CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219485Orig1s000

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 16, 2024
Application Type and Number:	NDA 219485
Product Name, Dosage Form, and Strength:	Livmarli (maralixibat) tablets, 10 mg, 15 mg, 20 mg, 30 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mirum Pharmaceuticals, Inc. (Mirum)
PNR ID #:	2024-1044725838
DMEPA 1 Safety Evaluator:	Kristine Needleman, RPh
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Associate Director for Nomenclature and Labeling:	Idalia Rychlik, PharmD

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Livmarli, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the Reference section and Appendix A, respectively. Mirum submitted an external name study, conducted by [redacted] (b) (4) for this proposed proprietary name on April 6, 2020. The submitted external name study was previously reviewed under IND 119917 (see Section 1.1 below).

1.1 REGULATORY HISTORY

Mirum previously submitted the proposed proprietary name, Livmarli, under IND 119917 on April 6, 2020, for the oral solution. They also submitted an external name study conducted by [redacted] (b) (4) We found the name acceptable under the IND.[a]

On November 12, 2020, Mirum submitted the proposed proprietary name, Livmarli, under NDA 214662 for the oral solution. We reassessed the name and maintained that the proposed name was acceptable.[b] Livmarli oral solution was approved under NDA 214662 on September 29, 2021.

On June 10, 2024, Mirum submitted the proposed proprietary name, Livmarli, under NDA 219485 for an oral tablet dosage form.

1.2 PRODUCT INFORMATION

The following product information for both the oral solution and the tablet dosage form of Livmarli is provided in the proprietary name submission received on June 10, 2024, and the prescribing information received on August 7, 2024.[c]

Table 1. Relevant Product Information for Livmarli		
	Oral solution (NDA 214662)	Oral tablets (NDA 219485)
Intended pronunciation:	liv-MAR-lee	
Active ingredient:	Maralixibat chloride	

[a] Vee, S. Proprietary Name Review for Livmarli (IND 119917). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 05. PNR ID No. 2020-39036616.

[b] Vee, S. Proprietary Name Review for Livmarli (NDA 214662). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 04. PNR ID No. 2020-43885167.

[c] Proposed prescribing information for Livmarli. Foster City (CA): Mirum Pharmaceuticals, Inc.; 2024 AUG 07. Available from: \\CDSESUB1\EVSPROD\nda219485\0003\m1\us\114-labeling\draft\labeling\livmarli-draft-labeling-text.pdf

Table 1. Relevant Product Information for Livmarli		
Indication:	• For the treatment of cholestatic pruritus in patients 3 months of age and older with Alagille syndrome (ALGS). • For the treatment of cholestatic pruritus in patients 12 months of age and older with progressive familial intrahepatic cholestasis (PFIC).	
Dosage Form:	Oral Solution	Tablet
Strength:	9.5 mg/mL, 19 mg/mL	10 mg, 15 mg, 20 mg, 30 mg
Route of administration:	oral	

Table 1. Relevant Product Information for Livmarli

Dose and frequency:

- ALGS: 380 mcg/kg once daily, taken 30 minutes before a meal in the morning

Table 1: 9.5 mg/mL Solution for Patients with ALGS: Volume per Dose (mL) by Weight

Patient Weight (kg)	Days 1-7 (190 mcg/kg once daily)	Beginning Day 8 (380 mcg/kg once daily)
	9.5 mg/mL Solution (for ALGS) Volume per Dose (mL)	
5 to 6	0.1	0.2
7 to 9	0.15	0.3
10 to 12	0.2	0.45
13 to 15	0.3	0.6
16 to 19	0.35	0.7
20 to 24	0.45	0.9
25 to 29	0.5	1
30 to 34	0.6	1.25
35 to 39	0.7	1.5
40 to 49	0.9	1.75
50 to 59	1	2.25
60 to 69	1.25	2.5
70 or higher	1.5	3

(b) (4)

[redacted]

Table 1. Relevant Product Information for Livmarli

Table 3: 19 mg/mL Solution for Patients with PFIC: Volume per Dose (mL) by Weight

