CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s000

OTHER REVIEW(S)

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	April 26, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 214755
Product Name, Dosage Form, and Strength:	Lumryz (sodium oxybate) for extended-release oral suspension, 4.5 g, 6 g, 7.5 g, and 9 g per packet
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Avadel CNS Pharmaceuticals, LLC
FDA Received Date:	March 1, 2023
TTT ID #:	2023-3985
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

The Applicant submitted NDA 214755 for Lumryz (sodium oxybate) for extended-release oral suspension on December 15, 2020. NDA 214755 received tentative approval on July 18, 2022. As such, the Applicant submitted NDA 214755 for final approval on March 1, 2023 as part of a Class 1 Resubmission.

Subsequently, the Division of Neurology 1 (DN 1) requested that we review the proposed Lumryz labels and labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

NDA 214755 is a 505(b)(2) NDA and the listed drug product is Xyrem, NDA 021196.

On October 5, 2021, we reviewed the labels, labeling, and human factors (HF) validation study results for Lumryz submitted under NDA 214755. While we noted the HF validation study results identified areas of vulnerability that could lead to medication errors, upon review of the subjective feedback, root cause analysis, our independent review of the proposed user interface, the risk mitigations implemented, and our postmarketing experience with similar currently approved products, we found the residual risks associated with these use errors acceptable.[a] Before this review was completed, we provided recommendations for the proposed labels and labeling via information request on September 13, 2021. The Applicant submitted revised container (packet) labels, carton labeling, and Instructions for Use (IFU) on September 16, 2021. We found the revised container labels and IFU acceptable; however, we had additional recommendations for the carton labeling and Prescribing Information (PI).

On October 6, 2021, the Applicant submitted revised carton labeling. On October 7, 2021, we reviewed the proposed revised carton labeling and determined that the Applicant implemented our recommendations, and we had no additional recommendations.[b] On November 4, 2021, the Applicant submitted revised container labels, carton labeling, IFU, and Medication Guide (MG). Then on November 15, 2021, the Applicant submitted revised carton labeling in response to the Agency's request to add the instruction of 'See the Medication Guide for additional dosage information.' to the inner flap of the carton.

On July 18, 2022, NDA 214755 received Tentative Approval under 21 CFR 314.105 with final approval being subject to patent-related issues (that is, paragraph IV certification requirements) under 505(c)(3)(C) of the FD&C Act.

On March 1, 2023, the Applicant submitted a Class 1 Resubmission to NDA 214755 to resolve the patent-related issues. Within the resubmission, the Applicant submitted a revised PI and IFU, which are the subject of this review. We note, DMEPA did not provide comment on the

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[a] Yokum, A. Label, Labeling, and Human Factors Results Review for Lumryz (NDA 214755). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 OCT 05. RCM No. 2020-2669 and 2020-2724.

[b] Yokum, A. Label and Labeling Review MEMO for Lumryz (NDA 214755). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2021 OCT 07. RCM No. 2020-2724-1.

container labels and MG received on November 4, 2021 or the carton labeling received on November 15, 2021. As such, we evaluated these labels and labeling as part of this review.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Regarding the proposed labels and labeling, Avadel noted the following under the Class 1 resubmission:

> Avadel confirms that there have been no changes to the conditions under which LUMRYZ was tentatively approved except for the following:
>
> - Avadel identified a discrepancy between the Instructions for Use (IFU) enclosed with the tentative approval letter and the last version of the IFU submitted to the NDA. The language in Step 1 was changed from (b) (4) to "At your bedside".
> - Subsections 10.2 and 10.3 of the LUMRYZ Prescribing Information (PI) were updated to add the occurrence of acidosis in overdose information reflected in the approval of NDA 021196/S-040.
> - In Section 6.1 Adverse Reactions – Clinical Trials Experience – Adverse Reactions Leading to Treatment Discontinuation, the rates of adverse reactions leading to treatment discontinuations were revised by the Agency in the PI edits provided on May 24, 2022. The Agency comment indicated that the numbers were revised to match Table 29 of the study report (CLFT218-1501). However, the rates were pulled from the row for "(b) (4) rather than "(b) (4) . Thus, Avadel will propose that "adverse reaction" be changed to (b) (4) in that section for accuracy.

As such, Avadel did not submit new container (packet) labels, carton labeling, or MG; however, we found the container labels submitted on September 16, 2021, and carton labeling submitted on October 6, 2021, under the original review of NDA 214755 to be acceptable from a medication error perspective (refer to reviews cited in Section 1.1).

