zip code. The participant's email address will be requested; but if this is not provided, the participant will still be able to proceed. These items will be used to generate a *Certificate of Completion* at the end of the training that is required to be submitted to enroll the pharmacy in the JUXTAPID REMS.

JUXTAPID Risk Evaluation and Mitigation Strategy (REMS)

Pharmacy Training Module and Knowledge Assessment

This interactive tool:

- Provides an overview of the JUXTAPID REMS
- Discusses the risk of hepatotoxicity with JUXTAPID
- Provides an overview of the prescriber, patient and pharmacy requirements for the JUXTAPID REMS

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Reference ID: 4930852

User Guide

To become certified to purchase, dispense and distribute JUXTAPID, all pharmacies must designate an **Authorized Representative** who must**:**

- **Successfully complete** this Pharmacy Training Module and Knowledge Assessment and **print** the *Certificate of Completion* at the end of the module
- **Submit** the *Certificate of Completion* and the **signed** *Pharmacy Enrollment Form* to the JUXTAPID REMS Coordinating Center either by fax: 1-855-898-2498 or email: REMS@amrytpharma.com

At the end of the Pharmacy Training Module there is a Knowledge Assessment with interactive questions that you must pass. If your answer is incorrect, you will be directed back to the relevant page in the materials and will be required to re-answer the question.

This Pharmacy Training Module and Knowledge Assessment is intended to be read in conjunction with the *Fact Sheet* and the JUXTAPID Prescribing Information.

This program is expected to take **10-15** minutes.

Click here to begin

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Contents

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Overview

Because of the risk of hepatotoxicity with JUXTAPID, it is only available through a restricted program called the "JUXTAPID Risk Evaluation and Mitigation Strategy (REMS)."

The purpose of this training module is to educate pharmacy representatives about the JUXTAPID REMS including the requirements for prescribers and pharmacies.

A Risk Evaluation and Mitigation Strategy is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some products to ensure that the benefits of the drug outweigh its risks.

JUXTAPID REMS Goals

The aim of the JUXTAPID REMS is **to mitigate the risk of hepatotoxicity associated with the use of JUXTAPID** by ensuring that**:**

❶ **Prescribers are educated** about:

- the approved indication for JUXTAPID
- the risk of hepatotoxicity associated with the use of JUXTAPID
- the need to monitor patients during treatment with JUXTAPID as per the product labeling

❷ JUXTAPID is **dispensed only to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia** (HoFH)

❸ **Patients are informed about the risk of hepatotoxicity** associated with the use of JUXTAPID and the need for baseline and periodic liver monitoring

Juxtapid (lomitapide) capsules

Contents

Reference ID: 4930852

Indication

JUXTAPID is indicated 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).

Limitations of use related to the REMS:

- The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).

Please see JUXTAPID full Prescribing Information for the limitations to use, and the **BOXED WARNING** on hepatotoxicity as included on www.juxtapidREMSprogram.com

Juxtapid (lomitapide) capsules

Appropriate Patient Selection

JUXTAPID is only indicated for use in patients with HoFH.

- Patients must have a clinical or laboratory diagnosis consistent with HoFH

Related Contraindications:

- **Moderate** or **severe hepatic impairment** or **active liver disease** including unexplained persistent abnormal liver function tests

Please see JUXTAPID full Prescribing Information for the limitations to use, and the **BOXED WARNING** on hepatotoxicity as included on www.juxtapidREMSprogram.com

Juxtapid (lomitapide) capsules

Boxed Warning – Risk of Hepatotoxicity

JUXTAPID can cause elevations in transaminases. In the JUXTAPID clinical trial, 10 (34%) of the 29 patients treated with Juxtapid had at least one elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3x upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), or alkaline phosphatase.

JUXTAPID also increases hepatic fat, with or without concomitant increases in transaminases. The median absolute increase in hepatic fat was 6% after both 26 and 78 weeks of treatment, from 1% baseline, measured by magnetic resonance spectroscopy. Hepatic steatosis associated with JUXTAPID treatment may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis.

Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT and AST regularly as recommended. During treatment adjust dose of JUXTAPID if the ALT or AST are ≥3x ULN. Discontinue JUXTAPID for clinically significant liver toxicity.

Please see JUXTAPID full Prescribing Information including the full **BOXED WARNING** as included on www.juxtapidREMSprogram.com

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ℝisk of Hepatotoxicity: JUXTAPID Can Cause Elevations in Transaminases

Although cases of hepatic failure have not been reported, there is concern that JUXTAPID could induce steatohepatitis, which can progress to cirrhosis over several years.

Elevations in transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) are associated with JUXTAPID. In the clinical trial, 10 (34%) of the 29 patients with HoFH had at least one elevation in ALT or AST ≥3x ULN, and 4 (14%) of the patients had at least one elevation in ALT or AST ≥5x ULN. There were no concomitant or subsequent clinically meaningful elevations in bilirubin, INR, or alkaline phosphatase.

If transaminase elevations are accompanied by clinical symptoms of liver injury, such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms, increases in bilirubin ≥2x ULN, or active liver disease, discontinue treatment with JUXTAPID and identify the probable cause.

Continued next slide

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Risk of Hepatotoxicity: JUXTAPID Increases Hepatic Fat *(continued from previous slide)*

JUXTAPID increases hepatic fat, with or without concomitant increases in transaminases.

The median absolute increase in hepatic fat was 6% after both 26 and 78 weeks of treatment, from 1% baseline, measured by magnetic resonance spectroscopy. Hepatic steatosis associated with JUXTAPID treatment may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis.

Clinical data suggest that hepatic fat accumulation is reversible after stopping treatment with JUXTAPID, but whether histological sequelae remain is unknown.

Contents

Reference ID: 4930852

JUXTAPID REMS Goals

The aim of the JUXTAPID REMS is **to mitigate the risk of hepatotoxicity associated with the use of JUXTAPID** by ensuring that**:**

❶ **Prescribers are educated** about:

- the approved indication for JUXTAPID
- the risk of hepatotoxicity associated with the use of JUXTAPID
- the need to monitor patients during treatment with JUXTAPID as per the product labeling

❷ JUXTAPID is **dispensed only to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia** (HoFH)

❸ **Patients are informed about the risk of hepatotoxicity** associated with the use of JUXTAPID and the need for baseline and periodic liver monitoring

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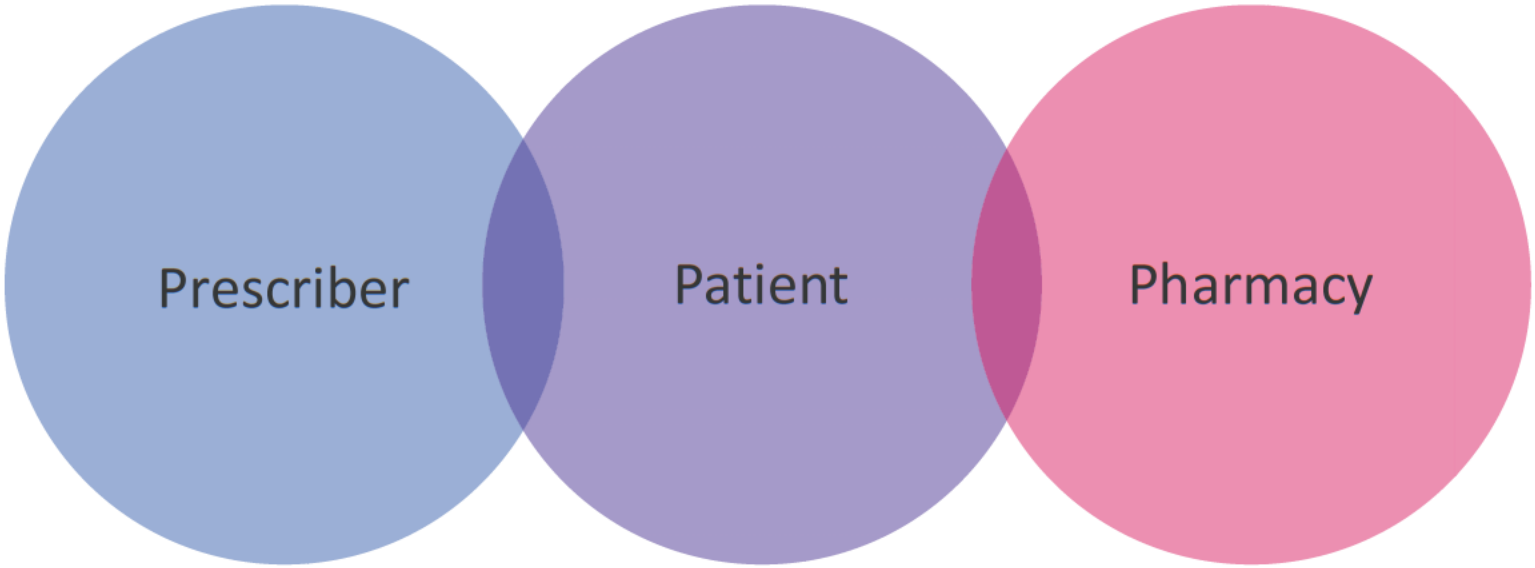
JUXTAPID REMS Key Elements



Prescribers must be certified to prescribe JUXTAPID

Patients must undergo education about the REMS, the approved indication for use the risk of hepatotoxicity with JUXTAPID and the need for regular liver monitoring

Pharmacies must be certified to distribute and dispense JUXTAPID

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Patient-Prescriber Acknowledgment

To enable **patient participation** in the treatment decision process, both patients and prescribers are required to review and complete the *Patient-Prescriber Acknowledgement Form (PPAF).* This form is attached to the *Patient Guide* and must be submitted to the JUXTAPID REMS Coordinating Center for all new patients.

The Prescriber must:

❶ **Review** the *Patient Guide* with the patient.

- This document provides a summary of JUXTAPID and the REMS requirements

❷ **Complete** the *Patient-Prescriber Acknowledgement Form (PPAF).*

- The PPAF is signed by both the patient and the prescriber and acknowledges that the patient has received education on the JUXTAPID REMS, understands the hepatic risk and the need for regular liver monitoring

Prescriptions will not be dispensed without a completed PPAF on record

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Pharmacy Certification Process

Reference ID: 4930852

Authorized Representative Requirements

For a pharmacy to be certified in the JUXTAPID REMS, the pharmacy must designate an Authorized Representative (AR).

