

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214662Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: September 22, 2021
From: Hitesh Shroff, Ph.D.
Application Technical Lead, Branch IV
Division of New Drug Products II
Office of New Drug Products

To: CMC Review #1 of NDA 214662

Subject: Final Recommendation for NDA 214662

At the time when the CMC Review #1 was completed on June 30, 2021, it had noted the following pending issues:

- The label/labeling issues were not resolved.
- The drug product related deficiencies were not resolved.

Because of these deficiencies, the NDA was not recommended for approval from the OPQ perspective.

On September 20, 2021 the applicant submitted revised labeling. The CMC sections of the labeling were reviewed and found to be acceptable (**Attachment -1**).

In the amendment dated August 26, 2021 the applicant committed to submit the drug product container closure system leachables data of 24-month long-term stability samples by August 31, 2022 via a CBE-0 supplement. (**Attachment -2**)

In the amendment dated September 17, 2021 the applicant committed to provide an extractables or leachables study report via a CBE-0 supplement by Oct 31, 2021 in response to the PMC from the Office of Pharmaceutical Manufacturing and Quality Assessment (OPMA). (**Attachment -3**)

Recommendation:

This NDA is now recommended for Approval from the OPQ perspective.

Application Technical Lead's Assessment and Signature

The NDA is recommended for Approval from OPQ from the product quality perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch IV
Division of New Drug Products II
September 22, 2021

Hitesh N. Shroff -S
Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 21, 2021

TO: Assessment #1 of NDA 214662 Quality Assessment – Drug Product and Labeling

FROM: Jane Chang, Ph.D.
Master Chemistry Reviewer, OPQ/ONDP/DNDP II/Branch 4

THROUGH Hong Cai, Ph.D.
Chief, OPQ/ONDP/DNDP II/Branch 4

SUBJECT: **Final Recommendation on Drug Product and Labeling**

SUMMARY

The previous Drug Product Review #1 (see [N214662-DP R01 dated 21-Jun-2021](#)) was concluded Inadequate due to lack of drug product container closure system (CCS) leachables data for long-term stability samples. In eCTD-0042, CCS leachables data for long-term stability samples of three registration batches stored for up to 17 months were evaluated and concluded to be acceptable. In eCTD-0047, the applicant commits to submitting the drug product CCS leachables data of the 24-month long-term stability samples by 8/31/2022 via a CBE-0 Supplement. Drug Product Chapter is Adequate.

In addition, the previous Quality Assessment – Labeling, Assessment Cycle #1 dated 27-May-2021, made a recommendation of not ready for approval because of labeling deficiencies (see [N214662-Labeling R01, Section 4.0](#)). These labeling issues have been satisfactorily resolved based on the revisions made in eCTD-0048, and eCTD-52. Labeling Chapter is Adequate.

RECOMMENDATION:

This application is now recommended for **Approval** from the CMC drug product and labeling/label perspective.

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received	Information
eCTD-0038 (SDN-38)	07/08/2021	Container and carton labels
eCTD-0042 (SDN-42)	07/23/2021	Drug product CCS leachables data
eCTD-0044 (SDN-44)	08/11/2021	Prescribing Information Labeling
eCTD-0047 (SDN-47)	08/26/2021	Commitment of a CBE-0 for 24-month CCS leachables data
eCTD-0048 (SDN-48)	09/07/2021	Prescribing Information Labeling, Container and carton labels
eCTD-0052 (SDN-52)	09/20/2021	Prescribing Information Labeling, Instruction for Use, Patient Information

1.0 DRUG PRODUCT

The previous Drug Product Review #1 (see [N214662-DP R01 dated 21-Jun-2021](#), see [pages a and 33](#)) was concluded Inadequate due to an unresolved issue, which was conveyed to the applicant on April 30, 2021. For convenience, the issue is listed below.

We acknowledge that you observed seven leachables (b) (4)



Please provide leachable data for the current long-term stability samples stored in inverted orientation, at a minimum, for Batches MP0993, MP0997, and MP1022, which correspond to 17, 14, and 14 months, respectively.

The leachable data for the long-term stability samples stored in inverted orientation up to the proposed expiration dating period for at least three primary stability batches should be provided later. The pathway for submitting the leachable data for the 24-month long-term stability samples will be decided later, based on the results of the current stability samples. An additional control (e.g., in the drug product specification) for leachables may be required unless justified.

In [eCTD-0042](#), updated leachables data for the long-term stability samples of three registration batches stored in inverted orientation were submitted. The ages of the stability samples were 14, 14, and 17 months for Batches MP1022, MP0997, and MP0993, respectively. The samples were evaluated by HS-GCMS, GC-MS, UHPLC-UV-MS, and ICP-MS. (b) (4)

(b) (4)

. Compounds detected in the control solution were not reported in the aged drug product samples. No reportable compounds (reporting threshold: (b) (4) µg/container) were present in any of the samples evaluated across the three lots tested and the four analysis techniques.

Assessment: Adequate

Leachable study on stability samples of the three registration batches aged at 14-17 months stored in inverted orientation under the long-term condition showed no compounds were detected at or above the reporting threshold of (b) (4) µg/container.

Reporting categories for the remaining CCS leachable data were discussed, as summarized below, within ONDP among this assessor, Dr. Hitesh Shroff (ATL), Dr. Hong Cai (Chief, ONDP/DNDPII/Branch 4) and Dr. Wendy Wilson (Division Director, ONDP/DNDPII).

- PMC: This assessor recommended not considering this option. Based on the 14-17 months leachables data, the risk of leachables above the AET of (b) (4) mcg/container for 24-month samples would be reasonably low. Furthermore, fulfilling the 24-month CCS leachable study fits the category of non-506B reportable CMC Commitments as described in FDA guidance entitled [*Reports on the Status of Postmarketing Study Commitments —Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997*](#). However, Dr. Shroff recommended a PMC with a CBE-0 Supplement (see below) for the reason that the data should be reviewed by both CMC and non-clinical.
- CBE-0 Supplement: Dr. Shroff recommended this option.
- Annual report: This assessor recommended this option for the following reasons:
 - Per 21 CFR 314.81(b)(2)(i), a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product should be submitted in Annual Report.
 - Per 21 CFR 318.81(b)(2)(iv), reports of experiences, investigations, studies, or tests involving chemical or physical properties, or any other properties of the drug (such as the drug's behavior or properties in relation to microorganisms, including both the effects of the drug on microorganisms and the effects of microorganisms on the drug) are recommended to be submitted in Annual Report.
 - The product quality risk of not having the remaining 24-month CCS leachables data is similar to not having the entire 24-month long-term stability data for primary stability lots prior to NDA approval (Up to 12 months long-term stability data of the drug product were provided in the NDA to support the 24-month expiration dating period). Per 21 CFR 318.81(b)(2)(viii), the remaining long-term stability data are to be submitted in annual report as a post-approval stability commitment. Therefore, it seems reasonable that the 24-month CCS leachables data be submitted in annual report.

In the 7/29/2021 email, Dr. Wilson recommended reaching out to OLDP for their preference on the reporting category. In the 7/29/2021 email, OLDP Branch Chief, Dr. David Lewis

recommended a CBE-0 Supplement as the reporting category for the 24-month leachables data based on requests of recently approved NDAs. In a teleconference dated August 2, 2021 with Dr. Shroff and this assessor, Dr. Hong agreed to the CBE-0 Supplement without a PMC for the CCS leachables data. Consequently, this CBE-0 Supplement recommendation was conveyed to the applicant as a Post-Meeting Comment in the NDA Late-Cycle Meeting Minutes dated 08/20/2021 and in the [8/25/2021 Information Request](#) as shown below.

As indicated in the Late-Cycle Meeting Minutes dated August 20, 2021 as a post-meeting comment, we recommend a CBE-0 Supplement as the reporting category for submitting the drug product container closure system leachables data of 24-month long-term stability samples by 8/31/2022. Please commit to this reporting category with the recommended deadline.