Under this resubmission, we performed a risk assessment of the container labels, carton labeling, PI, IFU, and MG for Lumryz to determine whether there are deficiencies that may lead to medication errors and other areas of improvement.

We reviewed the container (packet) labels and MG received on November 4, 2021 and carton labeling submitted on November 15, 2021, and did not identify any medication error concerns.

We reviewed the PI received on March 1, 2023, and note that our recommendations from previous reviews were considered and/or implemented. Further, we note that no revisions were proposed to Sections 2, 3, 16, or 17 of the PI or the MG, and therefore, we have no additional recommendations. We defer to the DN1 to determine the acceptability of the changes proposed to Sections 6.1, 10.2, and 10.3.

Finally, we reviewed the proposed revision to Step 1 of the IFU received on March 1, 2023. The Applicant proposes to replace the phrase "(b) (4)" to "At your bedside". We note the tentatively approved Lumryz IFU was approved based on our previous review of human factors validation study results. (See reference to human factors validation study results review in Section 1.1). We determine the proposed revision does not change how the user interacts with the user interface for preparation and administration of the product. Additionally, the Applicant does not propose to add or eliminate any use tasks previously validated. As such, we find the proposed revision to Step 1 of the IFU acceptable from a medication error perspective.

4 CONCLUSION

Our evaluation of the proposed Lumryz Prescribing Information, Instructions for Use, Medication Guide, container labels, and carton labeling did not identify areas of vulnerability that may lead to medication errors. We have also determined that no additional human factors validation data is required to support the proposed revisions at this time. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Lumryz that Avadel CNS Pharmaceuticals, LLC submitted on March 1, 2023, and the listed drug (LD), Xyrem[c].

Table 4. Relevant Product Information for Listed Drug and Lumryz		
Product Name	Xyrem	Lumryz
Initial Approval Date	07/17/2002	n/a
Active Ingredient	sodium oxybate	
Indication	treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy	treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy
Route of Administration	Oral	
Dosage Form	Oral solution	For extended-release oral suspension
Strength	0.5 g/mL	4.5 g, 6 g, 7.5 g, 9 g per packet
Dose and Frequency	Adult Dosing Information The recommended starting dosage is 4.5 grams (g) per night administered orally, divided into two doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later (see Table 1). Increase the dosage by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dosage range of 6 g to 9 g per night orally. The dosage may be gradually titrated based on efficacy and tolerability. Doses higher than 9 g per night have not been	Initiate dosage at 4.5 g once per night orally. Titrate to effect in increments of 1.5 g per night at weekly intervals. Recommended dosage range: 6 g to 9 g once per night orally.

[c] Xyrem PI accessed April 12, 2023, available at: http://fdalabel.fda.gov/fdalabel-r/services/spl/set-ids/926eb076-a4a8-45e4-91ef-411f0aa4f3ca/spl-doc?hl=xyrem

<table>
<tr>
<td></td>
<td>studied and should not ordinarily be administered.

Table 1: Recommended Adult Xyrem Dose Regimen (g = grams)
<table><tr><th>If a Patient's Total Nightly Dose is:</th><th>Take at Bedtime:</th><th>Take 2.5 to 4 Hours Later:</th></tr><tr><td>4.5 g per night</td><td>2.25 g</td><td>2.25 g</td></tr><tr><td>6 g per night</td><td>3 g</td><td>3 g</td></tr><tr><td>7.5 g per night</td><td>3.75 g</td><td>3.75 g</td></tr><tr><td>9 g per night</td><td>4.5 g</td><td>4.5 g</td></tr></table>
<u>Pediatric Dosing Information</u>
Xyrem is administered orally twice nightly.

The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight, as specified in Table 2.

