CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 214755

Review #1

Drug Product Name	LUMRYZ (sodium oxybate)
Dosage Form	for extended-release suspension
Strength	4.5 g, 6 g, 7.5 g, 9 g
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Avadel CNS Pharmaceuticals, LLC
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Gaetan Ladouceur	Donna Christner
Drug Product	Grace Chiou	Julia Pinto
Manufacturing	Huia T. (Ted) Chang	Yong Hu
Microbiology	Julie Nemecek	Denise Miller
Biopharmaceutics	Leah Falade	Ta-Chen Wu
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	--
Environmental	N/A	--

DOCUMENTS REVIEWED

Submission(s)	Document Date	Discipline(s) Affected
SD-, Original NDA	12/15/2020	All
SD-09, Response to information request (IR)	3/23/2021	Drug product
SD-17, Response to IR	5/14/2021	Biopharmaceutics
SD-19, Response to IR	5/27/2021	Drug product

SD-19, Response to IR	6/22/2021	Manufacturing
SD-23, Response to IR	7/22/2021	Drug product
SD-25, Response to IR	7/27/2021	Manufacturing
SD-30, Response to IR	8/31/2021	Biopharmaceutics

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II	(b) (4)	Sodium oxybate	Adequate	5/6/2019	
(b) (4)	III		(b) (4) packets	--	--	Adequate information in NDA. DMF was not reviewed

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
IND	126321	Avadel IND for development of Lumryz (sodium oxybate for extended-release oral suspension)
NDA	21196	Jazz Pharmaceuticals NDA for Xyrem (sodium oxybate oral solution). Referenced under 505(b)(2) to support safety of Lumryz.

2. CONSULTS

None

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The OPQ review team recommends that the Agency **APPROVE** NDA 214755, Lumryz (sodium oxybate for oral suspension). From a quality perspective, the application, as amended during the review, provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Sodium oxybate, also known as sodium gamma-hydroxybutyrate, is marketed Jazz Pharmaceuticals as Xyrem® (sodium oxybate) oral solution under NDA 21196 (AP 2002). Jazz also markets a mixed salt product, Xywav® (calcium, magnesium, potassium and sodium oxybates) oral solution (NDA 212690, AP 11/2020).

The applicant proposes marketing sodium oxybate as a powder for extended-release oral suspension. The product will be marketed in single-dose packets containing 4.5 g, 6 g, 7.5 g or 9 g sodium oxybate. The product should be constituted with approximately 80 mL water and taken at bedtime, while the patient is in bed.

The drug product formulation consists of a mixture of immediate-release pellets and delayed-release pellets. All excipients are commonly used in oral dosage forms. The manufacturing process involves (b) (4) .

Based on the initial risk assessment, the potential for alcohol dose dumping was considered a high-risk critical quality attribute (CQA). Stability, dissolution, and palatability were considered moderate risk CQAs: Content uniformity and microbial contamination were considered low risk.

Proposed indication(s) including intended patient population	Treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy
Duration of treatment	Chronic
Maximum daily dose	9 g
Alternative methods of administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Sodium oxybate drug substance is manufactured by [redacted] Information to support manufacture and control of sodium oxybate is cross-referenced to [redacted] DMF [redacted] The DMF was last reviewed on 5/6/2019 and deemed adequate. [redacted] assigns a [redacted]-month retest date for sodium oxybate.

The applicant provided general information, acceptance specifications, and certificates of analysis for sodium oxybate in the NDA. The information provided in the NDA is consistent with information in the referenced DMF and adequate to support approval.

Drug Product: Adequate

The proposed product is a powder for extended-release suspension containing 4.5 g, 6 g, 7.5 g, of 9 g of sodium oxybate per unit dose packet. The active ingredient is formulated as a mixture of IR and DR beads. To administer the dose, the patient is instructed to constitute the powder with liquid and take immediately at bedtime. The inactive ingredients are compendial excipients suitable for use in solid oral dosage forms. The primary packaging is a [redacted] pack. The product will be distributed in 7-count and 30-count cartons with a calibrated, [redacted] mixing cup. The container closure system is suitable for pharmaceutical use and available stability data show that it provides adequate protection for the drug product through the proposed shelf-life.

The proposed drug product specification is acceptable. The principal impurity, [redacted], is controlled to not more than [redacted]% and the limit for unspecified impurities, [redacted]% is consistent with ICH Q3B recommendations for the maximum daily dose. The proposed tests and acceptance criteria are appropriate to control the quality of this solid oral dosage form and all non-compendial methods are validated. The applicant has provided risk assessment in accordance with ICH Q3D to support the omission of test for elemental impurities. The applicant also provided a [redacted] risk analysis and assessment of the drug product; there is a negligible potential for [redacted] impurities. Exclusion of tests for particle size distribution and suspendability were justified.

Based on the stability data provided, the requested **36-month expiry for product stored at 20°C to 25°C (68°F to 77° F)** is granted.

Labeling: Adequate

Minor labeling deficiencies have been communicated to the clinical division and will be addressed during labeling negotiations. Additionally, due to the potential for dose dumping at pH levels or temperature, it is recommended that instructions to mix the powder with cold or room temperature tap water. The patient should be instructed to

use a mineral water with a bicarbonate ion concentration (HCO3-) concentration above 1400 mg/L.

Manufacturing: Adequate

The drug product manufacturing process includes [redacted]

All facilities proposed for commercial manufacture or testing of the sodium oxybate drug substance and Lumryz (sodium oxybate for extended-release suspension) are currently acceptable. Facility status should be verified prior to final action.

Biopharmaceutics: Adequate

The biopharmaceutics review evaluated the proposed dissolution method and acceptance criteria, formulation bridging, biowaiver request, dose-dumping potential, interaction with antacids and proton pump inhibitors (PPIs), and the extended-release designation claim.

