CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219488Orig1s000

PRODUCT QUALITY REVIEW(S)

Title:	NDA IQA Template Title Page- EXEC SUMMARY
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Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	219488
Applicant Name	Mirum Pharmaceuticals, Inc.
Drug Product Name	CTEXLI™ (chenodiol) Tablet, 250 mg
Dosage Form	Tablet
Proposed Strength(s)	250 mg
NDA Classification	Type 10 – New Indication Submitted as Distinct NDA – Not Consolidated
Route of Administration	Oral
Maximum Daily Dose	750 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of cerebrotendinous xanthomatosis
Drug Product Description	Mirum Pharmaceuticals, Inc. has submitted this 505(b)(2) new drug application for CTEXLI™ (chenodiol) Tablet, 250 mg for the treatment of cerebrotendinous xanthomatosis. The patients are to take a 250 mg tablet three times daily. The drug substance, chenodiol, was first approved as the active ingredient of the brand name drug product Chenix® indicated for patients with radiolucent stones in well-opacifying gallbladders, in whom selective surgery would be undertaken except for the presence of increased surgical risk due to systemic disease or age on July 28, 1983. Since its first approval, Chenix® has been discontinued but not because of safety or toxicity. However, chenodiol has been approved as a generic drug product under ANDA 019019 on October 22, 2009, and it is currently being marketed in the United States. ANDA 091019 is used as listed drug (LD) for this application.

	This application did not include Chemistry, Manufacturing and Controls (CMC) information in module 3. Module 3 for this application was cross-referenced to ANDA 091019. This application is for the same exact drug product in ANDA 091019 without any CMC changes or manipulations and is only submitted for the new indication, the treatment of cerebrotendinous xanthomatosis. CTEXLI is supplied as a white film-coated tablet imprinted with “MP” on one side and “250” on the other side. Each tablet contains 250 mg of chenodiol as the active ingredient and magnesium stearate, microcrystalline cellulose, pregelatinized starch; silicon dioxide, and sodium starch glycolate as inactive ingredients. The thin-film coating contains Opadry YS 2 7035 (consisting of glycerin and methylcellulose) and sodium lauryl sulfate. CTEXLI (chenodiol) tablets are packaged in bottles containing 100 tablets. This drug product should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Based on the currently available stability data, an expiration dating period of 36 months is granted to this drug product.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sukhamaya Bain, PhD	Lawrence Perez, PhD
	Drug Product/ Labeling	Zhengfang Ge, PhD	Hamid Shafiei, PhD/Julia Pinto, PhD
	Manufacturing	Mesfin Abdi, PhD	Vaikunth Prabhu, PhD.

	Biopharmaceutics	Tapash Ghosh, PhD	N/A
	Microbiology	N/A	N/A
	Other (specify)	N/A	N/A
	RBPM	Teshara Bouie, MSA	
	ATL	Hamid Shafiei, PhD	
Consults	N/A		

2. Final Overall Recommendation - Approval

This application did not include the CMC module for review. The CMC information for this application was cross-referenced to ANDA 091019. The right to cross reference ANDA 091019 was submitted to the application. ANDA 091019 was approved on October 22, 2009. The drug product in this application is same 250 mg chenodiol tablet for oral administration approved under ANDA 019019 without any CMC changes, modification, and/or manipulations. This 505(b)(2) new drug application has been submitted by a different applicant than the holder of ANDA 091019 for the use of chenodiol 250 mg tablet for a different indication. The IQA for this application will be brief and will only include the review of the PI labeling and container/carton labels, a memorandum from the biopharmaceutics perspective, and a brief review of the process and facilities. All CMC updates through post-approval supplements to date for ANDA 091019 have been reviewed and approved. The latest updates to drug substance submitted in DMF (b) (4) has been reviewed by Dr. Sukhamaya Bain on August 30, 2024 as a part ANDA 091019 post-approval review and found to be adequate.

Based on the CMC information provided in the approved ANDA 091019, and the review and approval of all CMC containing post-approval supplements to date submitted to this ANDA since its original approval, this application is recommended for approval from the OPQ perspective.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- Based on the up-to-date CMC information provided, reviewed, and approved for the cross-referenced ANDA 019019, it is concluded that the applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, chenodiol and the drug product, CTEXLI™ (chenodiol) Tablet, 250 mg.