The dosage may be gradually titrated based on efficacy and tolerability.
Table 2: Recommended Pediatric Xyrem Dosage for Patients 7 Years of Age and Older*
<table><tr><th rowspan="2">Patient Weight</th><th colspan="2">Initial Dosage</th><th colspan="2">Maximum Weekly Dosage Increase</th><th colspan="2">Maximum Recommended Dosage</th></tr><tr><th>Take at Bedtime:</th><th>Take 2.5 to 4 Hours Later:</th><th>Take at Bedtime:</th><th>Take 2.5 to 4 Hours Later:</th><th>Take at Bedtime:</th><th>Take 2.5 to 4 Hours Later:</th></tr><tr><td><20 kg**</td><td colspan="6">There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg.</td></tr><tr><td>20 kg to <30 kg</td><td>≤1 g</td><td>≤1 g</td><td>0.5 g</td><td>0.5 g</td><td>3 g</td><td>3 g</td></tr><tr><td>30 kg to <45 kg</td><td>≤1.5 g</td><td>≤1.5 g</td><td>0.5 g</td><td>0.5 g</td><td>3.75 g</td><td>3.75 g</td></tr><tr><td>≥45 kg</td><td>≤2.25 g</td><td>≤2.25 g</td><td>0.75 g</td><td>0.75 g</td><td>4.5 g</td><td>4.5 g</td></tr></table>* For patients who sleep more than 8 hours per night, the first dose of Xyrem may be given at bedtime or after an initial period of sleep.
**If Xyrem is used in patients 7 years of age and older who weigh less than 20 kg, a lower starting dosage, lower maximum weekly dosage increases, and lower total maximum nightly dosage should be considered.
Note: Some patients may achieve better responses with unequal doses at bedtime and 2.5 to 4 hours later.</td>
<td></td>
</tr>
<tr>
<td>How Supplied</td>
<td>One bottle of Xyrem with attached press in bottle adaptor, an oral measuring device (plastic syringe), and a Medication Guide.</td>
<td>Carton containing either 7 packets or 30 packets of Lumryz, a mixing cup, Prescribing Information and Medication Guide, and Instructions for Use</td>
</tr>
<tr>
<td>Storage</td>
<td>Xyrem should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see</td>
<td>LUMRYZ should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to</td>
</tr>
</table>

	USP Controlled Room Temperature).	86°F) (see USP Controlled Room Temperature).
Container Closure[de]	(b) (4) amber bottle, (b) (4) cap, and (b) (4) press-in-bottle-adaptor	(b) (4) foil (b) (4) packs

[d] Container closure specification for Xyrem available at: \\CDSESUB1\EVSPROD\nda021196\0615\m3\32-body-data\32p-drug-prod\xyrem\32p7-cont-closure-sys\container-closure-system.pdf

[e] Container closure specifications for Lumryz available at: \\CDSESUB1\EVSPROD\nda214755\0020\m3\32-body-data\32p-drug-prod\sodium-oxybate-ft218\32p7-cont-closure-sys\container-closure-system.pdf

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 12, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, Lumryz, sodium oxybate, and NDA 214755. Our search identified two previous reviews, which have been cited in Section 1.1 above.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Lumryz labels and labeling submitted by Avadel CNS Pharmaceuticals, LLC.

- Container labels received on November 4, 2021
- Medication Guide (image not shown) received on November 4, 2021, available from \\CDSESUB1\EVSPROD\nda214755\0040\m1\us\114-label\1141-draft-label\lumryz-mg-tc-word.docx
- Carton labeling received on November 15, 2021
- Prescribing Information (image not shown) received on March 1, 2023, available from \\CDSESUB1\EVSPROD\nda214755\0055\m1\us\114-labeling\114a-draft-label\proposed-tc.pdf
- Instructions for Use (image not shown) received on March 1, 2023, available from \\CDSESUB1\EVSPROD\nda214755\0055\m1\us\114-labeling\114a-draft-label\lumryz-ifu-tracked-changes-word.docx

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[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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STEPHANIE L DEGRAW
04/26/2023 10:39:03 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 19, 2021

To: Ranjit Mani, MD, Clinical Team Leader
Division of Neurology 1 (DN1)

Teresa Wheelous, Regulatory Project Manager, DN1

Tracy Peters, PharmD, Associate Director for Labeling, DN1

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for LUMRYZ™ (sodium oxybate) for extended-release oral suspension, CIII

NDA: 214755

In response to DN1's consult request dated May 6, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labels for the original NDA submission for LUMRYZ™ (sodium oxybate) for extended-release oral suspension, CIII.

Labeling: OPDP's comments on the proposed PI labeling are based on the draft labeling received by electronic mail from DN1 on October 7, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed on the proposed Medication Guide and IFU, and comments on the proposed Medication Guide and IFU were sent under separate cover on October 14, 2021.