The Authorized Representative is required to:

- **Complete** the Pharmacy Training Module and Knowledge Assessment
- **Oversee** the conduct of the JUXTAPID REMS at the pharmacy
- **Agree** to put processes in place, and to **train** applicable pharmacy staff on the JUXTAPID REMS requirements

The pharmacy must confirm the name of the authorized representative every year, and advise the REMS Coordinating Center promptly of any change in the AR. If the AR changes, the pharmacy must recertify within 30 days.

Pharmacy Certification Process

The Authorized Representative must:

❶ **Review** the:

- JUXTAPID Prescribing Information (PI)
- *Fact Sheet*

❷ **Complete** the:

- JUXTAPID REMS Pharmacy Training Module and Knowledge Assessment

❸ **Agree** to:

- Train all applicable pharmacy staff on the JUXTAPID REMS requirements
- Implement processes and procedures to ensure that the requirements of the REMS are met
- Be audited
- Provide all prescription records to Amryt

❹ **Submit** to the REMS Coordinating Center the:

- *Certificate of Completion* for the Pharmacy Training Module and Knowledge Assessment
- Completed *Pharmacy Enrollment Form*

The Pharmacy Must Agree to Put Procedures in Place to Verify Prior to Dispensing

1. The **Prescriber is certified.**

2. There is a **completed and signed** *Patient-Prescriber Acknowledgement Form* on file for the patient.

3. The *Prescription Authorization Form* is **completed**.

Where Do I Find the REMS Materials?

All JUXTAPID REMS materials can be found on the **JUXTAPID REMS website:**

www.juxtapidREMSprogram.com

REMS materials can also be requested by contacting the **JUXTAPID REMS Coordinating Center at:**

1- 855-898-2743

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Knowledge Assessment

Reference ID: 4930852

Question 1

The goals of the JUXTAPID REMS are:
(check the answer that is the most inclusive)

- ☐ To educate prescribers about the risk of hepatotoxicity with the use of JUXTAPID.
- ☐ To restrict the use of JUXTAPID to only those patients with a clinical and laboratory diagnosis of HoFH.
- ☐ To ensure both prescribers and patients understand the risk of hepatotoxicity with JUXTAPID and the need for monitoring of liver function.
- ☐ All of the above.

Question 1

The goals of the JUXTAPID REMS are:
(check the answer that is the most inclusive)

- ☐ **To educate prescribers about the risk of hepatotoxicity with the use of JUXTAPID.**
- ☐ To restrict the use of JUXTAPID to only those patients with a clinical and laboratory diagnosis of HoFH.
- ☐ To ensure both prescribers and patients understand the risk of hepatotoxicity with JUXTAPID and the need for monitoring of liver function.
- ☐ All of the above.

Partly correct

The education of prescribers about the risk of hepatotoxicity with the use of JUXTAPID is a key part of the JUXTAPID REMS. However, there are other goals too. Review the REMS goals and try again.

Question 1

The goals of the JUXTAPID REMS are:
(check the answer that is the most inclusive)

- ☐ To educate prescribers about the risk of hepatotoxicity with the use of JUXTAPID.
- ☐ **To restrict the use of JUXTAPID to only those patients with a clinical and laboratory diagnosis of HoFH.**
- ☐ To ensure both prescribers and patients understand the risk of hepatotoxicity with JUXTAPID and the need for monitoring of liver function.
- ☐ All of the above.

Partly correct

The restriction of the use of JUXTAPID to patients with a clinical or laboratory diagnosis of HoFH is a key part of the JUXTAPID REMS. However, there are other goals too. Review the REMS goals and try again.

Question 1

The goals of the JUXTAPID REMS are:
(check the answer that is the most inclusive)

- ☐ To educate prescribers about the risk of hepatotoxicity with the use of JUXTAPID.
- ☐ To restrict the use of JUXTAPID to only those patients with a clinical and laboratory diagnosis of HoFH.
- ☐ **To ensure both prescribers and patients understand the risk of hepatotoxicity with JUXTAPID and the need for monitoring of liver function.**
- ☐ All of the above.

Partly correct

The education of both prescribers and patients about the risk of hepatotoxicity with JUXTAPID and the need for monitoring is an important part of the JUXTAPID REMS. However, there are other goals. Review the REMS goals and try again.

Question 1

The goals of the JUXTAPID REMS are:
(check the answer that is the most inclusive)

- ☐ To educate prescribers about the risk of hepatotoxicity with the use of JUXTAPID.
- ☐ To restrict the use of JUXTAPID to only those patients with a clinical and laboratory diagnosis of HoFH.
- ☐ To ensure both prescribers and patients understand the risk of hepatotoxicity with JUXTAPID and the need for monitoring of liver function.
- ☐ **All of the above.**

Correct!

All three are goals of the JUXTAPID REMS.

Click here to advance

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Question 2

Which conditions are appropriate for the use of JUXTAPID?

- ☐ Mixed dyslipidemia.
- ☐ Homozygous familial hypercholesterolemia (HoFH).
- ☐ Heterozygous familial hypercholesterolemia (HeFH).
- ☐ All of the above.

Question 2

Which conditions are appropriate for the use of JUXTAPID?

- ☐ **Mixed dyslipidemia.**
- ☐ Homozygous familial hypercholesterolemia (HoFH).
- ☐ Heterozygous familial hypercholesterolemia (HeFH).
- ☐ All of the above.

Incorrect

JUXTAPID is indicated for use in patients with homozygous familial hypercholesterolemia (HoFH).

Review the Indication for JUXTAPID and try again.

Question 2

Which conditions are appropriate for the use of JUXTAPID?

- ☐ Mixed dyslipidemia.
- ☐ **Homozygous familial hypercholesterolemia (HoFH).**
- ☐ Heterozygous familial hypercholesterolemia (HeFH).
- ☐ All of the above.

Correct!

JUXTAPID is indicated for use 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).

Click here to advance

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Question 2

Which conditions are appropriate for the use of JUXTAPID?

- ☐ Mixed dyslipidemia.
- ☐ Homozygous familial hypercholesterolemia (HoFH).
- ☐ **Heterozygous familial hypercholesterolemia (HeFH).**
- ☐ All of the above.

Incorrect

JUXTAPID is indicated for use in patients with homozygous familial hypercholesterolemia (HoFH).

Review the Indication for JUXTAPID and try again.

Question 2

Which conditions are appropriate for the use of JUXTAPID?

- ☐ Mixed dyslipidemia.
- ☐ Homozygous familial hypercholesterolemia (HoFH).
- ☐ Heterozygous familial hypercholesterolemia (HeFH).
- ☐ **All of the above.**

Incorrect

JUXTAPID is indicated for use in patients with homozygous familial hypercholesterolemia (HoFH).

Review the Indication for JUXTAPID and try again.

Question 3

One of the key points of the REMS is patient education on the risks of hepatotoxicity with JUXTAPID.

- ☐ True
- ☐ False

Question 3

One of the key points of the REMS is patient education on the risks of hepatotoxicity with JUXTAPID.

- ☐ **True**
- ☐ False

Correct!

JUXTAPID is associated with a risk of hepatotoxicity and as a result there is a REMS in place to ensure that its benefits outweigh its risks. The REMS requires patients to participate in the treatment decision process. Knowledge of the risk of hepatotoxicity is expected to allow them to participate effectively in that process.

Click here to advance

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Question 3

One of the key points in the REMS is patient education on the risks of hepatotoxicity with JUXTAPID.

- ☐ True
- ☐ **False**

Incorrect

Review the goals of the JUXTAPID REMS and retry this question.

Question 4

How does a pharmacy become certified in the JUXTAPID REMS?

- ☐ Complete and submit the *Pharmacy Enrollment Form*.
- ☐ Successfully complete the Pharmacy Training Module and Knowledge Assessment and then submit the *Certificate of Completion*.
- ☐ Review the JUXTAPID PI and the *Fact Sheet*.
- ☐ Assign an authorized representative.
- ☐ All of the above.

Question 4

How does a pharmacy become certified in the JUXTAPID REMS?

- ☐ **Complete and submit the *Pharmacy Enrollment Form*.**
- ☐ Successfully complete the Pharmacy Training Module and Knowledge Assessment and then submit the *Certificate of Completion*.
- ☐ Review the JUXTAPID PI and the *Fact Sheet*.
- ☐ Assign an authorized representative.
- ☐ All of the above.

Partly Correct

To become a certified pharmacy in the JUXTAPID REMS you must assign an authorized representative for the pharmacy, who completes the enrollment form, training module and knowledge assessment, and reviews the JUXTAPID PI and *Fact Sheet*. The Authorized Representative must agree on behalf of the pharmacy to put processes and procedures in place and to train the pharmacy staff on the JUXTAPID REMS.

Review the Pharmacy Certification Process and try again.

Question 4

How does a pharmacy become certified in the JUXTAPID REMS?

- ☐ Complete and submit the *Pharmacy Enrollment Form*.
- ☐ **Successfully complete the Pharmacy Training Module and Knowledge Assessment and then submit the *Certificate of Completion*.**
- ☐ Review the JUXTAPID PI and the *Fact Sheet*.
- ☐ Assign an authorized representative.
- ☐ All of the above.

Partly Correct

To become a certified pharmacy in the JUXTAPID REMS you must assign an authorized representative for the pharmacy, who completes the enrollment form, training module and knowledge assessment, and reviews the JUXTAPID PI and *Fact Sheet*. The Authorized Representative must agree on behalf of the pharmacy to put processes and procedures in place and to train the pharmacy staff on the JUXTAPID REMS.

Review the Pharmacy Certification Process and try again.

Question 4

How does a pharmacy become certified in the JUXTAPID REMS?

- ☐ Complete and submit the *Pharmacy Enrollment Form*.
- ☐ Successfully complete the Pharmacy Training Module and Knowledge Assessment and then submit the *Certificate of Completion*.
- ☐ **Review the JUXTAPID PI and the *Fact Sheet*.**
- ☐ Assign an authorized representative.
- ☐ All of the above.

Partly Correct

To become a certified pharmacy in the JUXTAPID REMS you must assign an authorized representative for the pharmacy, who completes the enrollment form, training module and knowledge assessment, and reviews the JUXTAPID PI and *Fact Sheet*. The Authorized Representative must agree on behalf of the pharmacy to put processes and procedures in place and to train the pharmacy staff on the JUXTAPID REMS.

Review the Pharmacy Certification Process and try again.