In the 8/26/2021 amendment ([eCTD-0047](#)), the applicant commits to submitting the drug product container closure system leachables data of the 24-month long-term stability samples by 8/31/2022 via a CBE-0 Supplement. The response is acceptable.

2.0 PRESCRIBING INFORMATION (PI)

The information provided in eCTD-0052 is shown below.



Items	Information Provided in NDA	Assessor's Comments and Recommendations
Drug name [201.57(a)(2)]		
Proprietary name and established name	LIVMARLI™ (maralixibat) oral solution	Acceptable The proprietary name in the product title in Highlights is presented in uppercase letters. The established name adopts USP <1121> salt policy using the name of the active moiety "maralixibat".
Dosage form, route of administration	Oral solution	Acceptable
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval	2021	Acceptable The year that FDA initially approves an NME should be listed. The drug substance is an NME.
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage Forms and Strengths in metric system	Oral solution: 9.5 mg of maralixibat per mL	Acceptable The strength is based on maralixibat, i.e., the quaternary ammonium ion.

Conclusion: *Satisfactory*

Per [Labeling Review Tool](#), dosage form terminology (e.g., oral solution, for oral suspension) under the heading of DOSAGE FORMS AND STRENGTHS in Highlights (HL) of Prescribing Information should be identical to the dosage form terminology in the product title in HL.

The information provided in Highlights of Prescribing Information meets the regulatory requirements.

2.2 FULL PRESCRIBING INFORMATION (FPI)

1.2.1 Section 2: DOSAGE AND ADMINISTRATION



Items	Information Provided in NDA	Assessor's Comments and Recommendations
Special instructions for product preparation or storage after opening (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	A calibrated measuring device (0.5 mL, 1 mL or 3 mL oral dosing dispenser) will be provided by the pharmacy to measure and deliver the prescribed dose accurately. Store LIVMARLI between 20°C and 25°C (68°F and 77°F) [see <i>How Supplied/Storage and Handling (16)</i>]. Discard any remaining LIVMARLI 45 days after first opening of bottle.	Acceptable

Conclusion: *Satisfactory*

The information provided in DOSAGE AND ADMINISTRATION meets the regulatory requirements.

1.2.2 Section 3: DOSAGE FORMS AND STRENGTHS



Items	Information Provided in NDA	Assessor's Comments and Recommendations
Available dosage forms	Oral solution	Acceptable
Strengths: in metric system	9.5 mg of maralixibat per mL	Acceptable Strength is in metric system based on the active moiety, maralixibat. Equivalence statement is not required in Section 3.
Active moiety expression of strength (if applicable)	maralixibat	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	a clear, colorless to yellow solution	Acceptable

Conclusion: *Satisfactory*

Per [Labeling Review Tool](#), dosage form terminology (e.g., oral solution, for oral suspension) under the section of DOSAGE FORMS AND STRENGTHS of FPI should be identical to the dosage form terminology in the product title in HL.

The information provided in DOSAGE FORMS AND STRENGTHS meets the regulatory requirements.

1.2.3 Section 11: DESCRIPTION



(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	LIVMARLI (maralixibat) oral solution	Acceptable Per 201.10(g)(1), the established name shall accompany the proprietary name. The established name shall be used at least once in the running text in association with such proprietary name or designation.
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	Oral solution	Acceptable
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)	9.5 mg of maralixibat per mL (equivalent to 10 mg of maralixibat chloride per mL)	Acceptable
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any)]. Not required for oral use, except for colorant. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) per 21 CFR 201.10(d)(2).	edetate disodium, grape flavor, propylene glycol, purified water, and sucralose	Acceptable The USP title is used as the established name. Inactive ingredients are listed in alphabetical order. (b) (4)
Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	an ileal bile acid transporter (IBAT) inhibitor	Acceptable The pharmacological/ therapeutic class is consistent with the label of NDA 215498 Odevixibat, the first in class for the same mechanism.
Chemical name, structural formula [21 CFR 201.57(c)(12)(i)(F)]	Provided	Acceptable
Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	The pH of the oral solution is 3.8 – 4.8.	Acceptable

For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”	N/A	N/A

Conclusion: Satisfactory

Per [Labeling Review Tool](#), dosage form terminology (e.g., oral solution, for oral suspension) under the section of DESCRIPTION of FPI should be identical to the dosage form terminology in the product title in HL.

The information provided in DESCRIPTION meets the regulatory requirements.

1.2.4 Section 16: HOW SUPPLIED/STORAGE AND HANDLING



Items	Information Provided in NDA	Assessor’s Comments and Recommendations
Dosage form	oral solution	Acceptable
Strength of dosage form in metric system	Each mL contains 9.5 mg of maralixibat	Acceptable Strength is expressed based on the active moiety.
Available units (e.g., bottles of 100 tablets)	30 mL	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number. Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	a clear, colorless to yellow liquid NDC 79378-110-01	Acceptable

Special handling (e.g., protect from light, refrigerate).	Discard any remaining LIVMARLI 45 days after first opening of bottle	Acceptable In-use stability data support the proposed 45 days after first opening.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store between 20°C and 25°C (68°F and 77°F), excursion permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Always store with cap on the bottle.	Acceptable
Include information about child-resistant packaging (if manufacturer choose to include)	Not provided	Acceptable The manufacturer chooses not to include child-resistant cap information.

Conclusion: Satisfactory

Per [Labeling Review Tool](#), dosage form terminology (e.g., oral solution, for oral suspension) under the section of HOW SUPPLIED/STORAGE AND HANDLING of FPI should be identical to the dosage form terminology in the product title in HL.

The information provided in HOW SUPPLIED/STORAGE AND HANDLING meets the regulatory requirements.

1.2.5 Section 17: PATIENT COUNSELING INFORMATION



Item	Information Provided in NDA	Assessor's Comments and Recommendations
Manufacturer/distributor name [21 CFR 201.1(h)(5)]	Manufactured for: Mirum Pharmaceuticals, Inc. 950 Tower Lane, Suite 1050 Foster City, CA 94404	Acceptable

Conclusion: Satisfactory

Manufacturer/distributor information in PATIENT COUNSELING INFORMATION meets the regulatory requirement.

3.0 INSTRUCTION FOR USE

Assessor's Comment: Information pertaining to quality labeling submitted in eCTD-0052 is summarized below.

Title:

**LIVMARLI™ [liv-MAR-lee]
(maralixibat)
oral solution**

Storage Information:

- Store LIVMARLI at room temperature, between 68°F and 77°F (20°C and 25°C).
- Always store LIVMARLI with the cap on the bottle.
- Store the dosing dispenser in a clean, dry place when not in use.
- Keep LIVMARLI and all medicines out of the reach of children.

Section D: Disposal

- Throw away (dispose of) the bottle of LIVMARLI following the steps below 45 days after first opened, even if there is still medicine in it.
 1. Mix medicine with an unappealing substance such as dirt, cat litter, or used coffee grounds;
 2. Place the mixture in a container such as a sealed plastic bag;
 3. Throw away the container in your trash at home; and
 4. Delete all personal information on the prescription label of empty medicine bottles, then trash or recycle the empty bottle.
- Throw away (dispose of) used dosing dispensers in the household trash.

Conclusion: Satisfactory

The information provided in INSTRUCTION FOR USE meets the regulatory requirements.

4.0 PATIENT INFORMATION

Assessor's Comment: Information pertaining to quality labeling submitted in eCTD-0052 is summarized below.

Title:

**LIVMARLI™ [liv-MAR-lee]
(maralixibat)
oral solution**

How should I store LIVMARLI?

- Store LIVMARLI at room temperature between 68°F and 77°F (20°C and 25°C).
- Always store LIVMARLI with the cap on the bottle.
- Throw away any remaining LIVMARLI, following the steps below, 45 days after first opening the bottle.
 1. Mix medicine with an unappealing substance such as dirt, cat litter, or used coffee grounds;

2. Place the mixture in a container such as a sealed plastic bag;
3. Throw away the container in your trash at home; and
4. Delete all personal information on the prescription label of the empty medicine bottle, then throw away or recycle the empty bottle

Keep LIVMARLI and all medicines out of the reach of children.