- The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC-recommended revisions and comments regarding PI labeling as well as container and carton labels have been adequately addressed.
- The applicant's request for categorical exclusion from the preparation of environmental assessment has been found adequate and is granted.

Therefore, this application is recommended for approval from the OPQ perspective with an expiration dating period of 36 months.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**N/A**

Environmental Assessment: Choose an item.
QPA for EA(s): Yes
(refer to ANDA 019019)

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

Application Technical Lead Name:

Hamid Shafiei, Ph.D.
Senior Pharmaceutical Quality Assessor
DPQA VII/OPQA II/OPQ

APPEARS THIS WAY IN ORIGINAL

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 1/26/2025 06:03:33PM
GUID: 507d824300005f344cf8b5e5989f0057

Memorandum

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

Date: **Nov. 1, 2024**

From: **Zhengfang Ge, Ph.D.**
Reviewer, OPQ/OPQAII/Division VII

Through: **Julia Pinto, Ph. D.**
Supervisor, OPQ/OPQAII/Division VIII

To: **Labeling Review of NDA 219488: Ctexli (chenodiol) tablets**

Subject: **Final Recommendation for Labeling/Labels**

The CMC comments in the previous labeling review have been communicated to the applicant. The revised labeling is acceptable. The revised container label provided in the **Attachment** is satisfactory.

Recommendation:

The labeling/labels are now **adequate** from the CMC perspective.

Attachment:

Container Label:

Zhengfang Ge

Digitally signed by Zhengfang Ge
Date: 11/01/2024 02:18:11PM
GUID: 508da7210002a030e76df4f60ccd142a

Julia Pinto

Digitally signed by Julia Pinto
Date: 11/01/2024 02:19:46PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	219488
Assessment Cycle Number	1
Drug Product Name	Ctexli (chenodiol) tablets

Assessment Recommendation: Inadequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Inadequate	See recommendation below
Patient Information	Adequate	
Instruction for Use (IFU)	N/A	
Container Labels	Inadequate	See recommendation below
Carton Labeling	N/A	

Brief Description of Outstanding Issues:

The NDA cross referenced CMC information to ANDA 091019. The labeling is similar to the generic drug product approved in ANDA 091019. Some minor recommendations listed in section 4 **OUTSTANDING ISSUES AND RECOMMENDATIONS** should be communicated to the applicant and expected to be accepted by the applicant. The final labeling will be included in the executive summary by the SPQA.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0001	6/28/2024	Labeling

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

[redacted]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	Established name: chenodiol
Route(s) of administration	Adequate	- Tablets, for oral use
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	- Tablets
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8]	N/A	

Assessment: *Adequate*

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>
[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	- Taken orally with and without meal
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)
[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments
[11] §201.57(c)(3)(iv)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: *Adequate*

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	tablets

[12] USP General Notices 2.30 Legal Recognition
[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Strength(s) in metric system	Adequate	250 mg
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Inadequate	- Add the description of the tablets "white film-coated tablets imprinted with "MP" on one side and "250" on the other side"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: *Inadequate*

- Add description of the tablets "- The description of the tablets "white film-coated tablets and imprinted "MP" on one side and "250" on the other side" will be added

1.2.3 Section 11 (DESCRIPTION)[14]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Inadequate	- Change 1st sentence of the 2nd paragraph to read "CTEXLI (chenodiol) tablets"
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	- tablets
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg	N/A	

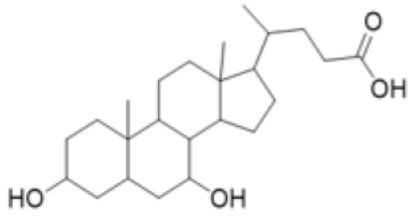
[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)
[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].		
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Inadequate	- Rearrange the excipients in alphabetic order.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	- Chenodiol is a naturally occurring human bile acid which is the same in ANDA labeling
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Inadequate	- Missing β for the 5-cholan. The correct chemical name should be 3α, 7α-dihydroxy-5β-cholan-24-oic acid

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
		
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	- a bitter-tasting white powder consisting of crystalline and amorphous particles freely soluble in methanol, acetone and acetic acid and practically insoluble in water
For oral prescription drug products, include gluten statement[19] (if applicable).	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	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: *Inadequate*
- The chemical name should be correct to "3α, 7α-dihydroxy-5β-cholan-24-oic acid"
- The excipients should be organized in alphabetic order.