Question 4

How does a pharmacy become certified in the JUXTAPID REMS?

- ☐ Complete and submit the *Pharmacy Enrollment Form*.
- ☐ Successfully complete the Pharmacy Training Module and Knowledge Assessment and then submit the *Certificate of Completion*.
- ☐ Review the JUXTAPID PI and the *Fact Sheet*.
- ☐ **Assign an authorized representative.**
- ☐ All of the above.

Partly Correct

To become a certified pharmacy in the JUXTAPID REMS you must assign an authorized representative for the pharmacy, who completes the enrollment form, training module and knowledge assessment, and reviews the JUXTAPID PI and *Fact Sheet*. The Authorized Representative must agree on behalf of the pharmacy to put processes and procedures in place and to train the pharmacy staff on the JUXTAPID REMS.

Review the Pharmacy Certification Process and try again.

Question 4

How does a pharmacy become certified in the JUXTAPID REMS?

- ☐ Complete and submit the *Pharmacy Enrollment Form*.
- ☐ Successfully complete the Pharmacy Training Module and Knowledge Assessment and then submit the *Certificate of Completion*.
- ☐ Review the JUXTAPID PI and the *Fact Sheet*.
- ☐ Assign an authorized representative.
- ☐ **All of the above.**

Correct!

To become a certified pharmacy in the JUXTAPID REMS you must assign an authorized representative for the pharmacy, who completes the enrollment form, training module and knowledge assessment, and reviews the JUXTAPID PI and *Fact Sheet*. The Authorized Representative must agree on behalf of the pharmacy to put processes and procedures in place and to train the pharmacy staff on the JUXTAPID REMS.

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Question 5

What is <u>not</u> a requirement of the Authorized Pharmacy Representative?

- ☐ Review the *Fact Sheet*.
- ☐ Oversee the conduct of the JUXTAPID REMS at the pharmacy.
- ☐ Complete the *Patient-Prescriber Acknowledgement Form.*
- ☐ Put processes and procedures in place to ensure the JUXTAPID REMS requirements are met.

Question 5

What is not a requirement of the Authorized Pharmacy Representative?

- ☐ **Review the *Fact Sheet*.**
- ☐ Oversee the conduct of the JUXTAPID REMS at the pharmacy.
- ☐ Complete the *Patient-Prescriber Acknowledgement Form.*
- ☐ Put processes and procedures in place to ensure the JUXTAPID REMS requirements are met.

Incorrect

The Authorized Representative of the pharmacy is required to review the *Fact Sheet* and Prescribing Information, oversee the conduct of the REMS, and to put processes and procedures in place to ensure the REMS requirements are met at the pharmacy.

The Prescriber and the Patient must complete the *Patient-Prescriber Acknowledgement Form*, which must be kept on file for all patients. Review the Authorized Representative Requirements and try again.

Question 5

What is not a requirement of the Authorized Pharmacy Representative?

- ☐ Review the *Fact Sheet*.
- ☐ **Oversee the conduct of the JUXTAPID REMS at the pharmacy.**
- ☐ Complete the *Patient-Prescriber Acknowledgement Form.*
- ☐ Put processes and procedures in place to ensure the JUXTAPID REMS requirements are met.

Incorrect

The Authorized Representative of the pharmacy is required to review the *Fact Sheet* and Prescribing Information, oversee the conduct of the REMS, and to put processes and procedures in place to ensure the REMS requirements are met at the pharmacy.

The Prescriber and the Patient must complete the *Patient-Prescriber Acknowledgement Form*, which must be kept on file for all patients. Review the Authorized Representative Requirements and try again.

Question 5

What is <u>not</u> a requirement of the Authorized Pharmacy Representative?

- ☐ Review the *Fact Sheet*.
- ☐ Oversee the conduct of the JUXTAPID REMS at the Pharmacy.
- ☐ **Complete the *Patient-Prescriber Acknowledgement Form.***
- ☐ Put processes and procedures in place to ensure the JUXTAPID REMS requirements are met.

Correct!

The Prescriber and the Patient must complete the *Patient-Prescriber Acknowledgement Form*, not the pharmacy authorized representative, however, the *Patient-Prescriber Acknowledgement Form* must be kept on file at the pharmacy for all patients.

Click here to advance

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Question 5

What is not a requirement of the Authorized Pharmacy Representative?

- ☐ Review the *Fact Sheet*.
- ☐ Oversee the conduct of the JUXTAPID REMS at the pharmacy.
- ☐ Complete the *Patient-Prescriber Acknowledgement Form.*
- ☐ **Put processes and procedures in place to ensure the JUXTAPID REMS requirements are met.**

Incorrect

The Authorized Representative of the Pharmacy is required to review the *Fact Sheet* and Prescribing Information, oversee the conduct of the REMS, and to put processes and procedures in place to ensure the REMS requirements are met at the pharmacy.

The Prescriber and the Patient must complete the *Patient-Prescriber Acknowledgement Form*, which must be kept on file for all patients. Review the Authorized Representative Requirements and try again.

Congratulations!

You have successfully completed the Pharmacy Training Module and Knowledge Assessment.

To finalize your certification, complete the following next steps:

- **Obtain** the *Certificate of Completion* for the Pharmacy Training Module and Knowledge Assessment

  Click here for a copy of your *Certificate of Completion*

- **Complete and sign** the *Pharmacy Enrollment Form*
- **Submit both** documents to the JUXTAPID REMS Coordinating Center either by fax: 1-855-898-2498 or email: REMS@amrytpharma.com

If all the certification requirements are met, the JUXTAPID REMS Coordinating Center will confirm you are certified as a pharmacy in the JUXTAPID REMS.

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Note to Reviewer:

The following slides are the “refresher” slides that are directed to after answering a question incorrectly. These slides are duplicates of the original slide with the exception of the hyperlink back to the question. These slides will not be visible in the training, unless the participant answers the question(s) incorrectly.

JUXTAPID REMS Goals

Redirect from Question 1

The aim of the JUXTAPID REMS is **to mitigate the risk of hepatotoxicity associated with the use of JUXTAPID** by ensuring that**:**

❶ **Prescribers are educated** about:

- the approved indication for JUXTAPID
- the risk of hepatotoxicity associated with the use of JUXTAPID
- the need to monitor patients during treatment with JUXTAPID as per the product labeling

❷ JUXTAPID is **dispensed only to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia** (HoFH)

❸ **Patients are informed about the risk of hepatotoxicity** associated with the use of JUXTAPID and the need for baseline and periodic liver monitoring

To retry Question 1 click here

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Indication

Redirect from Question 2

JUXTAPID is indicated 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).

Limitations of use Related to the REMS:

- The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).

Please see JUXTAPID full Prescribing Information for the limitations to use, and the **BOXED WARNING** on hepatotoxicity as included on www.juxtapidREMSprogram.com

To retry Question 2
click here

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JUXTAPID REMS Goals

Redirect from Question 3

The aim of the JUXTAPID REMS is **to mitigate the risk of hepatotoxicity associated with the use of JUXTAPID** by ensuring that**:**

❶ **Prescribers are educated** about:

- the approved indication for JUXTAPID
- the risk of hepatotoxicity associated with the use of JUXTAPID
- the need to monitor patients during treatment with JUXTAPID as per the product labeling

❷ JUXTAPID is **dispensed only to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia** (HoFH)

❸ **Patients are informed about the risk of hepatotoxicity** associated with the use of JUXTAPID and the need for baseline and periodic liver monitoring

To retry Question 3 click here

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Pharmacy Certification Process

Redirect from Question 4

The Authorized Representative must:

❶ **Review** the:

- JUXTAPID Prescribing Information (PI)
- *Fact Sheet*

❷ **Complete** the:

- Pharmacy Training Module and Knowledge Assessment

❸ **Agree** to:

- Train all applicable pharmacy staff on the JUXTAPID REMS requirements
- Implement processes and procedures to ensure that the requirements of the REMS are met
- Be audited
- Provide all prescription records to Amryt

❹ **Submit** to the REMS Coordinating Center the:

- *Certificate of Completion* for the Pharmacy Training Module and Knowledge Assessment
- Completed *Pharmacy Enrollment Form*

To retry Question 4 click here

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Redirect from Question 5

Authorized Representative Requirements

For a pharmacy to be certified in the JUXTAPID REMS, the pharmacy must designate an Authorized Representative (AR).

The Authorized Representative is required to:

- **Complete** the Pharmacy Training Module and Knowledge Assessment
- **Oversee** the conduct of the JUXTAPID REMS at the pharmacy
- **Agree** to put processes in place, and to **train** applicable pharmacy staff on the JUXTAPID REMS requirements

The pharmacy must confirm the name of the Authorized Representative every year, and advise the REMS Coordinating Center promptly of any change in the AR. If the AR changes, the pharmacy must recertify within 30 days.

To retry Question 5
click here

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AMRYT PHARMA

Reference ID: 4930852

What is the JUXTAPID Risk Evaluation and Mitigation Strategy (REMS)?

Due to the risk of hepatotoxicity, JUXTAPID is only available through a restricted distribution program required by the US Food and Drug Administration called the JUXTAPID REMS.

The goal of the JUXTAPID REMS is to mitigate the risk of hepatotoxicity associated with the use of JUXTAPID by ensuring that:

1. Prescribers are educated about the approved indication for JUXTAPID, the risk of hepatotoxicity associated with the use of JUXTAPID, and the need to monitor patients during treatment with JUXTAPID as per product labeling
2. JUXTAPID is dispensed only to patients with a clinical or laboratory diagnosis consistent with HoFH
3. Patients are informed about the risk of hepatotoxicity associated with the use of JUXTAPID and the need for baseline and periodic liver monitoring

JUXTAPID REMS Requirements

- Certification of prescribers of JUXTAPID
- Patient counseling
- Certification of pharmacies to dispense JUXTAPID
- A valid Prescription Authorization Form signed by a certified prescriber
- A completed Patient-Prescriber Acknowledgement Form signed by the patient and a certified prescriber must be on file

Because of the risk of hepatotoxicity with the use of JUXTAPID, prescribers are recommended to monitor liver function as described in the Prescribing Information.

Please see accompanying full Prescribing Information for JUXTAPID, including BOXED WARNING for hepatotoxicity.