Carton and Container Labels: OPDP has reviewed the attached proposed carton and container labels submitted by the Applicant to the electronic document room on September 16, 2021 (container labels) and October 6, 2021 (carton labels), and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 12, 2021
To:	Teresa Wheelous Regulatory Project Manager **Division of Neurology I**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Nyedra Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Samuel Fasanmi, Pharm D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	LUMRYZ (sodium oxybate)
Dosage Form and Route:	for extended-release oral supsension, CIII
Application Type/Number:	NDA 214755
Applicant:	Avandel CNS Pharmaceuticals, LLC

1 INTRODUCTION

On December 15, 2020, Avadel CNS Pharmaceuticals, LLC submitted for the Agency's review an original New Drug Application (NDA) 214755 for LUMRYZ (sodium oxybate). This NDA proposes the indication "for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy". The reference listed drug for this NDA is XYREM (sodium oxybate) oral solution NDA 021196.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology I on May 7, 2021 and May 6, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG), and Instructions for Use (IFU) for LUMRYZ (sodium oxybate) extended-release oral suspension, CIII.

2 MATERIAL REVIEWED

- Draft LUMRYZ(sodium oxybate) MG and IFU received on December 15, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 4, 2021.
- Draft LUMRYZ(sodium oxybate) Prescribing Information (PI) received on December 15, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 4, 2021.
- XYREM (sodium oxybate) comparator labeling dated October 26, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

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ALINE M MOUKHTARA
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Signed for Samuel Fasanmi

NYEDRA W BOOKER
10/12/2021 11:49:38 AM

LASHAWN M GRIFFITHS
10/14/2021 08:51:34 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 7, 2021
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 214755
Product Name and Strength:	Lumryz (sodium oxybate) extended-release oral suspension, 4.5 g, 6 g, 7.5 g, and 9 g
Applicant Name:	Avadel CNS Pharmaceuticals LLC (Avadel)
OSE RCM #:	2020-2724-1
DMEPA 2 Safety Evaluator:	Ankara (Nikki) Yokum, PharmD
DMEPA 2 Team Leader:	Colleen Little, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on October 6, 2021 for Lumryz. The Division of Neurology 1 (DN 1) requested that we review the revised carton labeling for Lumryz (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Yokum, A. Human Factors Results and Label and Labeling Review for Lumryz (NDA 214755). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 05. RCM No.: 2020-2669; 2020-2724.

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/s/

ANKARA N YOKUM
10/07/2021 09:27:36 AM

COLLEEN L LITTLE
10/07/2021 10:47:59 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM TO FILE

Date: October 6, 2021 **Date consulted**: August 26, 2021

From: Denise Pica-Branco, Ph.D. Senior Regulatory Health Project Manager
Pediatrics and Maternal Health
Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of Regulatory Operations

Through: Rosemary Addy, MHS, Supervisory Consumer Safety Officer
Pediatrics and Maternal Health
Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of Regulatory Operations

To: Teresa Wheelous, R.PH., Captain, Senior Regulatory Health Project Manager
Division of Neurology 1 (DN1)
Office of New Drugs (OND)

Subject: 505(b)(2)

Sponsor: Avadel CNS Pharm. LLC

Drug: sodium oxybate ER (Lumryz)

NDA: 214755

Indication: Narcolepsy in adults

Materials Reviewed:

file:////CDSESUB1/evsprod/NDA214755/0001
drugs@fda
orange book

Consult Question:
The New Patient Population (NPP) and ODE-231 exclusivity is listed under Xyrem.

The 505(b)(2) committee asked DN1 to submit a consult to Division of Pediatrics and Maternal Health (DPMH) for 505(b)(2) pediatric labeling. DPMH received the consult on 8/26/2021. DPMH consulted Office of Chief Counsel (OCC) for assistance with the 505(b)(2) labeling on 9/3/2021.

On 1/8/2018, Avadel (the Applicant) was granted orphan drug designation for sodium oxybate for extended-release oral suspension for treatment of narcolepsy.[1] The Pediatric Research Equity Act (PREA) requirements are not applicable to this product, and the Applicant is not seeking the approval of the pediatric indication. DPMH reviewed Lumryz labeling and proposed to include certain pediatric safety information included in section 5 and subsection 8.4 of the listed drug labeling. Subsequently, on 9/22/2021 DPMH and OCC discussed the other regulatory complexities of this 505(b)(2) application that could impact its approvability, timing of approval, and the resultant labeling. It was also noted that the pediatric information conveyed the same risk information as that already included for adults.