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	- change the 1st sentence to read "CTEXLI (chenodiol) tablets 250 mg
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	- 250 mg
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	- Bottle of 100
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	- white film-coated 250 mg tablets imprinted with "MP" on one side and "250" on the other
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Inadequate	- Add "excursions permitted to 15° - 30°C (59° - 86°F)"
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21]	N/A	

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Include information about child-resistant packaging[22] (if chosen by manufacturer).	N/A	

Assessment: *Inadequate*

- change the 1st sentence to read "CTEXLI (chenodiol) tablets 250 mg
- Add "excursions permitted to 15° - 30°C (59° - 86°F)"

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

None

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	Manufactured for: Mirum Pharmaceuticals, Inc. Foster City, CA 94404

Assessment: *Adequate*

[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

2.0 PATIENT LABELING

No CMC information for Patient Counseling Information is provided in section 17

3.0 CONTAINER AND CARTON LABELING[24]

Only bottle label is proposed. No carton label.

3.1 Container Labels[25]

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[26], (font size and prominence) [§ 201.10(g)(2)].	Inadequate	- The dose strength should be after dosage form as the following: Ctexli (chenodiol) tablets 250 mg

[24] Carton and Container Labeling Resources
[25] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.
[26] Established name = [Drug] [Route of Administration] [Dosage Form]

		- established name should be ½ size of the trade name
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[27]	Adequate	250 mg
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Inadequate	- Add “for oral use” in the c/c labels
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[28]	Adequate	- 100 tablets
“Rx only” displayed on the principal display [§ 201.100(b)(1)].	Adequate	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	
Lot number and expiration date [§ 201.18 & 201.17].	Inadequate	- Add Lot number and expiration date in the c/c labels
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Inadequate	- Add “excursions permitted between 15° to 30°C (59°to 86°F)”
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk	N/A	

[27] Express as “ XX mg per tablet” or “XX mg per capsule” for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[28] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

package, and these products require a “Not for direct infusion” statement. (See USP <659>).		
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Linear Bar code [§ 201.25(c)(2)].[29]	Adequate	
Adequate directions for use: “Recommended Dosage: See Prescribing Information” [§ 201.5 & 201.55].	Inadequate	- Add “Recommended Dosage: See Prescribing Information”
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	
“Keep out of reach of children” statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	

[29] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[30]	N/A	
And others if space is available.	N/A	

Assessment of Carton Labels and Container Labeling: *Inadequate*

- Established name should be ½ size of the trade name.
- Add "for oral use" in the c/c labels.
- Add Lot number and expiration date in the c/c labels.
- Add "excursions permitted between 15° to 30°C (59°to 86°F)" for the storage condition
- Add "Recommended Dosage: See Prescribing Information"

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

The following editorial changes should be made in the Prescribing Information

Section 3 Dosage Form and Strength

- Add the description of the tablets "white film-coated tablets imprinted with "MP" on one side and "250" on the other side".

[30] USP General Notices 3.20 Indicating Conformance

Section 11 Description

- Change 1st sentence of the 2nd paragraph to read “CTEXLI (chenodiol) tablets”.
- Missing β for the 5-cholan. The correct chemical name should be 3α, 7α-dihydroxy-5β-cholan-24-oic acid.
- Rearrange the excipients in alphabetic order.

Section 16 How Supplied/Storage and Handling

- Change the 1st sentence to read “CTEXLI (chenodiol) tablets 250 mg.
- Add “excursions permitted to 15° - 30°C (59° - 86°F)” to the storage condition.

The following changes for the C/C Labels should be communicated to the applicant

- Established name should be ½ size of the trade name.
- Add “for oral use” in the c/c labels.
- Add Lot number and expiration date in the c/c labels.
- Add “excursions permitted between 15° to 30°C (59°to 86°F)” for the storage condition.
- Add “Recommended Dosage: See Prescribing Information”.