Prescriber Requirements

Only certified healthcare providers can prescribe JUXTAPID. To become certified, prescribers must:

1. **Review** the Prescribing Information and this Fact Sheet
2. **Complete** the online Prescriber Training Module and the Prescriber Enrollment Form.
   Submit the Prescriber Enrollment Form and the Certificate of Completion for the Prescriber Training Module to the JUXTAPID REMS Coordinating Center by fax: **1-855-898-2498** or email: **REMS@amrytpharma.com**
3. **Agree**
   - To counsel each patient on the JUXTAPID REMS including the indication for use, the risk of hepatotoxicity and the need for monitoring using the Patient Guide
   - To complete a Patient-Prescriber Acknowledgement Form with each patient
   - To submit a Prescription Authorization Form for **each** prescription to the JUXTAPID REMS
   - To perform routine liver monitoring for each patient:
     - prior to initiating therapy
     - **monthly** during the first year of treatment
     - every three months thereafter, and before any dose adjustment

Pharmacy Requirements

Only certified pharmacies can purchase, dispense, and distribute JUXTAPID. To become certified, pharmacies must select a representative who will complete the certification process:

1. **Review** the Prescribing Information, and this Fact Sheet
2. **Complete** the online Pharmacy Training Module and the Pharmacy Enrollment Form.
   Submit the Pharmacy Enrollment Form and the Certificate of Completion for the Pharmacy Training Module to the JUXTAPID REMS Coordinating Center by fax: **1-855-898-2498** or email: **REMS@amrytpharma.com**
3. **Agree** to train all relevant pharmacy staff, to implement processes and procedures to ensure prescriber certification, to be audited if necessary, and to provide prescription data

Visit **www.juxtapidREMSprogram.com** to access training materials and begin certification.

Reference ID: 4930852

The JUXTAPID® Risk Evaluation and Mitigation Strategy (REMS)

A REMS is a strategy to manage known or potential serious risks associated with a drug and is required by the US Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

The JUXTAPID REMS was developed with the FDA.

The purpose of the JUXTAPID REMS is to mitigate the risk of hepatotoxicity associated with the use of JUXTAPID by ensuring that:

1. Prescribers are educated about:
   - The approved indication for JUXTAPID
   - The risk of hepatotoxicity associated with the use of JUXTAPID
   - The need to monitor patients during treatment with JUXTAPID, as per the product labeling
2. JUXTAPID is dispensed only to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia
3. Patients are informed about the risk of hepatotoxicity associated with the use of JUXTAPID and the need for baseline and periodic liver monitoring

Prescriber

All prescribers of JUXTAPID must become certified in the JUXTAPID REMS.

The 3-step process for Prescriber Certification is outlined below:

1. Review the JUXTAPID Prescribing Information and the Fact Sheet
2. Complete the online Prescriber Training Module and Prescriber Enrollment Form
3. Agree to counsel each patient using the Patient Guide, and to complete a Patient-Prescriber Acknowledgement Form with each patient

GO TO PRESCRIBER CERTIFICATION

INDICATIONS AND USAGE

Homozygous Familial Hypercholesterolemia

JUXTAPID is indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDLC), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

Limitations of Use

- The safety and effectiveness of JUXTAPID have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).
- The effect of JUXTAPID on cardiovascular morbidity and mortality has not been determined.

For additional information about JUXTAPID REMS, please call 1-85-JUXTAPID (1-855-898-2743)

Prescriber certification

Begin Now

To prescribe JUXTAPID®, healthcare professionals must be certified in the JUXTAPID Risk Evaluation and Mitigation Strategy (REMS).

Prescriber certification is a 3-step process:

1. Review

the Prescribing Information and Fact Sheet

2. Complete

- the online Prescriber Training Module, including Knowledge Assessment
- the Prescriber Enrollment Form
- Send the Prescriber Enrollment Form to the JUXTAPID REMS Coordinating Center by fax: 1-855-898-2498 or email: REMS@amrytpharma.com

3. Agree

to counsel each new patient on the risk of hepatotoxicity and the need for baseline and periodic monitoring using the Patient Guide. Complete a Patient-Prescriber Acknowledgement Form with each patient

How do I obtain Juxtapid for my patient?

Am I certified in the Juxtapid REMS?

No

I SHOULD:

- Review the JUXTAPID Prescribing Information and the Fact Sheet
- Complete the online Prescriber Training Module including the Knowledge Assessment
- Upon completion, download the Training Completion document provided at the end of the training module
- Complete the Prescriber Enrollment Form:
  - You may fill in the form online, then print it;
  - or print it, then manually input the data into all fields.
  - Sign the completed form and submit it with the Training Completion document
    - by faxing both documents to **1-855-898-2498**
    - or emailing both documents to REMS@amrytpharma.com
- You will be notified by the REMS call center of your certification within one business day.
- Once certified, proceed as per the "**yes**" options.

Yes

IS THIS A NEW PATIENT?

I SHOULD:

- Counsel the new patient on the risk of hepatotoxicity and the need for baseline and periodic monitoring using the Patient Guide
- Complete and sign a Patient-Prescriber Acknowledgement Form with the patient to enroll them into the Juxtapid REMS
- Complete and sign a Prescription Authorization Form
- Submit both forms to the Juxtapid REMS
  - by faxing both documents to **1-855-898-2498**
  - or emailing both documents to REMS@amrytpharma.com

IS THIS AN ESTABLISHED PATIENT WHO IS ALREADY ENROLLED IN THE JUXTAPID REMS?

I SHOULD:

- Complete and sign a Prescription Authorization Form each time and submit it to the Juxtapid REMS call center
  - by faxing to **1-855-898-2498**
  - or emailing to REMS@amrytpharma.com

Additional Program Resources

- Prescription Authorization Form
- Patient Guide and Patient Prescriber Acknowledgement Form

For additional information about JUXTAPID REMS, please call 1-85-JUXTAPID (1-855-898-2743)

Pharmacy certification

Prior to beginning certification process, please contact the JUXTAPID REMS, 1-85-JUXTAPID (1-855-898-2743) for consideration.

Begin Now

To purchase and dispense JUXTAPID® all pharmacies must be certified in the JUXTAPID Risk Evaluation and Mitigation Strategy (REMS). The pharmacy must identify an **Authorized Representative** to be certified in the JUXTAPID REMS. The pharmacy must be recertified within 30 days if the authorized person changes.

Pharmacy certification is a 3-step process:

1. Review

the Prescribing Information and Fact Sheet

2. Complete

- the online Pharmacy Training Module, including Knowledge Assessment
- the Pharmacy Enrollment Form
- Send the Pharmacy Enrollment Form and the Certificate of Completion for the Pharmacy Training Module to the JUXTAPID REMS Coordinating Center by fax: 1-855-898-2498 or email: REMS@amrytpharma.com

3. Agree

to train all relevant pharmacy staff, to implement processes and procedures to ensure prescriber certification, to be audited if necessary, and to provide prescription data

For additional information about JUXTAPID REMS, please call 1-85-JUXTAPID (1-855-898-2743)

Patient Education

Risk of Liver Problems

- JUXTAPID can cause liver problems such as increased liver enzymes or increased fat in the liver.
- Because of the risk of liver problems, JUXTAPID should only be taken by people with homozygous familial hypercholesterolemia (HoFH).
- Your doctor will order blood tests to check your liver:
  - before you start taking JUXTAPID
  - if your dose is increased
  - monthly during the first year
  - every 3 months after the first year

The JUXTAPID REMS

Because of the risk of liver damage with JUXTAPID, the Food and Drug Administration (FDA) has required a special program called a Risk Evaluation and Mitigation Strategy (REMS).

As part of REMS your prescriber will discuss the risks of JUXTAPID with you, and review the Patient Guide to the REMS.

After reviewing the JUXTAPID REMS information, both you and your healthcare provider will be asked to complete a form acknowledging that you understand the risks with the use of JUXTAPID.

For additional information about JUXTAPID REMS, please call 1-85-JUXTAPID (1-855-898-2743)

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
02/01/2022 10:25:47 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203858Orig1s023

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	203858
Supplement Number, Date Received	Supplement 23 received August 5, 2021 (sequence 388) and amended January 24 (sequence 0394), January 27, 2022 (sequence 0395)
Action Date	February 01, 2022
OSE RCM #	2021-1576
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D., Risk Management Analyst Kate Heinrich Oswell, MA, Health Communications Analyst Victoria Sammarco, Pharm.D., M.B.A., Risk Assessment Analyst
Team Leader	Naomi Boston, Pharm.D., Risk Management Team Leader Shelly Harris, ScD, REMS Assessment Team Leader
Associate Director for REMS Design and Evaluation	Laura Zendel, Pharm.D., BCPS
Review Completion Date	January 31, 2022
Subject	Review of proposed Major REMS Modification
Established Name	Lomitapide Mesylate
Trade Name	Juxtapid
Name of Applicant	Amryt Pharmaceuticals DAC
Therapeutic Class	Cholesterol-lowering agent
Formulation(s)	5 mg, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg Capsules

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EXECUTIVE SUMMARY

This is a review of the proposed modification to the Risk Evaluation and Mitigation Strategy (REMS) for Juxtapid (lomitapide mesylate), NDA 203858, submitted by Amryt Pharmaceuticals DAC's (Applicant) on August 5, 2021 and amended on January 24 and January 27, 2022.

The REMS for Juxtapid was originally approved on December 21, 2012 to ensure that the benefits of Juxtapid outweigh the risk of hepatotoxicity. A major REMS modification was approved on January 3, 2017 requiring recertification of all prescribers, completion of a new Prescription Authorization Form (PAF) for all patients, and counseling of all patients on the hepatic risk of Juxtapid and the REMS program requirements, as evidenced by the completion of the Patient Prescriber Acknowledgement Form (PPAF). The REMS was most recently modified on May 27, 2021 as a minor modification to add online fillable fields in the REMS forms and modified the design and formatting of the REMS materials.

The Juxtapid REMS is comprised of elements to assure safe use (ETASU) (healthcare providers who prescribe Juxtapid must be certified, pharmacies that dispense Juxtapid must be certified, Juxtapid must only be dispensed to patients with evidence or other documentation of safe-use conditions), an implementation system, and a timetable for submission of assessments.

Amryt Pharmaceuticals DAC's proposed modification to the REMS consist(s) of:

1) updating the format of the REMS document per the *Draft Format and Content of a REMS Document- Guidance for Industry, October 2017*
2) proposed 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,
3) the need to mirror attestation language updates from forms into the REMS Supporting document
4) obsolescence of old REMS materials (2017 Stakeholder letters) and
5) 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, and the REMS supporting document.