DPMH and OCC agreed that once the other complexities are resolved, and the applicant is ready to seek final approval of the application, it would be a useful to check whether the applicant could seek approval for the pediatric use and, if appropriate, recommend that the applicant do so. In addition, DPMH and OCC agreed that, in the future, if it was determined that it was necessary to retain pediatric information for safety reasons, we would further explore the legal and regulatory options for doing so in the context of those products. If information changes regarding this application, then DPMH should be consulted.

DPMH RPM:	Denise Pica-Branco
DPMH SCSO:	Rosemary Addy
DPMH Reviewer:	Ramy Abdelrahman
DPMH MTL:	Mona Khurana
DPMH Deputy Director:	John Alexander
OCC:	Sonal Vaid

[1] https://www.accessdata fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=530216

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/s/

DENISE J PICA-BRANCO
10/06/2021 01:30:35 PM

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
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:	October 05, 2021
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 214755
Product Type: Drug Constituent Name and Strength Device Constituent:	Combination Product (Drug/Device) Lumryz (sodium oxybate) for extended-release oral suspension, 4.5 g, 6 g, 7.5 g, and 9 g Dosing Cup
Rx or OTC:	Rx
Applicant Name:	Avadel CNS Pharmaceuticals LLC (Avadel)
Submission Date:	December 15, 2020; February 01, 2021; March 10, 2021; March 29, 2021; April 23, 2021; September 16, 2021
OSE RCM #:	2020-2669; 2020-2724
DMEPA Safety Evaluator:	Ankara "Nikki" Yokum, PharmD
DMEPA Team Leader (Acting):	Colleen Little, PharmD
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Deputy Director:	Danielle Harris, PharmD

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 214755 for Lumryz (sodium oxybate) extended-release for oral suspension.

1.1 PRODUCT DESCRIPTION

Lumryz (sodium oxybate) is a combination product supplied as single-dose packets containing the drug product powder that are co-packaged with a proposed dosing cup device constituent part. The proposed product is intended to be suspended with water prior to oral administration. Lumryz (sodium oxybate) is indicated to treat cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy. See Appendix A for more information.

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On June 12, 2015, a type B pre-IND meeting was held under IND 126321. We provided post meeting comments[1] advising Avadel to conduct a use-related risk analysis (URRA) to determine if an HF validation study would be warranted for this product.

On April 11, 2018, Avadel submitted the URRA and an HF validation study protocol under IND 126321. On July 12, 2018, we completed our review of the HF study protocol and identified areas of concern[2]. On August 03, 2018, we communicated our recommendations to Avadel in an Advice/Information Request Letter.[3]

On January 30, 2020, in response to the August 03, 2018 Advice/Information Request Letter, Avadel submitted a revised HF validation study protocol under IND 126321. On March 26, 2020, we completed our review of the HF study protocol and identified additional areas of concern[4]. On March 30, 2020, we communicated our recommendations to Avadel in an HF Advice Letter.[5]

On April 10, 2020, Avadel submitted a clarifying question in response to our recommendation in the March 30, 2020 HF Advice Letter to include a distinct pediatric user group with participants aged 16-17 years old in their proposed HF study. Avadel stated that patients 16-17 years old are considered part of the adult population for their proposed product and thus should be included in the adult user group instead of in a distinct user group in their HF study.

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[1] Kishore, V. Meeting Minutes for IND 126321, sodium oxybate. Silver Spring (MD): FDA, CDER, OND (US); 2015 JUN 22

[2] Stewart, J. Human Factors Validation Protocol for sodium oxybate (IND 126321). Silver Spring (MD): FDA CDER, OSE, DMEPA (US); 2018 JUL 12. RCM No.: 2018-813

[3] Kishore, V. HF Validation Study Protocol Advice for sodium oxybate. Silver Spring (MD): FDA, CDER, OND (US); 2018 AUG 03.

[4] White, L. Human Factors Validation Protocol for sodium oxybate (IND 126321). Silver Spring (MD): FDA, CDER OSE, DMEPA (US); 2020 MAR 26. RCM No.: 2020-215

[5] Ogbonna, C. HF Validation Study Protocol Advice for IND 126321, sodium oxybate . Silver Spring (MD): FDA, CDER, OSE (US); 2020 MAR 30.

We reviewed Avadel's justification and consulted with the Division of Neurology 1 (DN 1) clinical review team to inform our decision. On May 04, 2020, we issued an advice letter[6] to Avadel stating that we found their proposal to include 16 – 17 year old participants within the proposed adult user groups for the HF validation study reasonable.