Patient Weight (kg)	285 mcg/kg (once daily titrated to twice daily)	428 mcg/kg (twice daily)	570 mcg/kg (twice daily as tolerated)
	19 mg/mL Solution (for PFIC) Volume per Dose (mL)		
5	0.1	0.1	0.15
6 to 7	0.1	0.15	0.2
8	0.1	0.2	0.25
9	0.15	0.2	0.25
10 to 12	0.15	0.25	0.3
13 to 15	0.2	0.3	0.4
16 to 19	0.25	0.4	0.5
20 to 24	0.3	0.5	0.6
25 to 29	0.4	0.6	0.8
30 to 34	0.45	0.7	0.9
35 to 39	0.6	0.8	1
40 to 49	0.6	0.9	1
50 to 59	0.8	1	1
60 or higher	0.9	1	1

(b) (4)

- For ALGS the maximum daily dose should not exceed 28.5 mg (3 mL) per day for LIVMARLI oral solution and 30 mg per day for LIVMARLI tablets. For PFIC the maximum daily dose should not exceed 38 mg (2 mL) per day for LIVMARLI oral solution and 40 mg per day for LIVMARLI tablets.

How Supplied:	9.5 mg/mL in a 30 mL amber plastic bottle 19 mg/mL in a 30 mL amber plastic bottle	10 mg, 15 mg, 20 mg, and 30 mg oral tablets in bottles of 30 tablets.
Storage:	Store unopened LIVMARLI oral solution and tablets 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]. (b) (4) and discard any remaining LIVMARLI after 100 days.	

2 DISCUSSION

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Livmarli.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Livmarli would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) concurred with the findings of OPDP's assessment for Livmarli. The Division of Hepatology and Nutrition (DHN) concurred with the findings of OPDP's assessment for Livmarli.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name Livmarli.

2.2.1 UNITED STATES ADOPTED NAMES (USAN) SEARCH

There is no USAN stem present in the proposed proprietary name.[d]

2.2.2 COMPONENTS OF THE PROPOSED PROPRIETARY NAME

Mirum did not provide a derivation or intended meaning for the proposed proprietary name, Livmarli, in their submission. This proprietary name is comprised of a single word that contains the letters 'iv,' which is the abbreviation for the intravenous route of administration. Although we typically discourage the inclusion of medical abbreviations in proprietary names, we determined that the location of this abbreviation in the middle of the name and the lack of prominence of this abbreviation makes it unlikely that the letters 'iv' within the proposed proprietary name, Livmarli, could lead to confusion in this case.

Thus, we do not object to the inclusion of the letter string 'iv' in this case. Beyond this abbreviation, we note that Livmarli does not contain any additional components (i.e., a route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 COMMENTS FROM OTHER REVIEW DISCIPLINES AT INITIAL REVIEW

On July 17, 2024, the Division of Hepatology and Nutrition (DHN) did not forward any comments or concerns relating to Livmarli at the initial phase of the review.

2.2.4 FDA PRESCRIPTION SIMULATION STUDIES

Ninety-seven (97) practitioners participated in DMEPA's prescription simulation studies for Livmarli. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the prescription simulation studies.

[d] USAN stem search conducted on July 17, 2024.

2.2.5 MULTIPLE DOSAGE FORMS UNDER A SINGLE PROPRIETARY NAME

Under NDA 219485 the Applicant proposes a new dosage form of oral tablets, which will be available in four strengths: 10 mg, 15 mg, 20 mg, and 30 mg. We note that the proposed oral tablets share the same active ingredient, indications, route of administration, and frequencies of administration as that of the currently approved oral solution. However, the proposed oral tablets differ from the currently marketed Livmarli oral solution with respect to the dosage form, strength, and dosing parameters (see Section 1.2 Product Information, Table 1).

Based on discussions with the DHN clinical reviewers we note that any difference between the bioequivalence of the two dosage forms at the site of action as well as systemically is acceptable from a clinical and safety perspective. Thus, we find that the residual risk of confusion between the oral solution and tablet formulations of the product may be mitigated through label and labeling interventions.

Additionally, we have not identified any relevant medication errors involving name confusion with the proprietary name Livmarli through routine post-marketing surveillance monitoring. Therefore, given the considerations discussed above, we do not object to the Applicant's proposal to market the proposed product with the proprietary name Livmarli.

2.2.6 COMMUNICATION OF DMEPA'S DETERMINATION

On December 16, 2024, DMEPA 1 communicated our determination to the Division of Hepatology and Nutrition (DHN).

3 CONCLUSION

The proposed proprietary name, Livmarli, is conditionally acceptable.

3.1 COMMENTS TO MIRUM PHARMACEUTICALS, INC.

We have completed our review of the proposed proprietary name, Livmarli, and have concluded that this proprietary name is conditionally acceptable.