Primary Labeling Assessor Name and Date:

Zhengfang Ge, Ph. D.
Reviewer, OPQ/OPQAII/Division VII

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

Julia Pinto, Ph. D.
Supervisor, OPQ/OPQAII/Division VIII

Zhengfang Ge

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Julia Pinto

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QUALITY REVIEW

BIOPHARMACUTICS
NDA: NDA 219488
Drug Product Name / Strength: CTEXLI™ (chenodiol) 250 mg Tablet
Route of Administration: Oral
Applicant Name: Mirum Pharmaceuticals, Inc. (Mirum)
Indication: Treatment of cerebrotendinous xanthomatosis
Submission date: 06/28/2024
Primary Reviewer: Tapash Ghosh, Ph.D.
Recommendation: Adequate

BACKGROUND:

Mirum Pharmaceuticals, Inc. (Mirum) submitted this original NDA 219488, seeking approval for chenodiol 250-mg tablets for the treatment of cerebrotendinous xanthomatosis in patients via the 505(b)(2) pathway. This submission relies on Mirum's completed pivotal Phase 3 RESTORE clinical study (Cheno-CTX-301), entitled "A Phase 3 Study to Evaluate the Effects of Chenodeoxycholic Acid in Adult and Pediatric Participants with Cerebrotendinous Xanthomatosis" and supported by data available in the published literature, FDA's previous findings of safety and efficacy for chenodiol as reflected in approved labeling (NDA 018513 and authorized cross-reference to ANDA 091019 for the chemistry, manufacturing and controls content.

This NDA did not include the CMC module 3. Module 3 for this application was referred to ANDA 091019. It is the product approved under ANDA 091019 for a new indication.

Division of Biopharmaceutics was tasked to comment on the appropriateness of establishing the bridge between the chenodiol 250 mg tablets (proposed drug, Ctexli) submitted via 505 (b)(2) pathway to the relied-upon listed drug (LD), Leadiant Biosciences, Inc's Chenix (chenodiol, 250 mg tablets), which was approved under NDA 018583.

REVIEW SUMMARY:

The Applicant (Mirum Pharmaceuticals, Inc.) has established a bridge between the chenodiol 250 mg tablets (proposed drug, Ctexli) submitted under NDA 219488 to the relied-upon listed drug (LD), Leadiant Biosciences, Inc's Chenix (chenodiol, 250 mg tablets), which was approved under NDA 018513.

The LD product has been discontinued for reasons other than safety and efficacy. The reference standard (RS) for chenodiol 250 mg tablets is ANDA 091019 that is owned by LGM Pharma Solutions. The RS serves as the conduit to bridge all of FDA's previous findings of safety and efficacy for nonclinical toxicology, and chemistry, manufacturing, and controls (CMC) information in the LD, NDA 018513.

To rely on the Agency's previous finding of safety and efficacy of the LD, the applicant established their bridge between their proposed product to the LD as follows:

1. The Applicant provided a right of reference to LGM Pharma Solutions' chenodiol 250 mg tablets ANDA 091019. Both the proposed to-be-marketed product under NDA 219488 and the product marketed under ANDA 091019 are identical in composition (i.e., identical drug product (same active ingredient, inactive ingredients, route of administration, dosage form, and strength)), and both will be manufactured by LGM Pharma Solutions.

   Note that because both products are identical, the Office of Pharmaceutical Quality determined that it was unnecessary to conduct bioavailability studies between the to-be-marketed product proposed under NDA 219488 and the product marketed under ANDA 091019 because the products are identical and sourced from the same manufacturer.

2. For approval of LGM Pharma Solutions' generic chenodiol product (ANDA 091019), LGM Pharma demonstrated bioequivalence to NDA 018513 Chenix (chenodiol) 250 mg tablets.

Therefore, because the Applicant has a right-of-reference to RS ANDA 091019, and the to-be-marketed product proposed under NDA 219488 is identical to RS ANDA 091019, and bioequivalence has been demonstrated between the RS ANDA 091019 and the LD NDA 018513, the Applicant has established a bridge between their proposed product and the LD.

CONCLUSION AND RECOMMENDATION:

Form a Biopharmaceutics perspective, NDA 219488, CTEXLI™ (chenodiol) 250 mg Tablet is **adequate** for approval for the treatment of cerebrotendinous xanthomatosis.

Tapash Ghosh

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/s/

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