The proposed dissolution method (two-stage acid/buffer) is adequately justified and shown to be discriminatory toward control-release coating levels. The acceptance criteria for the acid phase were deemed acceptable. In response to an IR, the applicant agreed to adopt the FDA-recommended accepted acceptance criterion of NLT [redacted]% at four hours for the buffer stage. The agreed-upon method and acceptance criteria are summarized below.

Apparatus	Agitation Speed	Medium Volume	Temp.	Medium	Acceptance Criteria
2 (paddle)	100 rpm	900 mL	37°C	**Stage 1:** 0.1 N HCl for 2 hr **Stage 2:** pH 6.0 phosphate buffer for 6 hr	0.25 hr: [redacted]% 2 hr: [redacted]% 4 hr: NLT [redacted]%

Except for the two exploratory Phase 1 studies, the clinical formulation is the same as the to-be-marketed (TBM) formulation. Therefore, product bridging is not necessary.

The Applicant conducted a dose-proportionality study on the 4.5 g, 7.5 g, and 9 g strengths. Together with the proposed 6 g strength studied in the pivotal Phase 1 bridging study, a biowaiver is not needed.

In vitro alcohol dose-dumping was observed in 40% ethanol (~100% release in 1 hour). The presence of 20% alcohol increased drug release by 10% at 2 hours. In in vitro to investigate the impact of beverages, reconstitution time, and temperatures on the drug release, it was found that mineral water with a pH of 6.4 impacted the drug release after 15 and 30 min and hot water (90°C) impacts on drug release. The potential mechanisms for dose-dumping will be addressed in product labeling. In in vitro studies, there was no impact on the drug release in the presence of antacids or PPIs.

The information provided to support the extended-release designation claim were deemed acceptable as per requirements in 21 CFR 320.25(f).

Microbiology: Adequate

The drug product is non-sterile and packaged in single-dose (b) (4) packs. The pellets are suspended in water no more than 30 minutes prior to oral administration. Therefore, the product quality microbiology review is focused on microbiological control including microbial release testing. The proposed specification meets the regulatory expectations per USP <1111> for a nonaqueous preparation for oral use. Method suitability testing was performed and is acceptable.

Environmental: Adequate

The applicant claims a categorical exclusion pursuant to 21 CFR 25.31(a) because action on the NDA is not expected to increase use of the active moiety. A statement of no extraordinary circumstances has been submitted.

The Applicant's claim for categorical exclusion is acceptable.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Assay, stability	Formulation, container closure, moisture, process parameters	**Moderate**	The product is formulated as a dry powder to be mixed with liquid within 30 prior to use. Packaging is adequate to prevent moisture and stability is shown in long-term stability studies.	**Adequate**	
Content uniformity	API physical properties, formulation, process parameters, equipment, scale	**Low**	(b) (4)	**Adequate**	
Dissolution	API properties, formulation, process parameters, pellet size, equipment, scale	**Moderate**	The sponsor has developed an appropriate dissolution method that is discriminating with respect to variation in the release controlling coating. The method is suitable for routine quality control.	**Adequate**	
Alcohol dose dumping	API properties, formulation, process parameters, pellet size, equipment, scale	**High**	Alcohol dose dumping is observed in in vitro studies. This information will be included in labeling. Use of alcohol with sodium oxybate is contraindicated for safety reasons.	**Adequate**	
Palatability	Formulation, excipient change, process parameters	**Moderate**	The product does not include flavors or sweeteners to mask taste of sodium oxybate. It is noted that the listed drug, Xyrem, is an aqueous oral solution the also does not contain flavors or sweeteners.	**Adequate**	

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Microbial limits	Formulation, raw materials, moisture, container closure	**Low**	Risk is minimal. The product is a nonsterile powder in a single dose packet. The product complies with USP <1111> requirements for oral use.	**Adequate**	

D. List of Deficiencies for Complete Response

Not applicable.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
CMC Lead for Neurology Products
Office of New Drug Products

9/9/2021

Martha Heimann

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name Established name(s) Route(s) of administration	Lumryz (sodium oxybate for extended-release oral suspension), CIII	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4) for extended-release oral suspension: (b) (4) packets of 4.5 g, 6 g, 7.5 g, and 9 g	*Inadequate* (b) (4)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental 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.	NA	NA

1.2 FULL PRESCRIBING INFORMATION

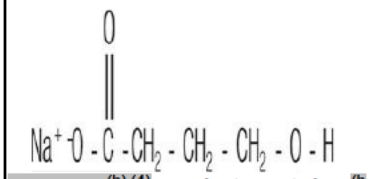
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	LUMRYZ is taken as a single dose at bedtime. Prepare the dose of LUMRYZ prior to bedtime. Prior to ingestion, (b) (4) dose of LUMRYZ should be suspended in approximately 1/3 cup (approximately 80 mL) of water (b) (4) .	*Inadequate* (b) (4) *evise so language is consistent with that used in the IFU and includes that it should be consumed within 30 minutes.*

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	LUMRYZ is a white to off-white powder (b) (4) (b) (4) provided in packets of 4.5 g, 6 g, 7.5 g, or 9 g.	*Inadequate* (b) (4) "
Strength(s) in metric system		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s) Dosage form(s) and route(s) of administration If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance. List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Sodium oxybate, a CNS depressant, is the active ingredient in LUMRYZ. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is $C_4H_7NaO_3$, and the molecular weight is 126.09 g/mole. The chemical structure is:  Sodium oxybate is a white to off-white solid powder. Each [redacted] packet contains [redacted] 4.5 g, 6 g, 7.5 g, or 9 g of sodium oxybate. The inactive ingredients are microcrystalline cellulose [redacted] povidone [redacted] hydrogenated vegetable oil, methacrylic acid copolymer, malic acid, xanthan gum, hydroxyethyl cellulose, carrageenan, and magnesium stearate.	*Inadequate* *Revise to ensure all inactive ingredients are listed in alphabetical order, include route of administration*
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.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA

Statement of being sterile (if applicable)	NA	NA
Pharmacological/ therapeutic class	See above	
Chemical name, structural formula, molecular weight	See above	
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Not provided	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) Strength(s) in metric system Available units (e.g., bottles of 100 tablets) Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	LUMRYZ is a blend of white to off-white granules for oral suspension in water. Each (b) (4) (b) (4) packets of LUMRYZ and a (b) (4) cup. Dose packets contain a single dose of LUMRYZ provided in 4.5 g, 6 g, 7.5 g, and 9 g doses. NDC XXXXX-XXX-XX	*Inadequate* (b) (4)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental 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.	NA	NA

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

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.)	LUMRYZ should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature). Suspensions should be consumed within 30 minutes.	*Inadequate* *Revise storage statement with a range rather than a single temperature (i.e. "stored at 20 to 25°C…")*
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.		
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."	NA	NA
Include information about child-resistant packaging	No information included	*Inadequate* *Revise to include child-resistant packaging statement*

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 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.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed By: Avadel CNS Pharmaceuticals, LLC Chesterfield, MO	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Revise medication guide so all inactive ingredients are in alphabetical order. In addition, temperature should be in °C instead of °F with storage at 20 to 25°C with excursion statement instead of 15 to 30°C. Also, "(b) (4)" should be replaced with "(b) (4) packet."

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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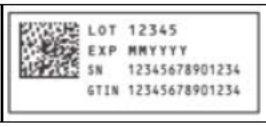
Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Lumryz Sodium oxybate for extended-release oral suspension CIII	Adequate
Dosage strength	4.5 g packet	Adequate
Route of administration	For oral use only	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance		
Net contents (e.g. tablet count)	7 individual [redacted] (b) (4) packets	*Inadequate* *Revise [redacted] (b) (4) to [redacted] (b) (4) packet"*
"Rx only" displayed on the principal display	Rx only	Adequate
NDC number	NDC XXXXX-XXX-XX	Adequate
Lot number and expiration date	LOT 12345 EXP MMYYYY SN 12345678901234 GTIN 12345678901234	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store between 59°F-86°F (15°C-30°C)	Inadequate *Replace "-" with "to" to avoid confusion with minus sign*
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	Must be prepared per Instructions for Use (see package insert)	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA

Bar code		Adeqyate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Avadel CNS Pharmaceuticals, LLC Chesterfield, MO	Adequate
Medication Guide (if applicable)	See discussion below	
No text on Ferrule and Cap overseal	NA	NA
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.	NA	NA
And others, if space is available	NA	NA

Assessment of Carton and Container Labeling: *Adequate*
Adequate, pending the Applicant's acceptance of the revisions noted above in red.

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

This application is recommended for approval per labeling/labels perspective once the following changes (in red) have been made to the label.

Grace Chiou

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Julia Pinto

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	214755
Assessment Cycle Number	01
Drug Product Name/ Strength	Sodium oxybate for extended release (FT218); 4.5 g, 6 g, 7.5 g and 9.0 g
Route of Administration	Immediate and controlled release pellets for oral suspension
Applicant Name	Avadel CNS Pharmaceuticals, LLC
Therapeutic Classification/ OND Division	CDER/OND/ON/DN1
Manufacturing Site	(b) (4)
Method of Sterilization	Non-sterile drug product

Assessment Recommendation: **Adequate**

Assessment Summary: The drug product is non-sterile and packaged in single-dose (b) (4) packs. Therefore the product quality microbiology review is focused on microbiological control including microbial release testing.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001	**12/15/2020**
0007	**3/10/2021**

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

Remarks: The drug product consists of immediate release and controlled release pellets. The pellets are suspended in water no more than 30 minutes prior to oral administration. Note that the current version of the labeling text is located in the 3/10/2021 submission.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents: N/A

S DRUG SUBSTANCE

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

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of the drug product:**
  The drug product consists of a mixture of Immediate-Release pellets (IR) and Controlled-Release (CR) coated pellets. The particles are white to off-white.

- **Drug product composition:**

Component	Function	Quantity per 4.5 g dose	Quantity per 6 g dose	Quantity per 7.5 g dose	Quantity per 9 g dose
		(b) (4)			
Sodium oxybate	Drug substance	4.5 g	6 g	7.5 g	9.0 g
Microcrystalline cellulose (b) (4)					(b) (4)
Povidone (b) (4) (b) (4)					
Hydrogenated vegetable oil (b) (4) NF (b) (4)					
Methacrylic acid (b) (4) (b) (4)					
Malic acid					
Carrageenan (b) (4)					
Hydroxyethyl cellulose (b) (4)					
Xanthan gum (b) (4)					
Magnesium stearate					

- **Description of container closure system**
  The drug product is packaged in child-resistant (b) (4) packs made of (b) (4) aluminum foil supplied by (b) (4) The drug

product is packaged in four single-dose presentations: 4.5 g, 6 g, 7.5 g, and 9 g. The drug product is packaged with a (b) (4) cup used for suspending the powder in water prior to use.

Assessment: *Adequate*

The applicant provided an adequate description of the drug product and the container closure.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-214755-ORIG-1
Drug Product Name/ Strength	LUMRYZ™ (Sodium Oxybate for Extended-Release Oral Suspension), 4.5, 6, 7.5, and 9 g
Route of Administration	Oral
Applicant Name	Avadel CNS Pharmaceuticals, LLC
Therapeutic Classification/ OND Division	Neurology/DN1
RLD/RS Number	NDA 021196. Xyrem® (sodium oxybate) solution 0.5 g/mL
Proposed Indication	For the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy
Primary Reviewer	Leah W. Falade, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.
Recommendation	Adequate

EXECUTIVE SUMMARY

The Applicant seeks approval for its LUMRYZ™ (sodium oxybate for extended-release oral suspension) (or FT218), 4.5, 6, 7.5, and 9 g, using Xyrem® (sodium oxybate) Solution, 0.5 mg as the Listed Drug (LD) under the 505(b)(2) pathway relying on previous established safety and efficacy findings for Xyrem®.