What are the ingredients in LIVMARLI?

Active ingredients: maralixibat chloride

Inactive ingredients: edetate disodium, grape flavor, propylene glycol, purified water, and sucralose.

Manufactured for: Mirum Pharmaceuticals, Inc., 950 Tower Lane, Suite 1050, Foster City, CA 94404

Conclusion: Satisfactory

The information provided in PATIENT INFORMATION meets the regulatory requirements.

5.0 CARTON AND CONTAINER LABELS

The information provided in eCTD-0048 (SDN-48) is summarized below.

5.1 CONTAINER LABEL



Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Livmarli™ (maralixibat) oral solution	Acceptable
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	oral	Acceptable
Active moiety expression of strength with equivalence	9.5 mg/mL	Acceptable

statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]		Strength is based on the active moiety per USP <1121>. The equivalence statement is not provided due to space limitation.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]&	30 mL	Acceptable
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Not provided	Acceptable Information on inactive ingredients is not required for oral drugs.
“Rx only” displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	Acceptable
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	79378-110-01	Acceptable
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Allocated on the right side	Acceptable
Storage conditions. If applicable, include a space for BUD.	Store unopened bottle at 20°C - 25°C (68°F - 77°F) [see USP controlled room temperature]. After first opening, store at 20°C - 25°C (68°F - 77°F).	Acceptable
Bar code [21CFR 201.25(c)(2)]	Provided	Acceptable
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or “Recommended Dosage and Administration: See Prescribing Information” (21 CFR 201.55)	Recommended Dosage: See prescribing information	Acceptable
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Manufactured for Mirum Pharmaceuticals, Inc. Foster City, CA 94404	Acceptable
And others, if space is available	Dispose of any remaining medicine 45 days after first opening. Space allocated for “Date of first opening”. Always store with cap on the bottle.	Acceptable

Conclusion: Satisfactory

The information provided on the container label meets the regulatory requirements.

5.2 CARTON LABELS

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B) , 21 CFR 201.10(g)(2)]	Livmarli™ (maralixibat) oral solution	Acceptable
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	oral	Acceptable
Active moiety expression of strength with equivalence	9.5 mg/mL	Acceptable

statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Each mL contains 9.5 mg of maralixibat (equivalent to 10 mg maralixibat chloride).	
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	30 mL	Acceptable
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	edetate disodium, grape flavor, propylene glycol, purified water, and sucralose	Acceptable
“Rx only” displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	Acceptable
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	79378-110-01	Acceptable
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Allocated	Acceptable
Storage conditions	Store unopened bottle at 20°C to 25°C (68°F to 77°F) [see USP controlled room temperature]. After first opening, store at 20°C to 25°C (68°F to 77°F).	Acceptable
Bar code [21 CFR 201.25(c)(2)]	Provided	Acceptable
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or “Recommended Dosage and Administration: See Prescribing Information” (21 CFR 201.55)	Recommended Dosage: See prescribing information	Acceptable
“Keep out of reach of children” (Required for OTC in CFR. Optional for Rx drugs)	Provided	Acceptable
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Manufactured for Mirum Pharmaceuticals, Inc. Foster City, CA 94404	Acceptable
And others, if space is available	Use within 45 days of first opening the bottle. Dispose of any remaining medicine 45 days after first opening. Always store with cap on the bottle.	Acceptable

Conclusion: Satisfactory

The information provided on the carton label meets the regulatory requirements.



Jane
Chang

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Hong
Cai

Digitally signed by Hong Cai
Date: 9/21/2021 08:14:03PM
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1.11.1 QUALITY INFORMATION AMENDMENT

1.11.1.1 RESPONSE TO FDA REQUEST FOR INFORMATION

We refer to the Information Request received August 25, 2021. The Agency's comment is presented in bold font followed by Mirum's response below in plain text.

FDA Comment 1

As indicated in the Late-Cycle Meeting Minutes dated August 20, 2021 as a post-meeting comment, we recommend a CBE-0 Supplement as the reporting category for submitting the drug product container closure system leachables data of 24-month long-term stability samples by 8/31/2022. Please commit to this reporting category with the recommended deadline.

Sponsor's Response

As requested by the Agency, Mirum commits to submitting the drug product container closure system leachables data of the 24-month long-term stability samples by 8/31/2022 via a CBE-0 Supplement.

1.11.1 QUALITY INFORMATION AMENDMENT

1.11.1.1 RESPONSE TO FDA REQUEST FOR INFORMATION

We refer to the Information Request received September 14, 2021 via email, and Mirum's Response in [Sequence 0030](#) submitted June 07, 2021. The Agency's comment is presented in bold font followed by Mirum's response below in plain text.

FDA Comment 1

Regarding NDA 214662, Livmarli (maralixibat) Oral Solution, submitted by Mirum Pharmaceuticals, received on January 29, 2021, and in continuing the discussions from the LCM, we have the follow proposed CMC-PMC and milestone date.

Please review and provide your feedback as soon as possible.

Provide data from an extractables or leachables study (b) (4) used during commercial manufacturing or a leachable study on the bulk solution. The extractables or leachables study conditions should adequately represent the worst-case manufacturing conditions (temperature, time of exposure, etc.) and should consider non-volatile, semi-volatile, and volatile type leachables. Demonstrate the analytical methods are suitable for detecting leachables from the (b) (4) manufacturing equipment and are sufficiently sensitive to detect and quantitate the leachables at or above AET. Include a discussion of the overall control strategy (b) (4) (during manufacturing) to be implemented during commercial manufacturing to limit the amount of leachables from the manufacturing equipment in the final drug product.

Final Report Submission as CBE-0 supplement: 10/31/2021

Sponsor's Response

As noted in the FDA Postmarketing Requirements/Postmarketing Commitments from the Late Cycle Meeting Background Package dated July 16, 2021, Mirum commits to submitting the extractable or leachable data for (b) (4) equipment in contact with the bulk solution during commercial manufacturing by 10/31/2021 via a CBE-0 Supplement.

Please refer to Mirum's Response to Information Request in [Sequence No. 0030 \(Comment 5\)](#) for the overall control strategy (pause time) to be implemented during commercial manufacturing.

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/

HITESH N SHROFF
09/22/2021 08:14:02 PM

RECOMMENDATION

☐ Approval
☒ Not Ready for Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214662 Assessment 1

Drug Product Name	Livmarli (maralixibat) Oral Solution
Dosage Forms	Solution
Strength	9.5 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Mirum Pharmaceuticals, Inc.; CA
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Jan 29, 2021	OPQ
Amendment	Apr 1, 2021	OPMA
Amendment	Apr 22, 2021	ONDP, DP
Amendment	Apr 27, 2021	ONDP, API, DP
Amendment	May 24, 2021	ONDP, DP
Amendment	May 25, 2021	ONDP, DP
Amendment	May 27, 2021	ONDP, DMA
Amendment	June 7, 2021	ONDP, DMA, OPMA
Amendment	June 11, 2021	ONDP, DP
Amendment	June 24, 2021	ONDP, API

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Sam Bain	Donna Christner
Drug Product	Jane Chang	Hong Cai
Manufacturing	Yan Zheng	David Anderson
Microbiology	Karthik Krishnan	Yeissa Chabrier Rosello
Regulatory Business Process Manager	Oumou Barry	
Application Technical Lead	Hitesh Shroff	
Laboratory (OTR)	N/A	N/A
Environmental	Jane Chang	Hong Cai

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	IV	(b) (4)	(b) (4)	Active	N/A	LOA: Feb 11, 2020
	III			Active	N/A	LOA: Sep 15, 2020
	III			Active	N/A	LOA: Aug 17, 2020
	III			Active	N/A	LOA: Aug 19, 2020
	III			Active	N/A	LOA: Aug 28, 2020

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	(b) (4)	In support of NDA 214662 for Nonclinical and clinical information
IND	119917	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Livmarli (maralixibat) oral solution.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made a final overall “**Approval**” recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

There are unresolved drug product related deficiencies at the time of this review.