The Division of Risk Management (DRM) finds the proposed modification to the Juxtapid REMS as submitted on August 5, 2021 and amended on January 24 and January 27, 2022 to be acceptable and recommends approval of the REMS Modification. The Timetable for submission of assessments to the REMS is revised in this modification; the Applicant must submit REMS Assessments every two years beginning with the 11-year REMS assessment due 12/21/2023. There are minor editorial changes to the Assessment Plan. The revised Assessment Plan will be included in the Approval Letter.

1. Introduction

This review evaluates Amryt Pharmaceuticals DAC's (Applicant) proposed Risk Evaluation and Mitigation Strategy (REMS) modification for Juxtapid (lomitapide mesylate), NDA 203858, initially received August 5, 2021 and amended on January 24 and January 27, 2022.

This modification addresses the following: 1) updating the format of the REMS document per the *Draft Format and Content of a REMS Document- Guidance for Industry, October 2017*[a], 2) proposed 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, 3) the need to mirror attestation language updates from the REMS forms into REMS Supporting document 4) obsolescence of old REMS materials (2017 Stakeholder letters) and 5) 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, and the REMS supporting document.

2. Background

2.1. Product Information

Lomitapide is a microsomal triglyceride transfer protein inhibitor indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including low-density lipoprotein (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). The recommended dose of lomitapide is to initiate treatment at 5 mg once daily. Titrate dose based on acceptable safety/tolerability: increase to 10 mg daily after at least 2 weeks; and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and up to the maximum recommended dose of 60 mg daily.

Juxtapid was originally approved with a REMS on December 21, 2012 to ensure that the benefits of Juxtapid outweigh the risk of hepatotoxicity. A major REMS modification was approved on January 3, 2017 requiring recertification of all prescribers, completion of a new Prescription Authorization Form (PAF) for all patients, and counseling of all patients on the hepatic risk of Juxtapid and the REMS program requirements, as evidenced by the completion of the Patient Prescriber Acknowledgement Form (PPAF). The REMS was most recently modified on May 27, 2021 as a minor modification to add online fillable fields in REMS forms and modified the design and formatting of the REMS materials.

The Juxtapid REMS is comprised of ETASU (healthcare providers who prescribe Juxtapid must be certified, pharmacies that dispense Juxtapid must be certified, Juxtapid must only be dispensed to patients with evidence or other documentation of safe-use conditions), an implementation system, and a timetable for submission of assessments.

The goal of the Juxtapid REMS is to mitigate the risk of hepatotoxicity associated with the use of Juxtapid by ensuring that:

- Prescribers are educated about the approved indication for Juxtapid, the risk of hepatotoxicity associated with the use of Juxtapid; and the need to monitor patients during treatment with Juxtapid as per product labeling.

- Juxtapid is dispensed only to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia (HoFH).

[a] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

- Patients are informed about the risk of hepatotoxicity associated with the use of Juxtapid and the need for baseline and periodic monitoring.

2.2. Regulatory History

The following is an overview of the regulatory history that pertains to S-023, received on August 5, 2021 and amended on January 24 and January 27, 2022.

- 08/05/2021: NDA 203858/S-023 received a proposed major REMS modification. Proposed changes impact the REMS Document, REMS Supporting Document, Prescriber Enrollment Form, Prescriber Training Module and Knowledge Assessment, Fact Sheet, Patient Guide and PPAF, PAF, Pharmacy Enrollment Form, Pharmacy Training Module and Knowledge Assessment, Program Website, Dear Healthcare Provider Letter and Dear Pharmacist Letter.
- 01/14/2022: The Agency issued an information request (IR) to the Applicant including edits to the REMS document, REMS materials and REMS Supporting Document.[1]
- 01/24/2022: The Applicant submitted a REMS amendment in response to the IR sent on 01/14/2022.
- 01/26/2022: The Agency issued an information request (IR) to the Applicant including edits to the REMS document, and REMS Supporting Document.[2]
- 01/27/2022: The Applicant submitted a REMS amendment in response to the IR sent on 01/26/2022 as a full REMS submission consisting of the REMS document, REMS supporting document and the REMS appended materials.

3. Review of Proposed REMS Modifications

3.1. REMS Goals

The Applicant did not propose changes to the REMS Goal.

3.2. REMS Document

The Applicant submitted a revised REMS Document incorporating the changes requested by the Agency in the comments issued January 14[1] and 26[2], 2022.

Reviewer Comment: *The REMS Document is acceptable, and no further changes are necessary.*

3.3. REMS Requirements

3.3.1. Addition or Removal of ETASU

The Applicant did not propose changes to the ETASU.

3.3.2. REMS Participant Requirements and Materials

3.3.2.1. Healthcare Provider

Prescriber Enrollment Form

The Applicant submitted an updated *Prescriber Enrollment Form* incorporating the changes requested by the Agency in the comments issued January 14, 2022.

On January 24, 2022, the Applicant amended the application to (b) (4) (b) (4) and this form is adjusted to direct the continued use of fax and email methods for submission of forms.

Reviewer Comment: *The changes are acceptable, and no further changes are necessary.*

3.3.2.2. Patients

Patient Guide and Prescriber-Patient Acknowledgement Form

The Applicant submitted an updated *Patient Guide and Prescriber-Patient Acknowledgement Form* incorporating the changes requested by the Agency in the comments issued January 14, 2022.

Reviewer Comment: *The changes are acceptable, and no further changes are necessary.*

Prescription Authorization Form

The Applicant submitted an updated *Prescription Authorization Form* incorporating the changes requested by the Agency in the comments issued January 14, 2022.

Reviewer Comment: *The changes are acceptable, and no further changes are necessary.*

3.3.2.3. Pharmacies that dispense

Pharmacy Enrollment Form

The Applicant submitted an updated *Pharmacy Enrollment Form* incorporating the changes requested by the Agency in the comments issued January 14, 2022.

On January 24, 2022, the Applicant amended the application to (b) (4) (b) (4) and this form is adjusted to direct the continued use of fax and email methods for submission of forms.

Reviewer Comment: *The changes are acceptable, and no further changes are necessary.*

3.3.3. REMS Applicant Requirements and Materials

3.3.3.1. Training

Prescriber & Pharmacy Training Module and Knowledge Assessment

The Applicant submitted the updated *Prescriber and Pharmacy Training Module and Knowledge Assessment* incorporating the changes requested by the Agency in the comments issued January 14, 2022.

Reviewer Comment: *The changes are acceptable, and no further changes are necessary.*

3.3.3.2. Communication

Fact Sheet

The Applicant submitted an updated *Fact Sheet* incorporating the changes requested by the Agency in the comments issued January 14, 2022.

Reviewer Comment: *The changes are acceptable, and no further changes are necessary.*

3.3.3.3. Operations

Website Screenshots

The Applicant submitted updated REMS Website Screenshots incorporating the changes requested by the Agency in the comments issued January 14, 2022.

On January 24, 2022, the Applicant amended the application to (b) (4) Materials are adjusted to direct the continued use of fax and email methods for submission of stakeholder forms. The Applicant also added a screenshot with further "How do I" instructions for prescribers to submit forms.

Reviewer Comment: *The changes are acceptable, and no further changes are necessary.*

3.4. REMS Assessment Timetable

The Applicant submitted a revised REMS Document incorporating the changes in regards to submission of assessments of the REMS requested by the Agency in the comments issued January 14, 2022.

Reviewer Comment: *The proposed changes to the REMS assessment timetable are acceptable, and no further changes are necessary.*

4. Supporting Document

The Applicant submitted an updated Supporting Document incorporating the changes requested by the Agency in the comments issued January 14[1] and 26[2], 2022.

Reviewer Comment: *The changes are acceptable, and no further changes are necessary.*

5. REMS Assessment Plan

Comments on the assessment plan were sent to the Applicant on January 19, 2022 and January 26, 2022. The Applicant submitted an amended supporting document that incorporated the Agency's edits to the assessment plan on January 27, 2022. The updated REMS Assessment Plan will be included in the REMS Modification Approval letter and includes 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. REMS Call Center, 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.

Reviewer Comment: *The changes are acceptable, and no further changes are necessary.*

6. Discussion

Amryt Pharmaceuticals DAC proposed a REMS modification for Juxtapid, NDA 203858, initially received August 5, 2021. These modifications included the insertion of the word "liver" into the "regular monitoring" or "periodic monitoring" text per QR recommendations to reinforce liver monitoring requirements in REMS materials, revisions to emphasize the "monthly" first year liver monitoring requirement, addition of electronic signature capture to the program coordinating center's capabilities, addition of instructions to complete enrollment online for both Prescribers and Pharmacies, and addition of instructions to 'email submission' as a new capability for the *Prescription Authorization Form.* Since the dissemination requirements of communication materials such as "*Dear Pharmacist Letter*" and "*Dear Healthcare Provider Letter*" have been completed in 2017 and are obsolete at this time, the Applicant proposed to remove reference to these documents in the REMS document as they are historical in nature only.

The Agency requested the Applicant to submit the website screenshots that appear when stakeholders go through the online certification process. The Applicant submitted a REMS Amendment on January 24 and 27, 2022 in response to the Agency's comments that were sent on January 14 and 26, 2022. The Applicant amended the application to (b) (4) Materials were adjusted to direct stakeholders to use fax and email methods for submission of stakeholder forms resulting in no change to the enrollment process for stakeholders. The Applicant also added a screenshot with further "How do

l" instructions for prescribers to submit forms. The Applicant appropriately incorporated the Agency's previous comments on the proposed modification into the REMS Document and appended materials. The Agency agrees that these changes are acceptable. The REMS assessment timetable is revised; the Applicant must submit REMS Assessments every two years beginning with the 11-year REMS assessment due 12/21/2023. In addition, the REMS Assessment Plan, as summarized in the REMS Supporting Document, has been revised. The Applicant did not propose any further changes to the REMS materials.

7. Conclusions and Recommendations

DRM finds the REMS for Juxtapid (lomitapide mesylate), (NDA 203858), as submitted on January 27, 2022 to be acceptable. DRM recommends approval of the REMS Modification for Juxtapid (lomitapide mesylate), NDA 203858, submitted August 5, 2021 and last amended on January 27, 2022, and appended to this review. The REMS assessment timetable is revised; the Applicant must submit REMS Assessments every two years beginning with the 11-year REMS assessment due 12/21/2023. The REMS Assessment Plan, as summarized in the REMS Supporting Document, has been revised and will be included in the REMS Modification Approval letter. Refer to Section 5 of this review for the assessment language to be included in the REMS Modification Approval letter.