The clinical package in support of this NDA includes ten clinical studies. One pilot study was conducted to compare PK profiles of three prototype formulations with the LD. Prototype 2 was selected, and this formulation was used in all subsequent clinical studies and is the same as the to-be-marketed (TBM) formulation.

In support of the Biopharmaceutics program, a suitable and discriminatory dissolution method was developed for the proposed extended-release drug product. In addition, in-vitro alcohol dose-dumping potential, impact of various beverages, reconstitution time and temperature, and impact of antacids and Proton Pump Inhibitors (PPIs) were investigated, as per the Agency's recommendation.

This review focuses on the Biopharmaceutics evaluation and acceptability of (1) the proposed dissolution method and acceptance criteria, (2) formulation bridging, (3) biowaiver request, (4) dose-dumping potential, (5) interaction with Antacids and PPIs, and (6) the extended-release designation claim with key finding summarized below:

1. **In Vitro Drug Release Method and Acceptance Criteria:** The Applicant proposed a 2-stage dissolution method using USP Apparatus 2 (paddle) at 100 rpm, 37°C. Stage 1 is 0.1 N HCl for 2 hours and Stage 2 is pH 6.0 phosphate buffer for 6 hours. The selection of the method/parameters are adequately justified. The proposed dissolution method was

demonstrated to have discriminating ability toward control-release (CR) coating levels. The Applicant's proposed dissolution method is deemed acceptable for batch release and stability testing of the proposed ER drug product.

The proposed acceptance criteria included 2 timepoints in the acid stage, and 1 timepoint in the buffer stage and were based on the mean dissolution profile data for the pivotal clinical and registration batches at release. The proposed acceptance criteria of (b) (4)% at 0.25 hour and (b) (4)% at 2 hours are data-driven and deemed appropriate. In response to the Information Request, the Applicant agreed to the FDA-recommended NLT (b) (4)% at 4 hours.

2. **Formulation Bridging:** Except for the two exploratory Phase 1 studies PKFT218-1301 (Part I and Part II), the same formulation was tested in all clinical studies which is also the to-be-marketed (TBM) formulation. Therefore, product bridging is not necessary.

3. **Biowaiver Request:** The Applicant conducted a dose-proportionality study #PKFT218-1601 on FT218 4.5, 7.5, and 9 g strengths (same as the proposed commercial product). Together with the proposed 6 g strength studied in the pivotal Phase 1 bridging study, a biowaiver is not needed.

4. **Dose-Dumping Potential**:
(1) In vitro alcohol dose-dumping studies were performed on the 4.5 and 9 g strengths using USP Apparatus 2 (paddle) at 100 rpm in 1800 mL of 0.1 N HCl with 0, 5, 10, 20, and 40% ethanol. Dose-dumping behavior was observed in 40% ethanol (~100% release in 1 hour). The presence of 20% alcohol increased drug release by 10% at 2 hours. The following recommendation will be provided for section 12.3 Pharmacokinetics of the proposed product labeling:

An in vitro study showed alcohol-induced dose-dumping of sodium oxybate from extended-release oral suspension at 1 hour and increase of drug release to approximately 60% at 2 hours in the presence of 20% alcohol. Effects of 5% and 10% alcohol on drug release were not significant up to 14 hours. There is no in vivo study conducted for the effect of alcohol on drug exposure.

(2) In vitro studies were performed to investigate the impact of beverages, reconstitution time, and temperatures on the drug release. It was found that mineral water with a pH of 6.4 impacted the drug release after 15 and 30 min. The Applicant's proposed pertinent statement in the drug product labeling is found acceptable from a Biopharmaceutics perspective.

(3) Hot water (90°C) impacts the drug release from the dosage form. The Applicant's proposed drug product labeling "(b) (4) (b) (4)." is acceptable from a Biopharmaceutics perspective.

5. **Interaction with Antacids and PPIs:** In vitro studies were performed to investigate the impact of antacids and PPIs on the drug release. There was no impact on the drug release in the presence of antacids or PPIs.

6. **Extended-Release Claim:** The information/data were provided to support the extended-release designation claim and were deemed acceptable as per requirements in 21 CFR 320.25(f):
   - The comparison of PK profiles between one dose of the proposed ER product and 2 doses of the LD taken 4 hours apart as per the respective labeling.
   - The dosing interval of the proposed ER tablet is once nightly, while the LD is dosed nightly divided into two doses (one at bedtime and one taken 4 hours later).
   - The drug product's performance provides consistent pharmacokinetic performance among individual dosage units.
   - Lack of dose-dumping potential by foods, beverages, or alcohol as per the labeling instruction.
   - The in vitro dissolution profile provides additional supportive evidence for the extended-release characteristics of the proposed drug product.

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA-214755-ORIG-1 for LUMRYZ™ (sodium oxybate for extended-release oral suspension), 4.5, 6, 7.5, and 9 g, is recommended for **approval**.

