NDA 214662/S-005
NDA 214662/S-008

SUPPLEMENT APPROVAL

Mirum Pharmaceuticals, Inc.
Attention: Rishabh Jain
Director of Regulatory Affairs
950 Tower Lane, Suite 1050
Foster City, CA 94404

Dear Rishabh Jain:

Please refer to your supplemental new drug applications (sNDAs) dated and received February 13, 2023, and September 28, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Livmarli (maralixibat) oral solution.

The Prior Approval sNDA (S-005) provides for expanding the prescribing information of Livmarli to include the treatment of cholestatic pruritus in patients five years of age and older with progressive familial intrahepatic cholestasis (PFIC), and revisions to the language in the WARNINGS AND PRECAUTIONS/Gastrointestinal Adverse Reactions subsection, and ADVERSE REACTIONS section for Alagille syndrome.

We acknowledge receipt of your major amendment for S-005 dated October 4, 2023, which extended the goal date by three months.

The "Changes Being Effected" sNDA (S-008) provides for changes to the ADVERSE REACTIONS/Liver Test Abnormalities subsection to update the incidence rates of elevations of ALT and AST, and changes to the NONCLINICAL TOXICOLOGY section/Carcinogenesis, Mutagenesis, Impairment of Fertility subsection to list the correct species in the bone marrow micronucleus assay.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use) with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling. If the content of labeling in SPL format initially submitted with this CBE-0 labeling supplement is identical to the attached approved labeling, an additional submission of content of labeling in SPL format is not required.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4571-1 Provide a final study report capturing the comprehensive safety experience of progressive familial intrahepatic cholestasis (PFIC) patients treated in trial MRX-503.

The timetable you submitted on February 12, 2024, states that you will conduct this study according to the following schedule:

Study Completion:	12/24
Final Report Submission:	06/25

4571-2 Provide a final study report capturing the comprehensive safety experience of progressive familial intrahepatic cholestasis (PFIC) patients treated in trial MRX-801.

The timetable you submitted on February 12, 2024, states that you will conduct this study according to the following schedule:

Study Completion:	12/24
Final Report Submission:	06/25

4571-3 Conduct a five-year registry-based study to collect data on the health of progressive familial intrahepatic cholestasis (PFIC) patients chronically treated with Livmarli (maralixibat).

Report yearly on the following endpoints:

- Incidence of biliary diversion surgery, liver transplantation, and all-cause mortality

The timetable you submitted on February 12, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/24
Final Protocol Submission:	01/25
Interim Report:	12/25
Interim Report:	12/26
Interim Report:	12/27
Interim Report:	12/28
Interim Report:	12/29

Study Completion:	06/30
Final Report Submission:	12/30

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND (b) (4) for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

REQUESTED PHARMACOVIGILANCE

We request that for LIVMARLI you submit all serious and non-serious domestic and foreign cases of hepatotoxicity as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)) through the fifth year following the date of this letter.

We also request that you provide separate narrative summaries and an analysis of hepatotoxicity, apart from your required analysis of 15-day "Alert reports," as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)], quarterly during the first three years after the initial U.S. approval date, then annually thereafter, through the fifth year following the date of this letter. Your analysis should include interval and cumulative data relative to the date of this letter.

Your narrative summaries should provide the following information:

- Indication
- Livmarli dosage
- Duration of therapy
- Temporal association
- Dechallenge/rechallenge
- Associated signs and symptoms
- Hepatic enzymes and liver function tests
- Concomitant medications
- Medical history

- Hospitalizations, testing (including imaging), and treatment given for the event
- Outcome at the time of the report
- Assessment of causality

To identify reports of hepatotoxicity, we request that you use the Standardised MedDRA Query (SMQ): *Drug related hepatic disorders – comprehensive search (SMQ) Broad search*.

If you have any questions, contact Terry Tsui, Regulatory Project Manager, at terry.tsui@fda.hhs.gov or at 240-402-1941.

Sincerely,

{See appended electronic signature page}

Frank A. Anania, MD, FACP, AGAF, FAASLD
Deputy Director
Division of Hepatology and Nutrition
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use

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/

FRANK A ANANIA
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