If any of the proposed product characteristics as stated in your submission received on June 10, 2024, and August 7, 2024, are altered prior to approval of the marketing application the proprietary name must be resubmitted for review.

4 REFERENCES

1. United States Adopted Names (USAN) Stems

USAN Stems List contains all the recognized USAN stems, available at https://www.ama-assn.org/about/united-states-adopted-names/united-states-adopted-names-approved-stems.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved brand name and generic drugs; therapeutic biological products, prescription and over-the-counter human drugs; and discontinued drugs (see Drugs@FDA Glossary of Terms, available at https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html).

Purple Book

The Purple Book is an online database that contains information about biological products, including biosimilar and interchangeable biological products, licensed (approved) by the FDA under the Public Health Service (PHS) Act. See Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations, available at https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or.

Division of Medication Errors Prevention and Analysis pending proprietary name requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis.

5 APPENDICES

APPENDIX A. FDA'S PROPRIETARY NAME RISK ASSESSMENT EVALUATES PROPOSED PROPRIETARY NAMES FOR MISBRANDING AND SAFETY CONCERNS

1. Misbranding Assessment: For prescription drug products, the Office of Prescription Drug Promotion (OPDP) assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by the Office of Non-Prescription Drugs (ONPD). OPDP or ONPD evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or ONPD provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

2. Safety Assessment: The safety assessment is conducted by DMEPA, and includes the following:

    a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 3. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.[e]

Table 3. Prescreening Checklist for Proposed Proprietary Name Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.	
Y/N	Is the proposed name obviously similar in spelling and pronunciation to other names?
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	Are there inert or inactive ingredients referenced in the proprietary name?
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	Does the proprietary name include combinations of active ingredients?
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	Is there a United States Adopted Name (USAN) stem in the proprietary name?
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.

[e] National Coordinating Council for Medication Error Reporting and Prevention. https://www.nccmerp.org/about-medication-errors. Last accessed 10/05/2020.

Table 3. Prescreening Checklist for Proposed Proprietary Name Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.	
Y/N	Is this proprietary name used for another product that does not share at least one common active ingredient?
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	Is this a proprietary name of a discontinued product?
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. FDA Prescription Simulation Studies: DMEPA also conducts prescription simulation studies using FDA health care professionals.

   Four separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions, verbal pronunciation of the drug name or during computerized provider order entry. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify vulnerability of the proposed name to be misinterpreted by healthcare practitioners during written, verbal, or electronic prescribing.

   In order to evaluate the potential for misinterpretation of the proposed proprietary name during written, verbal, or electronic prescribing of the name, written inpatient medication orders, written outpatient prescriptions, verbal orders, and electronic orders are simulated, each consisting of a combination of marketed and unapproved drug products, including the proposed name.

c. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND), Office of Generic Drugs (OGD), and/or Office of Pharmaceutical Quality (OPQ) for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the Safety Evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name.

   Additionally, other review disciplines opinions such as OPQ may be considered depending on the proposed proprietary name.

   When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

APPENDIX B. PRESCRIPTION SIMULATION SAMPLES AND RESULTS

Figure 1. Livmarli Study (Conducted on June 28, 2024)

Handwritten Medication Order Prescription	Verbal Prescription
Medication Order: Livmarli 20mg po BID	Livmarli 15 mg by mouth once daily in the morning 30 minutes before a meal Dispense #30
Outpatient Prescription: Livmarli 15 mg po once daily in the morning 30 minutes before a meal #30 tabs	
CPOE Study Sample (displayed as sans-serif, 12-point, bold font)	
Livmarli	

FDA Prescription Simulation Responses (Aggregate Report)					
Study Name: Livmarli People Received Study: 194 People Responded: 97					
Total	29	23	20	25	97
INTERPRETATION	INPATIENT	OUTPATIENT	VOICE	CPOE	TOTAL
LIMARVY	0	0	1	0	1
LIVEMARLEE	0	0	1	0	1
LIVMANLI	1	0	0	0	1
LIVMARLEY	0	0	6	0	6
LIVMARLI	28	20	4	25	77
LIVMARLY	0	0	7	0	7
LIVMARLYE	0	0	1	0	1
LIVMORLI	0	1	0	0	1
LIVONARLI	0	1	0	0	1
LIVRNARLI	0	1	0	0	1

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/s/

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