FDA-approved dissolution method and acceptance criteria for the proposed LUMRYZ™ (sodium oxybate for extended-release oral suspension, 4.5, 6, 7.5, and 9 g, for batch release and stability testing:

Apparatus	Agitation Speed	Medium Volume	Temp.	Medium	Acceptance Criteria
2 (paddle)	100 rpm	900 mL	37°C	**Stage 1:** 0.1 N HCl for 2 hr **Stage 2:** pH 6.0 phosphate buffer for 6 hr	0.25 hr: (b) (4)% 2 hr: (b) (4)% 4 hr: NLT (b) (4)%

BIOPHARMACEUTICS ASSESSMENT

LIST of SUBMISSIONS BEING REVIEWED

eCTD # (SND #)	Received date	Document
0001	12/15/2020	Original
0017	05/14/2021	Quality Information Amendment
0030	08/31/2021	Quality Information Amendment

BIOPHARMACEUTICS RELATED INFORMATION

<table>
<tr><td>BCS Class Designation</td><td>Not applicable or requested</td></tr>
<tr><td>Solubility</td><td>Highly soluble in pH 4.5-8. Degradation occurs below pH 4.
<table>
<tr><th>Medium (pH adjusted with HCl)</th><th>Solubility (mg/g)</th></tr>
<tr><td>50 mM KH2PO4 buffer pH 8</td><td>620</td></tr>
<tr><td>50 mM KH2PO4 buffer pH 7</td><td>598</td></tr>
<tr><td>50 mM KH2PO4 buffer pH 6</td><td>554</td></tr>
<tr><td>50 mM KH2PO4 buffer pH 4.5</td><td>439</td></tr>
</table></td></tr>
<tr><td>Permeability</td><td>Not provided</td></tr>
<tr><td>Polymorphic form</td><td>No polymorphism is reported in the literature.</td></tr>
<tr><td>Formulation</td><td>The drug product contains IR pellets and CR coated pellets in a (b) (4) w/w% ratio.</td></tr>
<tr><td>Dosing</td><td>Initiate dosage at 4.5 g nightly then titrate to effect in increments of 1.5 g per night at weekly intervals.</td></tr>
<tr><td>Absorption</td><td>Sodium oxybate is absorbed rapidly following oral administration with an absolute bioavailability of about 25%.</td></tr>
<tr><td>Dose Proportionality</td><td>Clinical study of single oral doses of 4.5, 7.5, and 9 g suggested that Cmax increases dose-proportionally and AUC increases slightly more than dose-proportionally across the dose range.</td></tr>
<tr><td>BE</td><td>BE of the proposed product (single dose of 6 g) and Xyrem (2×3 g taken 4 hours apart) was demonstrated in pivotal Phase 1 bridging study.</td></tr>
<tr><td>Tmax</td><td>1.5 hours</td></tr>
<tr><td>Food Effect</td><td>A high-fat meal reduced Cmax and AUC by 23% and 14%, respectively. Tmax was delayed by 0.5 hours. (b) (4)</td></tr>
</table>

DISSOLUTION

Applicant's Proposed Dissolution Method and Acceptance Criteria:

Strengths/sample per vessel	Apparatus	Agitation Speed	Medium Volume	Temp.	Medium	Acceptance Criteria
4.5, 6, 7.5 and 9 g	2 (paddle)	100 rpm	900 mL	37°C	Stage 1: 0.1 N HCl for 2 hr Stage 2: pH 6.0 phosphate buffer for 6 hr	0.25 hr: (b) (4) % 2 hr: (b) (4) % 4 hr: NLT (b) (4)

Dissolution Method Development:

(b) (4)

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Dissolution Acceptance Criteria:

The Applicant submitted individual unit dissolution data on the clinical and registration batches. The mean data from the clinical and registration batches is presented in ***Table* 1** and **Figure *5*** below.