The label/labeling has *not* been finalized as of this review.

Therefore, from the OPQ perspective, this NDA is *not* deemed ready for approval in its present form per CFR 314.125(b)(6) until the label/labeling is finalized. (see List of Deficiencies)

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Livmarli (maralixibat) oral solution, 9.5 mg/mL is a clear, colorless to yellow, grape-flavored liquid. Each mL of Livmarli contains 10 mg of maralixibat chloride. It is supplied in 30 mL round, amber plastic bottles. Calibrated 0.5 mL, 1 mL or 3 mL dosing dispensers will be provided by the pharmacy.

FDA has designated Livmarli as an orphan drug, breakthrough therapy and rare disease therapy for Alagille syndrome (ALGS).

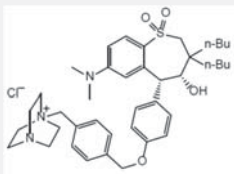
This NDA was submitted via a 505(b)(1) pathway. Livmarli is an NME because it has never been approved or lawfully marketed as a drug in US.

Proposed Indication(s) including Intended Patient Population	LIVMARLI is an apical sodium-dependent bile acid transporter inhibitor indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 1 year of age and older.
Duration of Treatment	As needed
Maximum Daily Dose	28.5 mg/day (3mL/day)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance in Livmarli is maralixibat chloride. It is a white to yellow solid. It is a chiral molecule containing two chiral centers and is a single stereoisomer with R, R-configuration. Two different crystalline polymorphs (b) (4) have been identified but the drug substance is prepared as (b) (4). It is soluble in water and sparingly soluble in alcohol. Its chemical name is (4*R*,5*R*)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl] phenoxy] methyl] phenyl] methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride. Its chemical structures, molecular formula and molecular weight are shown below.



Molecular formula: C₄₀H₅₆ClN₃O₄S
Molecular Weight: 710.41 g/mol

Maralixibat chloride is manufactured, tested and packaged in accordance with Good Manufacturing Practices (cGMP) at (b) (4)

The applicant has provided sufficient information for the starting materials including synthesis, specification and batch analyses data. The detailed CMC information regarding the raw materials, intermediates, drug substance manufacturing process, critical steps and in-process controls is deemed adequate. The potential genotoxic impurities are controlled in the drug substance specification per ICH Q3A guidelines.

The chemical structure of maralixibat chloride is determined by elemental analysis, proton (¹H) and carbon (¹³C) NMR spectroscopy; Infrared (IR) spectroscopy, Ultraviolet (UV) spectroscopy, mass spectroscopy, single crystal X-Ray crystallography (SXR) and X-Ray Powder Diffraction (XRPD).

The drug substance identity, purity and quality are controlled by its specification for appearance, identity by FTIR and HPLC; assay and chiral purity by HPLC assay, impurities by HPLC and GC-MS, residual solvents by GC-HS and water content per USP <921>. A risk assessment of the potential elemental impurities was conducted, and they are controlled per USP <232> and USP <233>.

The applicant provided detailed description of the non-compendial analytical methods and validated these methods per ICH Q2R1. The applicant has provided batch analyses of multiple batches made at (b) (4)

(b) (4) The batch analyses of the drug substance batches confirmed that the drug substance manufacturing process is robust.

Based on results of the long-term and accelerated stability testing per ICH Q1A(R2) of registration and supporting batches of drug substance a retest period of (b) (4) months is granted when stored in a (b) (4)

The drug substance reviewer concluded that the applicant has submitted adequate CMC information regarding the regulatory starting materials, raw materials, intermediates, manufacturing process and the drug substance specification for identity, purity and quality of the drug substance, Maralixibat Chloride. (see the **Drug Substance** review).

Drug Product: Inadequate

Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 1 year of age and older. Livmarli is a clear, colorless to yellow, grape flavored solution. It is supplied in multi-dose 30 mL amber (b) (4) bottle with a (b) (4) and a child resistant (CR) cap containing a foam liner. A 0.5 mL, 1mL or 3 mL calibrated dosing dispenser for oral use is provided by the pharmacy.

Each milliliter of Livmarli oral solution contains 9.5 mg of maralixibat (equivalent to 10 mg maralixibat chloride). The oral solution contains the following inactive ingredients: propylene glycol, sucralose, disodium ethylenediaminetetraacetic acid (EDTA) dihydrate, grape flavor (b) (4)

The identity, strength, purity and quality of the drug product is controlled by its specification. The release and stability specifications include the following tests: description by visual inspection, identity by HPLC and UV, strength by maralixibat HPLC assay, purity via assessment of the degradation products by HPLC and microbial enumeration per USP <61> and specified organism per USP <62> and USP <60>, content uniformity per USP <905> and contents of (b) (4) propylene glycol and (b) (4) disodium EDTA dihydrate by HPLC. The in-house developed, non-compendial analytical methods were validated per ICH Q2(R1). The specifications for Livmarli oral solution was reviewed by the drug product reviewer and deemed adequate.

Potential leachables from the proposed commercial container closure system has not been addressed. The applicant commits to provide interim leachable data for three primary stability batches stored in inverted orientation for approximately 14-17 months under the long-term condition by the end of July 2021. If the data

are not sufficient to address the leachable concern, a post marketing commitment for additional data, e.g., leachable data from stability samples stored for the proposed expiration dating period, identification of leachables, toxicological assessment, etc., will be recommended. (see Post-marketing Commitments (PMC))

In order to demonstrate the compatibility of the (b) (4), dosing dispenser and the solution the following qualification studies were conducted: delivered volume, accuracy, rinse studies, extractables and leachables. No compatibility issues were identified from these studies.

On the basis of the satisfactory long-term and accelerated stability data a 24-month expiration dating period from the date of the bulk (b) (4) manufacturing is granted when the drug product is stored at 20 to 25°C (68 to 77°F) with excursions permitted to 15 to 30°C (59 to 86°F). (See the **Drug Product review**).

Labeling: Inadequate

The label/labeling has not been finalized as of this review. (see **Labeling Review** and **Labeling Deficiencies**)

Manufacturing: Adequate

Livmarli oral solution is manufactured, tested and packaged by (b) (4). The drug product is manufactured (b) (4).

The applicant provided a process flow diagram and detailed drug product manufacturing process description containing a list of equipment used, in-process controls and process parameters for each manufacturing step. (b) (4)

The proposed manufacturing, testing, primary and secondary, labeling and packaging facilities for the drug substance and drug product were deemed adequate based on previous history and cGMP compliance status.

The OPMA reviewer concluded that the NDA applicant has submitted adequate CMC information regarding Livmarli oral solution manufacturing process. (see **Manufacturing Integrated Assessment** review)

Biopharmaceutics: Adequate

Maralixibat chloride is a highly soluble compound and the proposed drug product is intended for the oral administration. Maralixibat oral solution Fixed Dose

Volume (FDV) and Fixed Drug Substance Concentration (FDSC) has minor change in their composition which is believed not to cause any impact on efficacy and safety of the formulation. The drug product is intended to target small intestine surface with minimal absorption systemically. Hence, in vivo bioequivalence/comparative bioavailability studies are not required. Moreover, the proposed product is a solution dosage form, so dissolution is not required. Therefore, based on the totality of the information, it is determined that no further bridging information is necessary between the FDV and FDSC formulations.