8. Appendix

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

9. References

[1] REMS Major Modification Information Request memorandum for Juxtapid (lomitapide mesylate), NDA 203858, dated January 14, 2022. [Reference ID: 4920348]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed January 25, 2022.

[2] REMS Major Modification Information Request memorandum for Juxtapid (lomitapide mesylate), NDA 203858, dated January 26, 2022. [Reference ID: 4927320]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed January 26, 2022.

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KATE H OSWELL
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VICTORIA C SAMMARCO
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Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	203858
Supplement Number, Date Received	Supplement 23 received August 5, 2021 (sequence 388)
Action Date	February 1, 2022
OSE RCM #	2021-1576
Reviewer Name	Victoria Sammarco, PharmD, MBA
Team Leader	Shelly Harris, ScD
Deputy Division Director	Doris Auth, PharmD
Review Completion Date	January 18, 2022
Subject	Review of proposed Major REMS Modification
Established Name	Lomitapide
Trade Name	Juxtapid
Name of Applicant	Amryt Pharmaceuticals
Therapeutic Class	Microsomal triglyceride transfer protein inhibitor
Formulation	5 mg, 10 mg, 20 mg, 30 mg, 40 mg oral capsules

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1. Introduction

This review is in reference to the proposed modification to the risk evaluation and mitigation strategy (REMS) for Juxtapid (lomitapide, NDA 203858) submitted by Amryt Pharmaceuticals on August 5, 2021 (S-023). The Applicant's REMS assessment plan is the subject of this review. No changes to the assessment plan were proposed with this modification by the Applicant, however the Agency requires revisions.

2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- August 5, 2021: REMS Supplement 23 received
- January 14, 2022: Comments from review of major modifications sent

3. REMS Assessment Plan

The Applicant did not propose changes to the REMS assessment plan, as summarized in the REMS Supporting Document, with this modification. The assessment plan, last updated on July 24, 2020, includes metrics under the following categories: Program Implementation and Operations, Knowledge, and Health Outcomes and/or Surrogates of Health Outcomes.

Reviewer's Comment: The assessment plan requires revision of metrics to better capture data needed for the assessment, as well as the addition of metrics to account for new REMS operational changes. Some metrics were also added under safe use conditions to gauge the use of updated materials from this modification since recertification in the REMS is not required after this modification. The following revisions were indicated:

- updated terminology from (b) (4) to healthcare provider as appropriate throughout the assessment plan
- (b) (4)
- clarification of healthcare provider attributes for stratification
- an additional metric added to describe mechanism of stakeholders enrollment in the REMS (e.g., email, fax, or (b) (4))
- metrics added for the number of active REMS stakeholders (i.e., healthcare providers who prescribed or pharmacies that dispensed within the assessment reporting period)
- requirement of audit and noncompliance plans and instruments to be submitted with each assessment report. If there is a question regarding the audit methodology or compliance actions following a non-compliance event, the plans should be easily accessible with each report for further review if needed.
- (b) (4)
- a safe use condition category added that includes metrics on the proportion of prescriptions affiliated with updated materials from this modification to understand the penetration of the updated materials

- removal of reference to [redacted] (b) (4)

The revised REMS Assessment Plan can be found in the appendix.

4. REMS Timetable of Submission of Assessments

The timetable for submission of REMS assessments must be revised and the next REMS assessment will be due December 21, 2023. Since there is no requirement of recertification in the REMS, a longer interval is required before the next assessment to allow material dissemination to stakeholders, particularly so that healthcare providers have the opportunity to utilize the updated training materials and *Prescription Authorization Form*.

The REMS should be assessed every other year thereafter due to the small patient and healthcare provider populations that utilize Juxtapid.

5. Conclusions and Recommendations

Send the comments in Section 6 and the revised assessment plan in the appendix to the Applicant in an Information Request and instruct the Applicant to submit a REMS amendment within five business days.

The timetable for submission of assessments of the REMS must be revised and the next REMS assessment will be due on December 21, 2023.

The REMS Assessment Plan, as summarized in the REMS Supporting Document, must be revised to be consistent with the REMS Modification for Juxtapid.

6. Comments to the Applicant

We have the following comments on the proposed REMS modification, submitted on August 5, 2021. Review of the REMS proposal is ongoing; these comments should not be considered final. Submit a REMS amendment within five business days that addresses these comments. Include in your response an updated REMS supporting document containing your assessment plan; include a Word tracked changes version, a Word clean version, and a .pdf version.

General Comment

1. We have determined the next REMS assessment should be submitted on December 21, 2023 and every other year thereafter.

The revised Juxtapid REMS Assessment Plan includes but is not limited to the following changes:

1. Update terminology from [redacted] (b) (4) to healthcare provider as appropriate throughout the assessment plan.
2. [redacted] (b) (4)
3. Change healthcare provider attributes for stratification to mirror those listed on REMS materials.
4. Add metrics to describe stakeholders' method of enrollment in the REMS (e.g., through email, fax, or [redacted] (b) (4)) to capture stakeholder utilization of the recently added website and electronic capabilities.

5. Add metrics to capture the number of active REMS stakeholders (healthcare providers who prescribed, pharmacies that dispensed, and wholesalers/distributors that shipped Juxtapid within the assessment reporting period) to provide a clear picture of the current use of Juxtapid.
6. Submit audit and noncompliance plans and instruments with each assessment report for reference.
7. [redacted].
8. Add a Safe Use Condition category and include metrics to capture the proportion of prescriptions affiliated with updated materials from this modification to capture the usage of these updated REMS materials.
9. Remove references to [redacted].

7. Appendix

7.1. Juxtapid REMS Assessment Plan [Revised]

Program Implementation and Operations (per reporting period and cumulatively)

1. REMS Enrollment Statistics
   a. [redacted] Healthcare Provider Certification
      i. The number of newly certified healthcare [redacted] providers [redacted] and the number of active healthcare providers (prescribed at least once during the reporting period) in the Juxtapid REMS Program [redacted] stratified by [redacted] healthcare provider [redacted] 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 [redacted] type (e.g. individual practice group practice hospital university (academic) center) and geographic [redacted] region (as defined by US Census).
      ii. Method of certification (i.e. [redacted], through fax, or email).
   b. Pharmacy Enrollment
      i. The number of pharmacies that were newly certified [redacted] nd 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. [redacted] 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:

Commented [A1]: To Applicant: edited to align with preferred language

Commented [A2]: To Applicant: metric no longer needed

Commented [A3]: To Applicant: added to clarify active provider data

Commented [A4]: To Applicant: edited to clarify stratification by provider type and specialty

Commented [A5]: To Applicant: added to monitor ways in which providers are certifying in the REMS in light of the recent additional options to certify

Commented [A6]: To Applicant: metric no longer needed

Commented [A7]: To Applicant: added to clarify active dispensing pharmacy data

Commented [A8]: To Applicant: added to monitor ways in which providers are certifying in the REMS in light of the recent additional options to certify

Commented [A9]: To Applicant: added to clarify active distributor data

Commented [A10]: To Applicant: audit and noncompliance plans will be reviewed by the Agency and feedback may be given to ensure audit and compliance methodology support the REMS requirements

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. (b) (4), certified pharmacies, wholesalers/distributors, or other entities) including any auditing surveys or protocols used

iv. Report of audit findings for each stakeholder
- The number of audits expected, and the number of audits conducted
- The number and types of deficiencies noted for each group of audited stakeholders
- For those with deficiencies noted report the number that successfully completed a corrective and preventive action (CAPA) within one month of audit
- 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.

(b) (4)

Commented [A11]: To Applicant: (b) (4)

5. 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 (b) (4) 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 4 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)

1. 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
2. Survey to Evaluate Patient Knowledge of:
   a. The risk of hepatoxicity
   b. The need for baseline and periodic monitoring
3. Specification of measures that would be taken to increase awareness if (b) (4) surveys indicate that (b) (4) awareness of the risks associated to Juxtapid is not adequate.

Safe Use Conditions (per reporting period and cumulatively)

1. 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

2. 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)

1. 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 (b) (4) including outcome.

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.

Commented [A12]: To Applicant: new metric to measure the extent of use of the new REMS PAF

Commented [A13]: To Applicant: new metric to measure the extent of use of the new REMS PPAF

Commented [A14]: To Applicant: Remove reference to (b) (4)

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/s/

VICTORIA C SAMMARCO
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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	203858
Supplement Number, Date Received	Supplement 23 received August 5, 2021 (sequence 388)
Action Date	February 01, 2022
OSE RCM #	2021-1576
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D., Risk Management Analyst Kate Heinrich Oswell, MA, Health Communications Analyst Victoria Sammarco, Pharm.D., M.B.A., Risk Assessment Analyst
Team Leader	Naomi Boston, Pharm.D., Risk Management Team Leader
Associate Director for REMS Design and Evaluation	Laura Zendel, Pharm.D.
Review Completion Date	January 11, 2022
Subject	Review of proposed Major REMS Modification
Established Name	Lomitapide Mesylate
Trade Name	Juxtapid
Name of Applicant	Amryt Pharmaceuticals DAC
Therapeutic Class	Cholesterol-lowering agent
Formulation(s)	5 mg, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg Capsules

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EXECUTIVE SUMMARY

This is a review of the proposed modification to the Risk Evaluation and Mitigation Strategy (REMS) for Juxtapid (lomitapide mesylate), NDA 203858, submitted by Amryt Pharmaceuticals DAC (Applicant) on August 5, 2021.

The REMS for Juxtapid was originally approved on December 21, 2012 to ensure that the benefits of Juxtapid outweigh the risk of hepatotoxicity. A major REMS modification was approved on January 3, 2017 requiring, recertification of all prescribers, completion of a new Prescription Authorization Form (PAF) for all patients, and counseling of all patients on the hepatic risk of Juxtapid and the REMS program requirements, as evidenced by the completion of the Patient Prescriber Acknowledgement Form (PPAF), and was most recently modified on May 27, 2021 as minor modification to add online fillable fields in REMS forms and modified the design and formatting of the REMS materials.

The Juxtapid REMS is comprised of elements to assure safe use (ETASU) (healthcare providers who prescribe Juxtapid must be certified, pharmacies that dispense Juxtapid must be certified, Juxtapid must only be dispensed to patients with evidence or other documentation of safe-use conditions), an implementation system, and a timetable for submission of assessments.