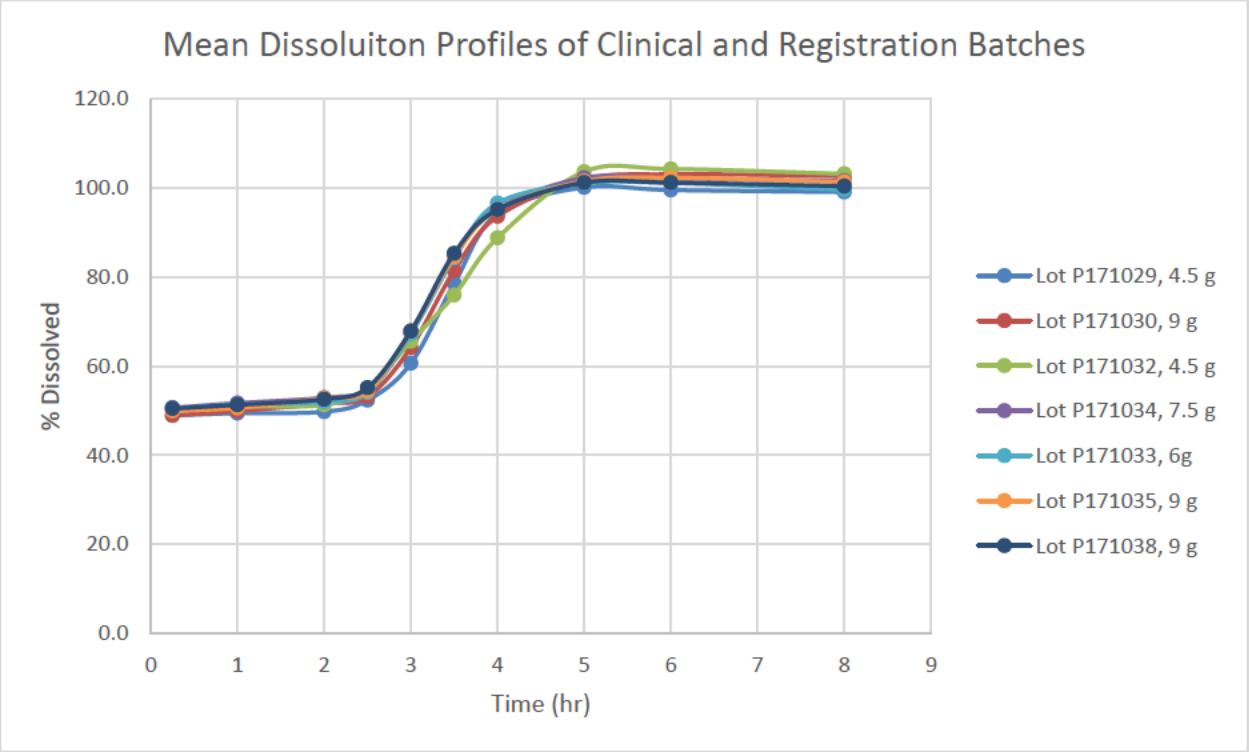

Figure 5. Mean dissolution profiles of clinical and registration batches

Table 1. Mean dissolution data of clinical and registration batches

Lot Number, Strength	0.25 hr	1 hr	2 hr	2.5 hr	3 hr	3.5 hr	4 hr	5 hr	6 hr	8 hr
Lot P171029, 4.5 g										(b) (4)
Lot P171030, 9 g										
Lot P171032, 4.5 g										
Lot P171034, 7.5 g										
Lot P171033, 6g										
Lot P171037, 4.5 g										
Lot P171038, 9 g										
Mean	**49.98**	**50.72**	**51.57**	**54.13**	**65.45**	**81.41**	**93.50**	**101.47**	**101.93**	**101.25**
S.D.	**0.77**	**0.83**	**1.08**	**1.06**	**2.54**	**3.58**	**2.77**	**1.25**	**1.52**	**1.57**

The Applicant proposed the following acceptance criteria:

Acid Stage	0.25 hr: (b) (4)% 2 hr: (b) (4)%
Buffer Stage	4 hr: NLT (b) (4)%

The drug product is formulated to contain (b) (4)% IR beads and (b) (4)% CR beads. (b) (4)

(b) (4)

. This reviewer finds the proposed acceptance criteria (b) (4)% at 0.25 hour and (b) (4)% at 2 hours acceptable for QC release and stability testing. After 4 hours, (b) (4)% release is achieved from the clinical and registration batches (***Table 1***). Therefore, this Reviewer determines that NLT (b) (4)% at 4 hours is appropriate. In response (08/31/2021), the Applicant agreed to the FDA-recommended "4 hr: NLT (b) (4)%" dissolution acceptance criterion. Note that the submitted stability data for up to 36 months showed no downward trend and conform to the recommended acceptance criteria.

BRIDGING THROUGHOUT PRODUCT DEVELOPMENT

Except for the two exploratory Phase 1 studies PKFT218-1301 (Part I and Part II), the same formulation was tested in all clinical studies which is also the to-be-marketed (TBM) formulation. Therefore, product bridging is not necessary.

BIOWAIVER REQUEST

Study #PKFT218-1601 was an open-label, single dose, sequential three-period study to evaluate the pharmacokinetics and dose-proportionality of FT218 (4.5, 7.5, and 9 g strengths, same as the proposed commercial product). The study results will be assessed by OCP to determine the dose proportionality. Of note, one subject was withdrawn due to a SAE after receiving the 9 g dose. Therefore, the Agency agreed that 9 g should not be used in healthy volunteers and subsequent clinical studies were performed on the 6 g dose. The proposed 6 g strength was studied in the pivotal Phase 1 bridging study. Therefore, a biowaiver is not needed.

ALCOHOL-INDUCED DOSE-DUMPING

In vitro alcohol dose dumping studies were performed on the 4.5 and 9 g strengths using USP Apparatus 2 (paddle) at 100 rpm in 1800 mL of 0.1 N HCl with 0, 5, 10, 20, and 40% ethanol. The alcohol dose dumping studies were submitted in the original submission (b) (4)

he use of 1800 mL for the alcohol dose dumping studies is therefore justified. The dose dumping profiles are presented in **Figure *6*** and **Figure *7*** below.

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Results showed that [redacted] (b) (4) In 20% ethanol, approximately 10% more is released at 2 hr, while 100% is released in 1 hour in 40% ethanol. Therefore, the drug product exhibits dose-dumping behavior in 40% ethanol. The Applicant proposed in the labeling (Sections 4, 5, and 7) that LUMRYZ is contraindicated in combination with alcohol, and in Section 12.3 Pharmacokinetics of the labeling: "*Effect of Ethanol: An in vitro* [redacted] (b) (4) "

The pertinent information for the Section 12.3 of the labeling is recommended by this Reviewer as follows:

> *An in vitro study showed alcohol-induced dose-dumping of sodium oxybate from extended-release oral suspension at 1 hour and increase of drug release to approximately 60% at 2 hours in the presence of 20% alcohol. Effects of 5% and 10% alcohol on drug release were not significant up to 14 hours. There is no in vivo study conducted for the effect of alcohol on drug exposure.*

IMPACT OF ANTACIDS AND PROTON PUMP INHIBITORS

The Applicant submitted Study #ETD 218-006 in a Pre-IND meeting dated 07/02/2020[1]. Results of the study showed no dose-dumping from the proposed product observed for a 7.5 g dose with the maximum dose of Tums (calcium carbonate, 3 g) and 20 mL of Rite Aid suspension (aluminum hydroxide/magnesium hydroxide/simethicone) after 1 hour. Therefore, the Agency agreed that an interaction study in humans is not needed.

Note that a 2-stage dissolution test was used to conduct the testing on a 4.5 g dose for the PPI in vitro study. Stage 1 was 2 hours in 0.1 N HCl (reference), pH 6 (maximum gastric pH after PPI administration according to the literature), and phosphate buffer at pH 6.2, 6.4, and 6.5 to simulate extreme cases of increased gastric pH following antacid administration). Stage 2 was pH 6.8 phosphate buffer. The results showed that there was no dose-dumping behavior at pH 6.0 which is the maximum gastric pH after PPI administration according to the literature. This Reviewer finds the results of the studies acceptable.