From a Biopharmaceutics perspective, NDA 214662 for Maralixibat Chloride Oral Solution, 9.5 mg/mL is recommended for approval. (see **Biopharmaceutics Review**)

Microbiology: Adequate

Livmarli oral solution is a non-sterile drug product. It is supplied in a multi-dose plastic bottle. The drug product formulation (b) (4)

The analytical test methods, method validations, acceptable limits and results of antimicrobial effectiveness testing per USP <51>, microbial enumeration testing per USP<61>, specified microorganisms testing per USP <60> and USP <62>, overall manufacturing process, bulk home time study to establish maximum acceptable holding time, expiration dating period, stability data and post-approval stability protocol and stability commitment were reviewed and deemed adequate from the microbiology perspective. (see **Microbiology Review**)

Environmental Assessment: Adequate

The applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the estimated amount of drug to be produced for direct use, and a statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable. (see the **Drug Product Review**).

**Post-marketing Commitments (PMC):
Drug Product Comments for PMC**

PMC and #	4105-2
PMC Description:	Provide leachable data of at least three drug product primary stability batches stored in inverted orientation under the long-term condition for approximately 14-17 months (interim data) and for 24 months (the proposed expiration dating period). Provide a justification, e.g., identification of leachables, toxicological assessment, etc., for leachables above the analytical evaluation threshold (AET) of (b) (4) µg/container. An additional control (e.g., in the drug product specification) for concerned leachables may be required. Commit to fulfill this post marketing commitment with an interim report for the interim data by October 31, 2021 and a final report by August 31, 2022.
Final Report Submission	08/31/2022

**Office of Pharmaceutical Manufacturing Assessment (OPMA) Comments
for PMC**

PMC and #	4105-1
PMC Description:	Provide data for an extractable or leachable study (b) (4) no later than the end of July 2021. The extractable or leachable study should test conditions adequately represent the worst-case manufacturing conditions.
Final Report Submission	10/31/2021

Lifecycle Management Considerations: None

C. Risk Assessment

Product Attribute / CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	LifeCycle consideration/ Comments
Assay and content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	(b) (4)	The drug product is expected to be safe for oral administration during the entire shelf life from product quality perspective. Low to None	None
(b) (4) Propylene glycol	• Formulation	L	(b) (4)	Low to None	None
(b) (4) Disodium EDTA dihydrate	• Formulation • Manufacturing process	L	(b) (4)	Low to None	None
Related Substances Impurities / Degradants	• Raw materials • Process parameters • Container/closure system	L	(b) (4)	Low to None	None
Microbial Purity	• Raw materials • Process parameters • Container/closure system	L	(b) (4)	Low to None	None

D. List of Deficiencies

I. Drug Product Deficiencies:

As the date of this assessment, the following issue, which was conveyed to the applicant on April 30, 2021, remained unresolved.

1. We acknowledge that you observed seven leachables in the aged MRX Oral Solution, (b) (4)



Please provide leachable data for the current long-term stability samples stored in inverted orientation, at a minimum, for Batches MP0993, MP0997, and MP1022, which correspond to 17, 14, and 14 months, respectively.

The leachable data for the long-term stability samples stored in inverted orientation up to the proposed expiration dating period for at least three primary stability batches should be provided later. The pathway for submitting the leachable data for the 24- month long-term stability samples will be decided later, based on the results of the current stability samples. An additional control (e.g., in the drug product specification) for leachables may be required unless justified.

II. Labeling Deficiencies

A. Regarding PI

a) Highlight Section

1. Delete (b) (4)

b) Full Prescribing Information

Section 3: Dosage Forms and Strengths

2. Delete (b) (4)

Section 11: Description

3. Include the establish name, which should accompany the proprietary name, i.e., LIVMARLI (maralixibat) oral solution.
4. Use the title of USP monograph as the established name for

inactive ingredients. List inactive ingredients in alphabetical order, i.e., edetate disodium, grape flavor, propylene glycol, purified water, and sucralose.

5. Add the pH of the oral solution.

Section 16: How Supplied/Storage and Handling

6. Delete [REDACTED] (b) (4)
7. Delete the statement [REDACTED] (b) (4)

B. Regarding the Container/Carton Labels

8. Please address the following issues for the container and carton labels:
- a. Delete [REDACTED] (b) (4) Per USP <1121>, the active moiety should be used for the established name, i.e., maralixibat oral solution. Relocate the strength to be after the established name, such as the following:

Livmarli™
maralixibat oral solution
9.5 mg/mL

- b. Revise the storage conditions to list the temperature in centigrade first, followed by the temperature in Fahrenheit in parenthesis, as the following:

Store [REDACTED] (b) (4)

- c. Replace [REDACTED] (b) (4) with “Recommended Dosage and Administration: See Prescribing Information”.

9. If space permits, include the statement “Each mL contains 10 mg of maralixibat chloride” for the container label.

10. Please address the following issues for the carton label:

- a. Replace the list of inactive ingredients “propylene glycol, sucralose, [REDACTED] (b) (4), grape flavor and purified water” with “edetate disodium, grape flavor, propylene glycol, purified water, and sucralose”.

- b. Replace [REDACTED] (b) (4) with “Each mL contains 9.5 mg of maralixibat (equivalent to 10 mg of maralixibat chloride).”

- c. Replace [REDACTED] (b) (4)

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch IV
Division of New Drug Products II
June 30, 2021

Hitesh N.
Shroff -S

Digitally signed by Hitesh N. Shroff -
S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=200034
8333, cn=Hitesh N. Shroff -S
Date: 2021.06.30 18:51:50 -04'00'

CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received
eCTD-0002 (SDN-2)	11/12/2020

1.0 PRESCRIBING INFORMATION (PI)



Items	Information Provided in NDA	Assessor's Comments and Recommendations
Drug name [201.57(a)(2)]		
Proprietary name and established name	LIVMARLI™ (b) (4) (b) (4) oral solution	Unacceptable The proprietary name in the product title in Highlights is presented in uppercase letters. However, established name should follow USP <1121> (b) (4)
Dosage form, route of administration	oral solution	Acceptable
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval	YYYY	Acceptable The year that FDA initially approves an NME should be listed. The drug substance is an NME. The year will be updated later to reflect the year that this drug is approved.
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage Forms and Strengths in metric system	Oral solution: 9.5 mg (b) (4)	Unacceptable Indicate that the strength is based on maralixibat, i.e., the quaternary ammonium ion.

Conclusion: Unsatisfactory

The established name of the drug product should be the name of the active moiety per USP <1121>. Per USP <7>, the labels and labeling of liquids other than injectable products should state the percentage content of each active moiety or drug substance or the amount of each active moiety or drug substance in a specified volume. Strength should correspond to the established name. (b) (4)

Per [Labeling Review Tool](#), dosage form terminology (e.g., oral solution, for oral suspension) under the heading of DOSAGE FORMS AND STRENGTHS in Highlights (HL) of Prescribing Information should be identical to the dosage form terminology in the product title in HL.

The recommended revisions are shown below:

PRODUCT TITLE:

LIVMARLI™ (b) (4) oral solution

DOSAGE FORMS AND STRENGTHS:

Oral solution: 9.5 mg of maralixibat per (b) (4)

1.2 FULL PRESCRIBING INFORMATION (FPI)

1.2.1 Section 2: DOSAGE AND ADMINISTRATION

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Special instructions for product preparation or storage after opening (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	A calibrated measuring device (0.5 mL, 1 mL or 3 mL oral dosing dispenser) will be provided by the pharmacy to measure and deliver the prescribed dose accurately (b) (4) (b) (4)	Unacceptable (b) (4) Include temperature range.