Amryt Pharmaceuticals DAC's proposed modification to the REMS consist(s) of:

1) updating the format of the REMS document per the *Format and Content of a REMS Document-Guidance for Industry,*
2) proposed 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,
3) (b) (4)
4) mirror attestation language updates from forms into REMS Supporting document
5) obsolescence of old materials (2017 Stakeholder letters) and
6) 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, and the REMS supporting document.

The Division of Risk Management (DRM) does not find the Juxtapid REMS as submitted on August 5, 2021 to be acceptable. Further changes to the REMS Document, appended materials, and REMS Supporting Document are required for the modification to be acceptable.

1. Introduction

This review evaluates Amryt Pharmaceuticals DAC's (Applicant) proposed Risk Evaluation and Mitigation Strategy (REMS) modification for Juxtapid (lomitapide mesylate), NDA 203858, initially received August 5, 2021.

This modification addresses the following: 1) updating the format of the REMS document per the *Format and Content of a REMS Document- Guidance for Industry*[a], 2) proposed 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, 3) (b) (4) 4) mirror attestation language updates from forms into REMS Supporting document 5) obsolescence of old materials (2017 Stakeholder letters) and 6) 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, and the REMS supporting document.

2. Background

2.1. Product Information

Lomitapide is a microsomal triglyceride transfer protein inhibitor indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including low-density lipoprotein (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). The recommended dose of lomitapide is to initiate treatment at 5 mg once daily. Titrate dose based on acceptable safety/tolerability: increase to 10 mg daily after at least 2 weeks; and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and up to the maximum recommended dose of 60 mg daily.

Juxtapid was originally approved with a REMS on December 21, 2012 to ensure that the benefits of Juxtapid outweigh the risk of hepatotoxicity. A major REMS modification was approved on January 3, 2017 requiring, recertification of all prescribers, completion of a new Prescription Authorization Form (PAF) for all patients, and counseling of all patients on the hepatic risk of Juxtapid and the REMS program requirements, as evidenced by the completion of the Patient Prescriber Acknowledgement Form (PPAF), and was most recently modified on May 27, 2021 as minor modification to add online fillable fields in REMS forms and modified the design and formatting of the REMS materials.

The Juxtapid REMS is comprised of ETASU (healthcare providers who prescribe Juxtapid must be certified, pharmacies that dispense Juxtapid must be certified, Juxtapid must only be dispensed to patients with evidence or other documentation of safe-use conditions), an implementation system, and a timetable for submission of assessments.

The goal of the Juxtapid REMS is to mitigate the risk of hepatotoxicity associated with the use of Juxtapid by ensuring that:

- Prescribers are educated about the approved indication for Juxtapid, the risk of hepatotoxicity associated with the use of Juxtapid; and the need to monitor patients during treatment with Juxtapid as per product labeling.

[a] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

- Juxtapid is dispensed only to patients with a clinical or laboratory diagnosis consistent with homozygous familial hypercholesterolemia (HoFH).

- Patients are informed about the risk of hepatotoxicity associated with the use of Juxtapid and the need for baseline and periodic monitoring.

2.2. Regulatory History

The following is an overview of the regulatory history that pertains to S-023, received on August 5, 2021.

- 08/05/2021: NDA 203858/S-023 received a proposed major REMS modification. Proposed changes impact the REMS Document, REMS Supporting Document, Prescriber Enrollment Form, Prescriber Training Module and Knowledge Assessment, Fact Sheet, Patient Guide and PPAF, PAF, Pharmacy Enrollment Form, Pharmacy Training Module and Knowledge Assessment, Program Website, Dear Healthcare Provider Letter and Dear Pharmacist Letter.

3. Review of Proposed REMS Modifications

3.1. REMS Goals

The Applicant did not propose changes to the REMS Goal.

3.2. REMS Document

The Applicant submitted a revised REMS Document using the REMS template as described in the Draft Guidance for Industry, *Format and Content of a REMS Document*[a].

Reviewer Comment: *The REMS Document requires further changes to be acceptable. We have revised the document to ensure it accurately reflects the operational aspects of the REMS. Additional revisions are intended to align with instructions and language described in the Draft Guidance for Industry, Format and Content of a REMS Document. A redlined version of the REMS Document is appended to the review and will be provided to the Applicant.*

3.3. REMS Requirements

In general, the Applicant has made editorial revisions on such as added demographic fields to Patient Guide, PPAF and PAF and other editorial revisions related to punctuation, grammar, spelling, defining acronyms, flow, font, simplification, and consistency to REMS appended materials, and the REMS supporting document, and these are acceptable. Other specific changes are outlined below.

3.3.1. Addition or Removal of ETASU

The Applicant did not propose changes to the ETASU.

3.3.2. REMS Participant Requirements and Materials

3.3.2.1. Healthcare Provider

Prescriber Enrollment Form

The Applicant submitted a revised *Prescriber Enrollment Form.* The Applicant added a "Lab Requirements" heading for the three lab bullets in "Hepatotoxicity Risk" under the section of "Prescriber Attestations" per the QR recommendations in order to add prominence to lab requirements. Per QR recommendations, the Applicant has also revised the 2nd sub bullet under "Hepatotoxicity Risk" in regards of the first-year statement to put "monthly" before "prior to each increase in dose" to emphasize the "monthly" first year liver monitoring requirement. The Applicant's proposed change to Attestation (2nd sub bullet under "Hepatotoxicity Risk") is shown below:

> "- During the first year of treatment, liver-related laboratory tests (ALT and AST at a minimum) must be measured monthly or prior to each increase in dose, whichever comes first."

The Applicant has also added an electronic signature capture field to the program coordinating center's capabilities and added instructions to complete enrollment online towards the end of page 2 of *Prescriber Enrollment Form*.

Reviewer Comment: *The addition of online functionality is acceptable. We will recommend that the Applicant replace the current attestations with the revised attestations provided by the FDA. We have better aligned the attestations with the REMS Document and the goals of the REMS. In addition to the review by the DRM, the attestations for the prescriber have been reviewed by the Office of Chief Counsel (OCC). The revisions to these materials include OCC's comments. We have also made edits to simplify the name of the Juxtapid REMS and REMS materials. See redlined version of the Prescriber Enrollment Form, attached.*

3.3.2.2. Patients

Patient Guide and Prescriber-Patient Acknowledgement Form

The Applicant submitted a revised *Patient Guide and Prescriber-Patient Acknowledgement Form.* The Applicant made editorial changes in Pages 1 and 3 to remind patients and prescribers about the frequency of required liver monitoring, and to emphasize the "monthly" first year liver monitoring requirement per QR recommendations. In order to obtain additional patient demographic and contact information at initial enrollment, the Applicant added fields for gender, phone and email.

Reviewer Comment: *The changes are acceptable. We will recommend that the Applicant replace the current attestations in the Patient-Prescriber Acknowledgement Form with the revised attestations provided by the FDA. We have better aligned the attestations with the REMS Document and the goals of the REMS, including adding the symptoms of liver injury. In addition to the review by the DRM, the attestation for the Prescriber-Patient Acknowledgement Form has*

been reviewed by the OCC. The revisions to these materials include OCC's comments. We have also modified the language about the testing requirements to simplify and put in plain language in the Patient Guide. We reordered the content in the Patient Guide to bring up the important information on patient actions. See the redlined version of the Patient-Prescriber Acknowledgement Form and Patient Guide, attached.

Prescription Authorization Form

The Applicant submitted a revised *Prescription Authorization Form. T*he Applicant added email and phone number fields to facilitate maintaining current patient contact information in the Coordinating Center database in Page 1, and added a heading, "Prescriber Attestation of REMS Requirements" to improve differentiation and importance in Page 2. The Applicant inserted the table, which was sourced from Table 3 in the PI, highlighting liver monitoring requirements replacing the bulleted text, to add additional prominence to lab requirements. The Applicant also added instructions to 'email submission' as a new capability towards the end of page 2 of the *Prescription Authorization Form*.

Reviewer Comment: *The changes are acceptable. We have made changes to the attestations on the Authorization Form to better focus the messaging for prescribers on the indication and lab testing requirements. See redlined version of the Prescription Authorization Form, attached.*

3.3.2.3. Pharmacies that dispense

Pharmacy Enrollment Form

The Applicant submitted a revised *Pharmacy Enrollment Form.* The Applicant added "within 30 days when" to item #1 in Page 1 and towards the end of Page 2, to emphasize the time period for re-attestation when the authorized representative changes. The Applicant has also added an electronic signature capture field to the program coordinating center's capabilities and added instructions to complete enrollment online towards the end of page 2 of the *Pharmacy Enrollment Form*.

Reviewer Comment: *The changes and addition of online functionality are acceptable. We will recommend that the Applicant replace the current attestations with the revised attestations provided by the FDA. We have better aligned the attestations with the REMS Document and the goals of the REMS. In addition to the review by the DRM, the attestation for the Pharmacy Enrollment Form has been reviewed by the OCC. The revisions to these materials include OCC's comments. See redlined version of the Pharmacy Enrollment Form, attached.*

3.3.3. REMS Applicant Requirements and Materials

3.3.3.1. Training

Prescriber Training Module and Knowledge Assessment

The Applicant submitted a revised *Prescriber Training Module and Knowledge Assessment.* The Applicant inserted "liver" into the "regular monitoring" or "periodic monitoring" text per QR recommendations to reinforce liver monitoring requirements. The Applicant also updated the

"*During the first year of treatment"* text to "monthly, or prior to each increase in dose, whichever occurs first" to emphasize the "monthly" first year liver monitoring requirement. The Applicant also updated instructions to include online enrollment.

Reviewer Comment: *The changes are acceptable. We have made edits to simplify the name of the Juxtapid REMS and REMS materials, as well as formatting recommendations to highlight the first year monitoring schedule. See redlined version of the Prescriber Training Module, attached.*

Pharmacy Training Module and Knowledge Assessment

The Applicant submitted a revised *Pharmacy Training Module and Knowledge Assessment.* The Applicant inserted "liver" into the "regular monitoring" or "periodic monitoring" text per QR recommendation to reinforce liver monitoring requirements. The Applicant also updated instructions to include online enrollment.