IMPACT OF BEVERAGES USED FOR RECONSTITUTION

The Applicant submitted Study #ETD 218-005 in a Pre-IND meeting dated 07/02/2020[1]. Results of the study showed a lack of dose-dumping potential in selected beverages (with pH of 5.8, 6.4, and 8.5) or in warm water (50°C). Therefore, the Agency agreed that an interaction study in humans is not needed. The dissolution was evaluated in 0.1 N HCl after reconstitution in the selected beverages (reconstitution time 5 min) for 3 g and 9 g doses. The dissolution profiles were all similar for both doses (see **Figure *8 - 10***).

[1] https://darrts fda.gov/darrts/faces/ViewDocument?documentId=090140af805782bb&_afrRedirect=1615910906202651

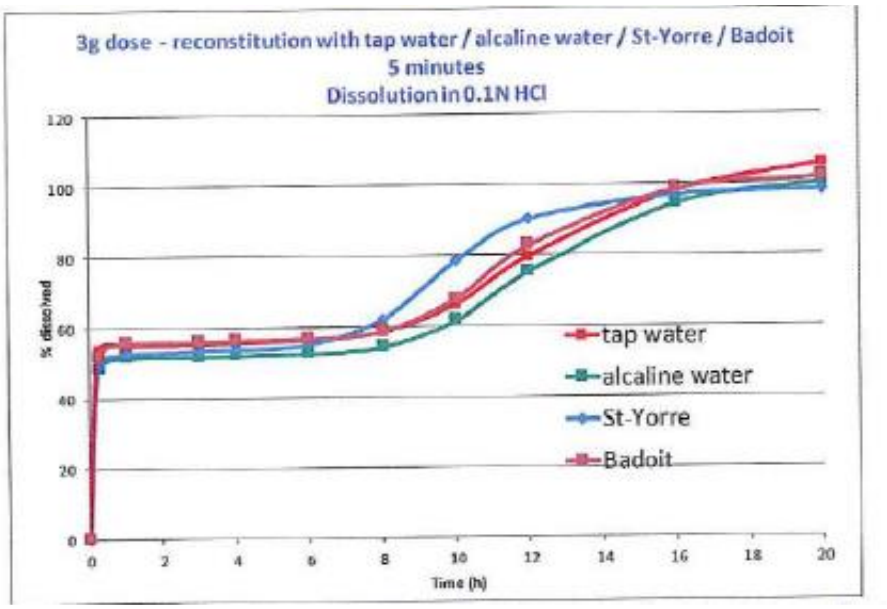

Figure 8. Dissolution profile of a 3 g dose using different pH waters vs. tap water

Experiments were also conducted at longer time intervals to justify the interval between reconstitution and intake that will appear on the drug product labeling. These experiments were conducted using a 2-stage dissolution method which is more representative of the GI tract. Note that the dissolution profile of the water with pH 6.4 was not similar to tap water with reconstitution time of either 15 min or 30 min (***Figure 9)***. Therefore, the Applicant proposed to include the following statement in the drug product labeling: "(b) (4) " This Reviewer finds the proposal acceptable from a Biopharmaceutics perspective.

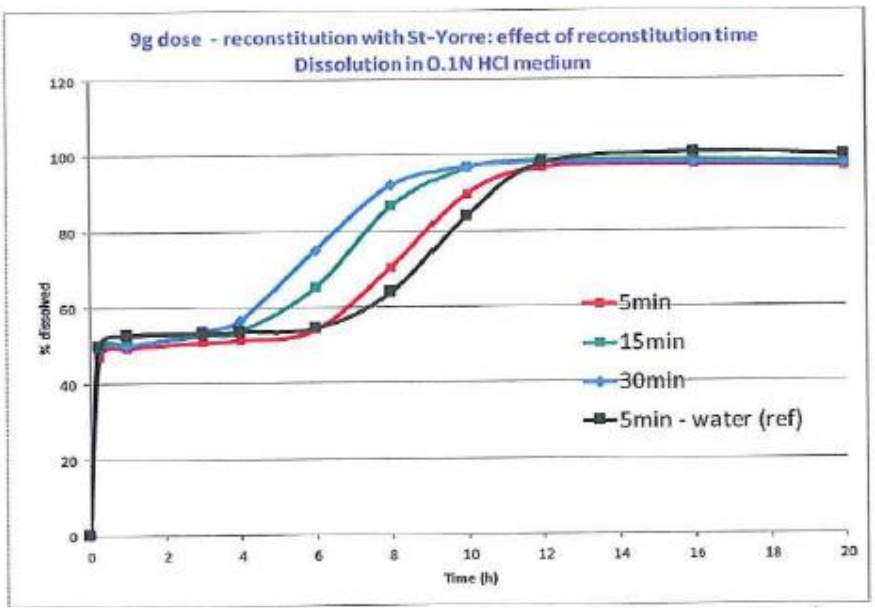

Figure 9. Dissolution profile of 9 g dose using pH 6.4 water

Coca-Cola (pH 3.1) and Crystal Light (pH 5.1) were evaluated and are shown to have similar release profile as tap water. Warm water (50°C) and hot water (90°C) were also tested. It was found that hot water resulted in dose-dumping phenomenon for the release of API (

Figure *10*). Therefore, the Applicant proposed to include the following statement in the drug product labeling: "(b) (4) [redacted]" This Reviewer finds the proposal acceptable.