Conclusion: Inadequate

The recommended revisions are shown below:

A calibrated measuring device (0.5 mL, 1 mL or 3 mL oral dosing dispenser) will be provided by the pharmacy to measure and deliver the prescribed dose accurately (b) (4)

(b) (4)

(b) (4)

1.2.2 Section 3: DOSAGE FORMS AND STRENGTHS

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Available dosage forms	Oral solution	Acceptable
Strengths: in metric system	9.5 mg (b) (4)	Unacceptable Strength is in metric system based on the active moiety. However, the active moiety "maralixibat" should be added for clarity. Equivalence statement is not required in Section 3.
Active moiety expression of strength (if applicable)	Active moiety	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	clear, colorless to yellow solution	Acceptable

Conclusion: Unsatisfactory

(b) (4)
 Per [Labeling Review Tool](#), dosage form terminology (e.g., oral solution, for oral suspension) under the section of DOSAGE FORMS AND STRENGTHS of FPI should be identical to the dosage form terminology in the product title in HL.

The recommended revisions are shown below:

Oral solution: 9.5 mg of maralixibat per (b) (4)
 as a clear, colorless to yellow solution.

1.2.3 Section 11: DESCRIPTION

(b) (4)



(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	Proprietary name: LIVMARLI	Unacceptable (b) (4) Per 201.10(g)(1), the established name shall accompany the proprietary name. The established name shall be used at least once in the running text in association with such proprietary name or designation.
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	Oral solution	Acceptable
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)	9.5 mg (b) (4)	Unacceptable The strength in metric system is based on the active moiety. However, no equivalence statement is provided.
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any)]. Not required for oral use, except for colorant. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) per 21 CFR 201.10(d)(2).	Inactive ingredients: propylene glycol, sucralose, (b) (4) grape flavor, (b) (4) (b) (4)	Unacceptable (b) (4) Inactive ingredients are recommended to be listed in alphabetical order. (b) (4) (b) (4) is not required per 21 CFR 201.100(b)(5)(i).
Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	(b) (4)	Acceptable with a minor edit Revise to (b) (4) bile acid transporter inhibitor”.
Chemical name, structural formula [21 CFR 201.57(c)(12)(i)(F)]	Provided	Acceptable with minor edits Relocate “(4R,5R)”.

Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	Not provided	Unacceptable Add pH information
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”	N/A	N/A

Conclusion: Unsatisfactory

Per [Labeling Review Tool](#), dosage form terminology (e.g., oral solution, for oral suspension) under the section of DESCRIPTION of FPI should be identical to the dosage form terminology in the product title in HL.

The recommended revisions are shown below:

LIVMARLI (maralixibat) oral solution is an (b) (4) **bile acid transporter inhibitor.**
Maralixibat is (b) (4) **present as a chloride salt with the chemical name (4R,5R)-1-[[4-[[4-[(4R,5R)-3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]-phenoxy]-methyl]-phenyl]-methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride.** (b) (4) **The molecular formula of maralixibat chloride is C₄₀H₅₆ClN₃O₄S with a molecular weight of 710.42** (b) (4) **It has the following chemical structure:**

LIVMARLI is supplied (b) (4) **in a multiple-dose bottle containing 9.5 mg of maralixibat per mL (equivalent to 10 mg of maralixibat chloride per mL)** (b) (4)
 (b) (4) **The oral solution contains the following inactive ingredients: edetate disodium, grape flavor, propylene glycol, purified water, and sucralose** (b) (4)

The pH of the oral solution is 3.8 – 4.8.

1.2.4 Section 16: HOW SUPPLIED/STORAGE AND HANDLING



(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Dosage form	oral solution	Acceptable
Strength of dosage form in metric system	9.5 mg (b) (4)	Acceptable with minor edits Strength is expressed based on the active moiety.
Available units (e.g., bottles of 100 tablets)	30 mL bottle	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number. Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	clear, colorless to yellow, liquid (b) (4) NDC 79378-110-01	Unacceptable (b) (4) does not facilitate identification of the dosage forms. Therefore, it should be deleted.
Special handling (e.g., protect from light, refrigerate).	(b) (4)	Acceptable with minor edits (b) (4)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Always store with cap on the bottle.	Acceptable
Include information about child-resistant packaging (if manufacturer choose to include)	Not provided	Acceptable The manufacturer chooses not to include child-resistant cap information.

Conclusion: Unsatisfactory

Per [Labeling Review Tool](#), dosage form terminology (e.g., oral solution, for oral suspension) under the section of HOW SUPPLIED/STORAGE AND HANDLING of FPI should be identical to the dosage form terminology in the product title in HL.

The recommended revisions are shown below:

How Supplied

LIVMARLI™ (b) (4) oral solution is a clear, colorless to yellow; (b) (4) liquid supplied in a 30 mL amber plastic bottle (NDC 79378-110-01). Each mL contains 9.5 mg of maralixibat. (b) (4)

(b) (4)

Storage and Handling

(b) (4)

Always store with cap on the bottle.

(b) (4)

1.2.5 Section 17: PATIENT COUNSELING INFORMATION

(b) (4)

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Manufacturer/distributor name [21 CFR 201.1(h)(5)]	Manufactured for: Mirum Pharmaceuticals, Inc. 950 Tower Lane, Suite 1050 Foster City, CA 94404	Acceptable

Conclusion: Satisfactory

Manufacturer/distributor information in PATIENT COUNSELING INFORMATION meets the regulatory requirement.

2.0 INSTRUCTION FOR USE

Assessor's Comment: Information pertaining to quality labeling is summarized below.

Title:

LIVMARLI™ [LIV-mar-lee]

(b) (4)

Oral Solution

Storage Information:

- Store (b) (4) at room temperature, between 68°F to 77°F (20°C to 25°C).

(b) (4)

- Always store LIVMARLI with cap on the bottle.
- Store the dosing dispenser in a clean, dry place when not in use.

(b) (4)

Conclusion: Unsatisfactory

The recommended revisions are shown below:

Title:

LIVMARLI™ [LIV-mar-lee]

(b) (4)

Oral Solution

(b) (4)

3.0 PATIENT INFORMATION

Title:

LIVMARLI™ [LIV-mar-lee]
(b) (4) oral solution

How should I store LIVMARLI?

(b) (4)

Keep LIVMARLI and all medicines out of the reach of children.

What are the ingredients in LIVMARLI?

Active ingredients: maralixibat chloride

Inactive ingredients: propylene glycol, sucralose, (b) (4)
(b) (4), grape flavor (b) (4)

Manufactured for:

Mirum Pharmaceuticals, Inc., 950 Tower Lane, Suite 1050, Foster City, CA 94404

Conclusion: Unsatisfactory

The recommended revisions are shown below:

(b) (4)

Inactive ingredients: **edetate disodium, grape flavor, propylene glycol, purified water, and sucralose-** (b) (4)

4.0 CARTON AND CONTAINER LABELS

4.1 CONTAINER LABEL



Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Livmarli™ (b) (4) oral solution	Unacceptable Per USP <1121>, the established name should use the name of the active moiety "maralixibat". (b) (4) Strength should be relocated to be after "oral solution"
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	oral	Acceptable
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	9.5 mg/mL	Unacceptable Strength is based on the active moiety per USP <1121>. Equivalence statement should also be provided if space permits.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]&	30 mL	Acceptable
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Not provided	Acceptable Information on inactive ingredients is not required for oral drugs.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	Acceptable
NDC number [per 21 CFR 201.2, requested, but not required for all labels or	79378-110-01	Acceptable

labeling, also see 21 CFR 207.35(b)(3)(i)]		
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Allocated on the right side	Acceptable
Storage conditions. If applicable, include a space for BUD.	Store unopened bottle at 68°F to 77°F (20°C to 25°C). After first opening, store (b) (4)	Unacceptable List the temperatures in centigrade first, followed by temperatures in Fahrenheit in parenthesis.
Bar code [21CFR 201.25(c)(2)]	Provided	Acceptable
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or “Recommended Dosage and Administration: See Prescribing Information” (21 CFR 201.55)	(b) (4)	Acceptable with minor edits Recommended statement: Recommended Dosage (b) (4) (b) (4) : See Prescribing Information
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Manufactured for Mirum Pharmaceuticals, Inc. Foster City, CA 94404	Acceptable
And others, if space is available	(b) (4) Space allocated for “Date of first opening”. Always store with cap on the bottle.	Acceptable

Conclusion: Unsatisfactory

Per USP <7>, a Beyond-Use Date (BUD), (b) (4) is recommended to be included on the container label. However, USP <7> states, “the dispenser shall label a container with a suitable beyond-use date to limit the patient's use of the article.” Therefore, it seems that BUD is typically provided by the dispenser. Whether to include a BUD, which will be determined by patients, on the container label has been consulted with DMEPA assessors, Sarah Vee and Matthew Barlow via email on March 29, 2021. As the date of this assessment, a final recommendation on this issue has not been made.