Reviewer Comment: *The changes are acceptable. We have made edits to simplify the name of the Juxtapid REMS and REMS materials. See redlined version of the Pharmacy Training, attached.*

3.3.3.2. Communication

Dear Pharmacist Letter and Dear Healthcare Provider Letter

The Applicant proposed to remove the Dear Pharmacist Letter and Dear Healthcare Provider Letter. The dissemination requirements of these communication materials were completed in 2017, therefore, they are obsolete and are historical in nature only at this time.

Reviewer Comment: *We agree with the Applicant's proposal to remove the Dear Pharmacist Letter and Dear Healthcare Provider Letter as they are no longer relevant. JUXTAPID REMS does not have a communication plan so removal of these materials does not trigger a change to the statutory elements.*

Fact Sheet

The Applicant submitted a revised *Fact Sheet.* The Applicant inserted "liver" into the "periodic monitoring" text to item #3 in Page 1, and added the following bullet per QR recommendation to reinforce liver monitoring requirements in Page 2:

> "To perform routine liver monitoring for each patient prior to initiating therapy, monthly during the first year of treatment and every three months thereafter, and before dose any adjustment."

Instructions were updated to submit the enrollment forms online as part of #2 under Prescriber Requirements and Pharmacy Requirements, respectively.

Reviewer Comment: *The changes are acceptable. We have made edits to simplify the name of the Juxtapid REMS and REMS materials, as well as minor formatting edits. See redlined version of the Factsheet, attached.*

3.3.3.3. Operations

Website Screenshots

The Applicant made changes to the screenshots to align with the changes described above to the appended materials. These changes included insertion of the word "liver" into the "periodic monitoring" text per QR recommendation to reinforce liver monitoring requirements, and insertion of the text "within 30 days" in Pharmacy Page to emphasize the time period for re-attestation when the authorized representative changes.

Reviewer Comment: *We agree with the changes that align the website screenshots with the changes described above to the appended materials. The Applicant did not include screenshots showing the full functionality of the REMS website. Screenshots showing the online layout of the Prescriber and Pharmacy enrollment forms, detailing the enrollment process online, including how to submit these forms, must be reviewed by the FDA, similar to all other REMS website content and included as part of the REMS. We will instruct the Applicant to submit the website screenshots detailing the online enrollment process. We have made edits to simplify the name of the Juxtapid REMS and aligned the screenshots with our other comments made to the communication materials. See the REMS website with FDA comments, attached.* (b) (4)

[redacted]

3.4. REMS Assessment Timetable

The Applicant did not propose any changes to the REMS assessment timetable. The assessment timetable must be updated. The Applicant must submit REMS Assessments every two years beginning with the 11-year REMS assessment due 12/21/2023.

4. Supporting Document

The Applicant submitted an updated Supporting Document by removing the reference to the 2017 REMS modification, communications and re-certifications requirements, which are obsolete, and are consistent with the updated REMS document. The Applicant inserted lab testing recommendations tables to match additions in related materials that are addressed in the other sections. The Applicant has also added an electronic signature capture field to the program coordinating center's capabilities and added instructions to complete enrollment online for both Prescribers and Pharmacies.

Reviewer Comment: *The proposed changes are acceptable. The REMS Supporting Document should align with the changes in the REMS Document and materials. We have made a few additional edits to the attestations for Prescribers, Patients, and Pharmacies to align with the requirements in the REMS Document, and the Applicant will need to update the REMS Supporting Document with these attestations. The Applicant should review the Supporting Document and make appropriate changes to ensure consistency. We also recommend that the Applicant describe the process and procedures for submission via online, fax or email for Prescriber Enrollment and Pharmacy Enrollment Forms, and the time frame to notify Prescribers and Pharmacies that they are certified should be described in the respective sections. Process and procedures for submission via fax or email for the Prescription*

Authorization Form needs to be described in the respective section. We recommend that the Applicant update this document with the most recent modification date.

5. REMS Assessment Plan

The Applicant did not propose any changes to the REMS assessment plan, however, the assessment plan requires revision. Changes to the assessment plan are still under discussion and will be discussed in a separate review.

6. Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on November 29, 2021 to provide feedback on the following:

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

The OPDP review was completed by Charuni Shah on December 14, 2021[1]. OPDP did not have any comments on the materials.

7. Discussion

Amryt Pharmaceuticals DAC proposed a REMS modification for Juxtapid, NDA 203858, initially received August 5, 2021. These modifications included the insertion of the word "liver" into the "regular monitoring" or "periodic monitoring" text per QR recommendations to reinforce liver monitoring requirements in REMS materials, revisions to emphasize the "monthly" first year liver monitoring requirement, addition of electronic signature capture to the program coordinating center's capabilities and addition of instructions to complete enrollment online for both Prescribers and Pharmacies, and addition of instructions to 'email submission' as a new capability for the *Prescription Authorization Form.* Since the dissemination requirements of communication materials such as "*Dear Pharmacist Letter*" and "*Dear Healthcare Provider Letter*" have been completed in 2017 and are obsolete at this time, the Applicant proposed to remove reference to these documents in the new REMS document as they are historical in nature only. The Agency agrees that these changes are acceptable. Finally, the Applicant made editorial changes throughout the REMS materials and the REMS Supporting Document for clarity and consistency, and these are acceptable.

The Applicant made additional revisions to the prescriber, patient, and pharmacy attestations on their respective enrollment forms. However, further changes are required for the modification to be acceptable. The Agency has completed a review of the converted REMS Document and will provide a

redlined version of the REMS Document to the Applicant. Additional changes to the REMS Materials and REMS Supporting Document are required to ensure alignment across the REMS.

8. Conclusions and Recommendations

DRM does not find the REMS for Juxtapid (lomitapide mesylate), (NDA 203858), as submitted on August 5, 2021 to be acceptable. Further changes to the REMS Document, appended materials, and REMS Supporting Document are required for the modification to be acceptable.

9. Comments to the Applicant

We have the following comments on the proposed REMS modification, submitted on August 5, 2021. Submit a REMS amendment within 5 business days that addresses these comments. Include the REMS document, all appended materials and the REMS supporting document, submitted as separate documents in the same submission; include a Word tracked changes version, a Word clean version, and a PDF version of the REMS Document, all appended materials and supporting document, and one clean compiled PDF file that includes the REMS Document and all REMS materials in their final format.

General Comments:

We remind you that the REMS Document, appended materials, and REMS Supporting Document must be aligned. Changes to the REMS assessment timetable and assessment plan are currently under discussion and you will receive comments in a separate correspondence.

REMS Document

Your REMS Document requires revisions to ensure the stakeholder requirements are clear and align with the current REMS operations. The REMS Document has been cleared; therefore, any additional substantive changes may result in a delay in the review of your REMS. A redlined REMS Document is attached to this communication.

The assessment timetable must be updated. Submit REMS assessments every two years beginning with the 11-year REMS assessment due 12/21/2023.

Appended Materials

We agree with your proposal to remove the Dear Healthcare Provider and Dear Pharmacy Letters.

The Agency's current thinking has changed regarding the naming of REMS programs. The term "program" is no longer used in the complete title of the REMS in the communication materials and when referring the Juxtapid REMS within the materials. Therefore, all references to the word "program" ensuing the term REMS, and following the name of drug product should be revised accordingly. The REMS Document is excluded from this naming convention. The language "Juxtapid REMS Program" is to remain in the REMS Document.

In addition, repeating the language (b) (4) (b) (4) We have removed the (b) (4) from the materials in order to simplify them and improve readability.

Other key changes are summarized below, and redlined versions are attached to this communication.

Attestations for the Prescriber and Pharmacy Enrollment forms, and Patient-Prescriber Acknowledgement Form

Note that the attestations have been revised and are provided as a separate document at the beginning of the PDF file of the compiled materials. Replace the attestations in your Prescriber and Pharmacy Enrollment forms, and Patient-Prescriber Acknowledgement Form with these. We have better aligned the attestations with the REMS document and the goals of the REMS.

Patient Guide

We have modified the language about the testing requirements to simplify and put in plain language.

Reorder the content to bring up the important information on patient actions. See redlined version of the Patient Guide.

Prescription Authorization Form

We have made changes to the attestations on the Authorization Form to better focus the messaging for prescribers on the indication and lab testing requirements. See redlined Version of the Prescription Authorization Form, attached.

Prescriber Training Module and Knowledge Assessment

We have made edits to the formatting to highlight the first-year monitoring schedule. See redlined version of the Prescriber Training Module, attached.

Fact Sheet

We have made minor formatting edits. See redlined version of the Factsheet, attached.

Website Screenshots

Screenshots showing the online layout of the Prescriber and Pharmacy enrollment forms, detailing the enrollment process online, including how to submit these forms, must be reviewed by the FDA, similar to all other REMS website content and included as part of the REMS. Include a Word tracked changes version, and a Word clean version, and a PDF version for the REMS Program Website screenshots detailing online enrollment process for the stakeholders.

We have made edits to align the screenshots with our other comments made to the communication materials. See the REMS website with FDA comments, attached.

(b) (4)

REMS Supporting Document

The REMS Supporting Document should align with the changes in the REMS Document and materials.

We have made a few additional edits to the attestations for Prescriber, Patients and Pharmacy to align with the requirements in the REMS Document as described above, and the Applicant will need to update the REMS Supporting Document with these attestations. Amryt Pharmaceuticals DAC should review the Supporting Document and make appropriate changes to ensure consistency.

Please describe the process and procedures for submission via online, fax or email for Prescriber Enrollment and Pharmacy Enrollment Forms. Provide the time frame to notify Prescribers and Pharmacies that they are certified in the respective sections. Describe the process and procedures for submission via fax or email for Prescription Authorization Form in the respective section.

We recommend updating this document with the date of the most recent REMS modification.

10. Appendix

- Attestations for the Prescriber and Pharmacy Enrollment forms, and Patient-Prescriber Acknowledgement Form
- REMS Document
- Prescriber Enrollment Form
- Patient Guide and Prescriber-Patient Acknowledgement Form
- Prescription Authorization Form
- Pharmacy Enrollment Form
- Prescriber Training Module and Knowledge Assessment
- Pharmacy Training Module and Knowledge Assessment
- Fact Sheet
- Website Screenshots

11. References

[1] Shah C. Office of Prescription Drug Promotion (OPDP), Comments on Draft Risk Evaluation and Mitigation Strategies Materials, Juxtapid (lomitapide mesylate), NDA 203858, dated December 14, 2021. [Reference ID: 4904094]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed December 22, 2021.

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