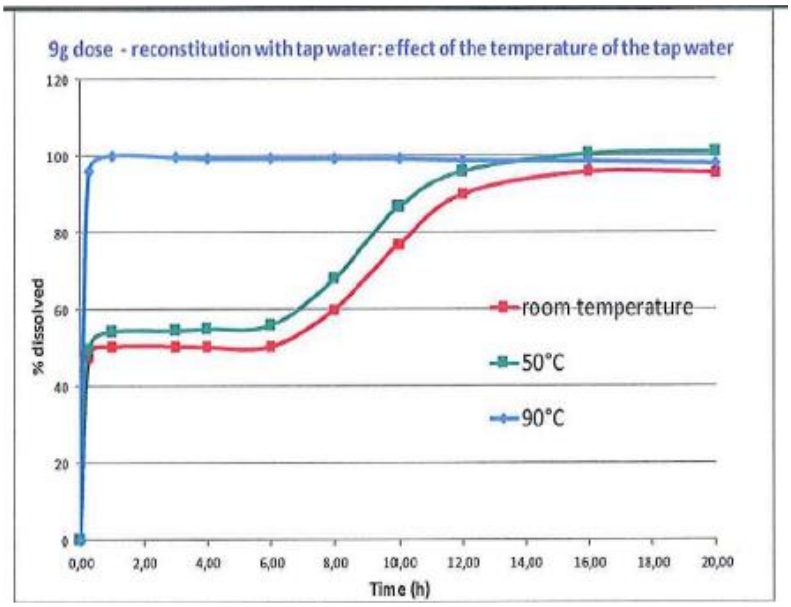

Figure 10. Dissolution profile of a 9 g dose using tap water at various temperatures

EXTENDED-RELEASE CLAIM

The Applicant conducted a pivotal clinical bridging study to support the extended-release claim for it proposed drug product. The study demonstrated that one 6-g dose of its proposed sodium oxybate for extended-release suspension is bioequivalent to Xyrem® (sodium oxybate) solution, 2 × 3 g taken 4 hours apart. The dosing interval of the proposed product is once per night, while Xyrem® is dosed nightly divided into two doses (one at bedtime and one taken 4 hours later). The comparative mean plasma-concentration profiles of the proposed product and LD exhibited rapid initial absorption, followed by different rates of decline, with Cmax of proposed oral suspension being 88% of Cmax of LD (**Figure *11***).

The reported terminal half-life is approximately 0.6 hours, which this Reviewer does not expect accumulation at the end of 24 hours interval and thus the steady-state PK profile, hence the steady-state PK comparison, can be sufficiently represented by the single-dose PK profile as seen in ***Figure 11***.

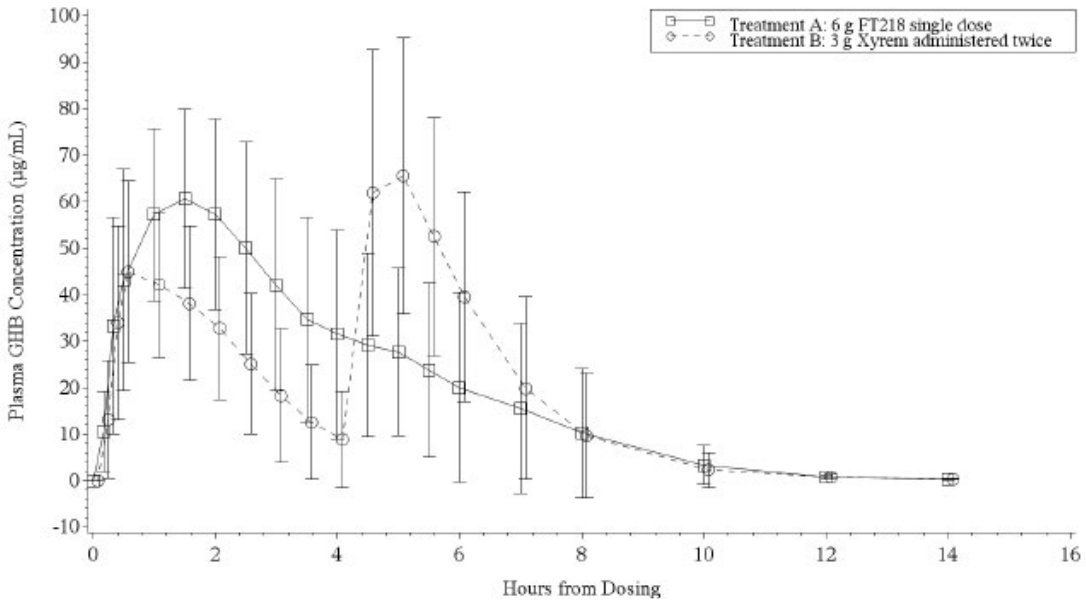

Figure 11. Mean plasma concentration vs. time profiles following administration of 6 g FT218 and 6 g (2×3g of Xyrem® administered 4 hours apart)

To demonstrate consistent PK performance between individual dosage units, the data from the dose-proportionality study was analyzed. Mean API exposure exhibited moderate variability, i.e., %CV for Cmax and AUC parameters of 31-53% as reported. It was shown that the intra-subject variability was low and the pK performance was consistent (dose normalized AUCinf and Cmax) across the doses (***Table 2***).

Table 2. Study PKFT218-1601 Intrasubject Coefficient of Variation-PK Analysis Set

Parameter	Geometric LS Mean FT218 4.5 G	Geometric LS Mean FT218 7.5 G	Geometric LS Mean FT218 9 G	Intra-Subject Coefficient of Variation (%CV)
Dose Normalized AUC_{inf} (h•ug/mL/g)	36.543	42.222	46.414	16.43
Dose Normalized C_{max} (ug/mL/g)	8.935	8.973	9.196	22.65

LS: Least Squares
Note that the analysis is based on the mixed effect model with natural-log-transformed dose-normalized PK parameter as dependent variable, planned dose (FT218 4.5g, FT218 7.5g, and FT218 9g) as fixed effect, and a compound symmetry covariance matrix to model within subject variability. Geometric LS mean is obtained from back transformation of the LS mean in the log scale.

It is also noted that the in vitro dissolution profiles, as presented in **Figure *5*** provide additional supportive evidence for the extended-release characteristics of the proposed drug product and for seeking Extended-Release claim. Additionally, there is a lack of dose-dumping potential with food and beverage under recommended usage, per labeling.

Leah Falade

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Ta-Chen Wu

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Date: 9/01/2021 11:03:40AM
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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/

MARTHA R HEIMANN
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