The following issues are identified for the container label:

1. (b) (4) Per USP <1121>, the active moiety should be used for the established name, i.e., maralixibat oral solution. Relocate the strength to be after the established name, such as the following:

Livmarli™
maralixibat oral solution
9.5 mg/mL
2. If space permits, include the statement “Each mL contains 10 mg of maralixibat chloride”.

3. Revise the storage conditions to list the temperature in centigrade first, followed by the temperature in Fahrenheit in parenthesis, as the following:

Store unopened bottle (b) (4) 20°C (b) (4) 25°C (68°F (b) (4) 77°F).

After first opening, store (b) (4)

4. Replace (b) (4) with
“Recommended Dosage (b) (4): See Prescribing Information”.

4.2 CARTON LABELS

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Livmarli™ (b) (4) oral solution	Unacceptable Per USP <1121>, the established name should use the name of the active moiety "maralixibat". (b) (4) Strength should be relocated to be after "oral solution"
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	oral	Acceptable
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	9.5 mg/mL Each (b) (4) contains (b) (4) 9.5 mg (b) (4) maralixibat (equivalent to 10 mg (b) (4) maralixibat chloride).	Acceptable with minor edits
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	30 mL	Acceptable
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	propylene glycol, sucralose, (b) (4), grape flavor and purified water.	Unacceptable (b) (4) Inactive ingredients are recommended to be listed in alphabetical order.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	Acceptable
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	79378-110-01	Acceptable
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Allocated	Acceptable
Storage conditions	Store unopened bottle at 68°F to 77°F (20°C to 25°C). After first opening, store (b) (4)	Unacceptable List the temperatures in centigrade first, followed by temperatures in Fahrenheit in parenthesis.
Bar code [21 CFR 201.25(c)(2)]	Provided	Acceptable

Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or “Recommended Dosage and Administration: See Prescribing Information” (21 CFR 201.55)	(b) (4)	Acceptable with minor edits Recommended statement: Recommended Dosage (b) (4): See Prescribing Information
“Keep out of reach of children” (Required for OTC in CFR. Optional for Rx drugs)	Provided	Acceptable
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Manufactured for Mirum Pharmaceuticals, Inc. Foster City, CA 94404	Acceptable
And others, if space is available	(b) (4) Always store with cap on the bottle.	Unacceptable Delete (b) (4)

Conclusion: Unsatisfactory

The issues of Items 1, 3, and 4 identified in the container assessment section are also applicable to the carton label. Additional issues for the carton label are listed below:

1. Replace the list of inactive ingredients “propylene glycol, sucralose, (b) (4) grape flavor and purified water” with “edetate disodium, grape flavor, propylene glycol, purified water, and sucralose”.
2. Replace “Each (b) (4) 9.5 mg (b) (4) maralixibat (equivalent to 10 mg (b) (4) maralixibat chloride).” with “Each mL contains 9.5 mg of maralixibat (equivalent to 10 mg of maralixibat chloride).”
3. Replace (b) (4)

4.0 LIST OF DEFICIENCIES:

A. Regarding PI

a) Highlight Section

1. Delete (b) (4)

b) Full Prescribing Information

Section 3: Dosage Forms and Strengths

2. Delete (b) (4)

Section 11: Description

3. Include the establish name, which should accompany the proprietary name, i.e., LIVMARLI (maralixibat) oral solution.
4. Use the title of USP monograph as the established name for inactive ingredients. List inactive ingredients in alphabetical order, i.e., edetate disodium, grape flavor, propylene glycol, purified water, and sucralose.
5. Add the pH of the oral solution.

Section 16: How Supplied/Storage and Handling

6. Delete (b) (4).
7. Delete the statement (b) (4)

B. Regarding the (b) (4)

8. Please address the following issues for the container and carton labels:
 - a. Delete (b) (4) Per USP <1121>, the active moiety should be used for the established name, i.e., maralixibat oral solution. Relocate the strength to be after the established name, such as the following:

Livmarli™
maralixibat oral solution
9.5 mg/mL

- b. Revise the storage conditions to list the temperature in centigrade first, followed by the temperature in Fahrenheit in parenthesis, as the following:
Store unopened bottle (b) (4) 20°C (b) (4) 25°C (68°F (b) (4) 77°F). After first opening, store (b) (4)
 - c. Replace (b) (4) with “Recommended Dosage (b) (4): See Prescribing Information”.
9. If space permits, include the statement “Each mL contains 10 mg of maralixibat chloride” for the container label.
10. Please address the following issues for the carton label:
 - a. Replace the list of inactive ingredients “propylene glycol, sucralose, (b) (4), grape flavor and purified water” with “edetate disodium, grape flavor, propylene glycol, purified water, and sucralose”.
 - b. Replace “Each (b) (4) contains (b) (4) 9.5 mg (b) (4) maralixibat (equivalent to 10 mg (b) (4) maralixibat chloride).” with “Each mL contains 9.5 mg of maralixibat (equivalent to 10 mg of maralixibat chloride).”
 - c. Replace (b) (4)

OVERALL ASSESSMENT:

Issues on the established name, product description, inactive ingredients established name, and the location of the strength on the contain and carton labels are identified.

Recommendation:

From the ONDP perspective, this application is *not* ready for approval in its present form per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Jane Chang, Ph.D.
Master Chemistry reviewer
ONDP/ DNDP II/Branch 4
05/27/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Hong Cai, Ph.D.
Chief, Branch 4
ONDP/ DNDP II
05/27/2021



Jane
Chang

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Cai

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CHAPTER VII: MICROBIOLOGY

[IQA NDA Assessment Guide Reference](#)

Product Information	
NDA Number	214662
Assessment Cycle Number	01
Drug Product Name/ Strength	Livmarli (Maralixibat chloride)/ 9.5 mg/mL
Route of Administration	Oral
Applicant Name	Mirum Pharmaceuticals Inc.
Therapeutic Classification/ OND Division	CDER/OII/DHN
Manufacturing Site	(b) (4)
Method of Sterilization	N/A - Non-sterile aqueous product

Assessment Recommendation: Adequate

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD seq #0002	11/12/2020
eCTD seq #0003	01/29/2021
eCTD seq #0028	05/27/2021
eCTD seq #0030	06/07/2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is indicated for the treatment of cholestatic pruritus in patients ≥ 1 -year-old with Alagille syndrome (ALGS). The drug product has been granted orphan drug designation, rare pediatric disease designation, and breakthrough therapy designation. This is a rolling eCTD submission.

Concise Description of Outstanding Issues: None identified.

Supporting Documents: None

S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug product is non-sterile.

MICROBIOLOGY LIST OF DEFICIENCIES

None identified

*Primary Microbiology Assessor Name and Date: Karthik Mosur Krishnan, Ph.D.,
06/07/2021*

*Secondary Assessor Name and Date: Yeissa Chabrier Rosello, Ph.D.,
06/08/2021*

NDA/ANDA: NDA 214662

Drug Product Name / Strength: Maralixibat Chloride Oral Solution, 9.5 mg/mL (30 mL multi-dose bottle)

Route of Administration: Oral Solution

Applicant Name: Mirum Pharmaceuticals, Inc.

Indication: Maralixibat Chloride Oral Solution is indicated for the treatment of Cholestatic pruritus in patient with Alagille syndrome (ALGS) 1 year of age and older

Submission date: 08/31/2020

Primary Reviewer: Kamrun Nahar, Ph.D.

Secondary Reviewer: Tapash Ghosh, Ph.D.

Recommendation: Adequate

1. REVIEW SUMMARY:

Background:

The proposed drug product, Livmarli™ (Maralixibat Chloride) Oral Solution, 9.5 mg/mL in 30 mL multi-dose bottle is a *ready-to-use fixed concentration* of Maralixibat free base solution 9.5 mg/mL (equivalent to 10 mg/mL of Maralixibat Chloride) which will be administered to the patient based on the body weight and will be taken once a day. The product is indicated for the treatment of Cholestatic pruritus in patient with Alagille syndrome (ALGS) 1 year of age and older. While the proposed commercial formulation of Maralixibat Chloride Oral, 9.5 mg/mL (30 mL) is a fixed concentration of Maralixibat, the formulation used in the clinical study was slightly different. In the clinical study, the Applicant used a fixed volume of diluent and drug concentration was adjusted as per the body weight of the patient. The Biopharmaceutics review will assess the bridging between the clinical and commercial formulation.

Solubility of Maralixibat Chloride:

The Applicant claimed that Maralixibat is a BCS class III compound. Solubility data across physiological pH indicated that the drug substance is highly soluble.

Table 1: Solubility of Maralixibat in aqueous media across physiological pH

Aqueous Medium or Buffer	Solubility at 37°C, 24 hours (mg/mL)	Solubility Classification
Water	≥ 100 ^a	Soluble
85 mM Hydrochloric Acid and 50 mM Potassium Chloride, pH 1.2	≥ 75	Soluble
42 mM Hydrochloric Acid and 50 mM Potassium Hydrogen Phthalate, pH 2.4	64	Soluble
22 mM Sodium Acetate, pH 4.5	88	Soluble
50 mM Monobasic Potassium Phosphate, pH 6.0	68	Soluble
50 mM Monobasic Potassium Phosphate, pH 6.8	64	Soluble
50 mM Monobasic Potassium Phosphate, pH 7.4	74	Soluble
50 mM Monobasic Potassium phosphate, pH 7.8	59	Soluble

^a Aqueous sample agitated for 168 hours, due to potential micelle formation.

Submission summary:

Maralixibat tablet and capsules with various strengths were developed for previous clinical studies in healthy adults' studies and patients with hypercholesterolemia, primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). Subsequently, Maralixibat Chloride oral solution was developed to administer in children patient. For the clinical trials in children, the liquid formulation was originally supplied with varying concentration of Maralixibat chloride (0.14 mg/mL to 50 mg/mL) using a diluent and fixed dosing volumes (FDVs). The Maralixibat Chloride oral solution was originally compounded on a patient based on their body weight and target dose group. The required amount of Maralixibat chloride was added to a (b) (4) glass vial containing 30 ml of diluent and mixed to form a clear solution. The FDV formulation was used in phase 2 clinical studies, including the clinical studies for the proposed indication. Slight optimization in the formulation composition was done to develop fixed drug substance concentration (FDSC) formulation later which is the proposed commercial drug product, (b) (4)

(b) (4)

The proposed commercial formulation of Maralixibat Chloride oral solution, 9.5 mg/mL is presented in a 30 mL multi-dose bottle for oral administration to the pediatric patient.

Table 2: Composition of fixed dose volume (FDV) formulation

Ingredients	Quality Standard	Function	Formulation ^{a, b}
Maralixibat Chloride	In-House	MRX Drug Substance (API)	(b) (4)
(b) (4)			

^a Amount of drug substance is determined based on the patient body weight and the dosing schedule per the applicable clinical study protocol.

^b The % w/w values are listed only for the components of the diluent vehicle.

(b) (4)			

Table 3: Composition of Maralixibat Chloride oral solution, 9.5 mg/mL (FDSC)

Ingredient	Compendial Status	Function	Quantity per Unit Dose	
			mg/mL	% w/w
Maralixibat Chloride ^a	In-House	Active Pharmaceutical Ingredient	10.0	(b) (4)
Propylene Glycol	USP, Ph. Eur.	(b) (4)	(b) (4)	(b) (4)
Purified Water ^b	USP, Ph. Eur.	(b) (4)	(b) (4)	(b) (4)
Disodium EDTA Dihydrate	USP, Ph. Eur.	(b) (4)	(b) (4)	(b) (4)
Sucralose	NF, Ph. Eur.	(b) (4)	(b) (4)	(b) (4)
Grape Flavor (b) (4)	In-House	(b) (4)	(b) (4)	(b) (4)
Total				
Total ^c			1.0 (mL)	-

Abbreviations: EDTA = ethylenediaminetetraacetic acid

^a The quantity of maralixibat chloride is adjusted based on its assay value. Quantity is expressed as maralixibat chloride (salt form), which can be converted to maralixibat (free base) using a conversion factor of 0.95.

^b Amount of purified water to be used is adjusted based on the assay value for maralixibat chloride.

^c The weight (mg) of the unit formula is converted to volume (mL) using the density of the respective solution.

Table 4: Comparative composition of the Maralixibat oral solution, fixed dosing volumes (FDV) vs fixed drug substance concentration (FDSC) formulations

Ingredient	Grade	Function	Quantity per Unit Dose (% w/w)	
			FDV Formulation ^c	FDSC Formulation
Maralixibat Chloride ^a	In-House	MRX Drug Substance (API)	Variable concentrations up to 50 mg/mL	Fixed concentration (b) (4)
Propylene Glycol	USP Ph. Eur.		(b) (4)	
Purified Water ^b	USP Ph. Eur.			
Disodium EDTA Dihydrate	USP Ph. Eur.			
Sucralose	NF Ph. Eur.			
Grape Flavor (b) (4)	In-House			
Total %				

Abbreviations: API = active pharmaceutical ingredient

- ^a The quantity of maralixibat chloride is adjusted based on its assay value. Quantity is expressed as maralixibat chloride (salt form), which can be converted to maralixibat (free base) using a conversion factor of 0.95.
- ^b Amount of purified water is adjusted based on the assay of maralixibat chloride in order maintain the weight of 1.00 mL of the solution.
- ^c The % w/w values are listed only for the components of the diluent vehicle.

Applicant's justification for the differences between the FDV and FDSC formulations:

- a. Maralixibat is a BCS class III compound and the proposed drug product is an oral solution. ≤ 3 mL of drug solution will be administered. Hence, the change (b) (4) in this volume will not cause any impact on the drug bioavailability and efficacy.
- b. The proposed Maralixibat is a fully soluble oral solution. Therefore, dissolution method is not relevant to the proposed commercial product.
- c. Maralixibat after ingestion targeting the small intestine surface. At the therapeutically relevant doses minimal amount of drug is absorbed which results in very low plasma drug levels. Therefore, it is difficult to measure plasma pharmacokinetic (PK) of Maralixibat and estimate absolute bioavailability which is below 1%. Similarly, bioequivalence/comparative bioavailability studies have not been conducted across formulations.

Reviewer's assessment:

Maralixibat chloride is a highly soluble compound and the proposed drug product is intended for the oral administration. Maralixibat oral solution FDV and FDSC has minor change in their composition which is believed not to cause any impact on efficacy and safety of the formulation. The drug product is intended to target small intestine surface with minimal absorption systemically. Hence, in vivo bioequivalence/comparative bioavailability studies are not required. Moreover, the proposed product is a solution dosage form dissolution is not required. Therefore,

based on the totality of the information, it is considered that no further bridging information is necessary between the FDV and FDSC formulations.

Conclusion and Recommendation:

From a Biopharmaceutics perspective, NDA 214662 for Maralixibat Chloride Oral Solution, 9.5 mg/mL is adequate for approval.

Documents reviewed in the NDA 022408:

1. Sequence 0001, dated 08/31/2020



Kamrun
Nahar

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Tapash
Ghosh

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Date: 6/02/2021 03:47:24PM

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