On July 02, 2020 in response to a pre-NDA meeting request under IND 126321, we informed Avadel that the HF validation study results must be submitted at the time of the original NDA submission. [7]

On December 15, 2020, Avadel submitted NDA 214755 which included the results of all tasks evaluated in their initial HF validation study (HFVS 1). Per Avadel, the following labeling changes were made after HFVS 1 to address observed use errors associated with certain tasks:

Instructions for Use

- Added the statement, "Avoid getting out of your bed after taking FT218" under the "Important Information" section
- Removed bold font for the statement "Store FT218 and all medicines out of the reach of children"
- Modified the visual and text in Step 3 "Open 1 (b) (4) packet" to provide instructions to use scissors as the first option followed by instructions to tear open the packet by hand using the tear mark as the secondary option
- Added the warning "Take only one (b) (4) packet per day at bedtime" under "Important Information" and in bold for Step 10
- Added the statement "At your bedside…" to the beginning of Step 1 "Open the dosing cup" (b) (4) "
- Updated the section title "Mix the FT218 solution" to "Mix the FT218 solution at your bedside"
- Updated the section title "Take the FT218 solution" to ""Take the FT218 solution at your bedside"
- Added the statement "IMPORTANT: Make sure to prep FT218 at bedside" as a highlighted warning under the "Before each use" section
- Added the statement "DO NOT use FT218 with alcohol" under the "Important Information" section
- Added the statement "DO NOT drive or operate heavy machinery within 6 hours" under the "Important Information" section

[6] Ogbonna, C. FDA Communication: Advice/Information request for IND 126321, sodium oxybate. Silver Spring (MD): FDA, CDER, OSE (US); 2020 MAY 04. IND 126321

[7] Wheelous, T. Meeting Preliminary Comments for IND 126321, sodium oxybate. Silver Spring (MD): FDA, CDER, OND (US); 2020 JUL 02.

- Removed the warning "Do not use [redacted] (b) (4) if the tamper-evident seal is missing or broken" from the [redacted] (b) (4) " section

Container Label

- Reformatted the front of the container label to emphasize the following warning statement "Warning: Take only one [redacted] (b) (4) packet per day at bedtime"

To validate the above labeling changes, Avadel conducted a supplemental HF validation study (HFVS 2) to provide HF data for the impacted tasks for the changes listed above. Thus, on February 01, 2021, Avadel submitted a supplemental HF report , which provides the results from HFVS 2 for the tasks that were impacted by the above labeling changes. As such, both HFVS 1 and supplemental HFVS 2 reports are the subjects of this review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Reports	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, use errors/close calls/use difficulties observed with HFVS 1 and HFVS 2, and our analysis to determine if the results indicate that the user interface has been optimized to support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design for HFVS 1 and HFVS 2. See Appendix C for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Studies		
Study Design Elements	Details of HFVS 1	Details of HFVS 2
Participants	• sodium oxybate experienced, n=15; Age range: 21-55 years old • sodium oxybate naïve, n=16; Age range: 16-57 years old	• sodium oxybate experienced, n=15; Age range: 21 to 64 years old • sodium oxybate naïve, n=15; Age range: 17 to 58 years old
Training	No training was provided to participants for either study.	
Test Environment	HFVS 1 and HFVS 2: Multi-site study with each site configured to represent a home environment with separate spaces and illuminated by incandescent and/or fluorescent lights. The room was relatively quiet with occasional acoustic distractions such as footsteps, phones ringing, doors opening and closing filtering from the surrounding office space. The first space was a simulated bedroom area, including a representation of a bed and a bedside table on which was a lamp and small clock. The study product was placed on a table in a space across from the bedroom area which represented a separate storage area in the home. Also on the table with the kit was bottled water, scissors, and a second table lamp.	
Study Sequence	HFVS 1 and HFVS 2: Simulated Use Root Cause Analysis (RCA) Label Comprehension Tasks RCA Final Usability Feedback	

As noted in section 1.2, the report for HFVS 1 provides the results for all tasks evaluated in the initial HF validation study and the supplemental report for HFVS 2 provides the results for the tasks that were impacted by the labeling changes made after HFVS 1. Thus, the supplemental HFVS 2 report only provides data for the following tasks:

- Place supplies at bedside
- Pour the entire contents of the nightly dose packet into the dosing cup
- Drink the entire contents of the dosing cup
- Fill the dosing cup with water to Line B
- Store the carton in a secure place
- Place the supplies at bedside
- Drink the entire contents of the dosing cup
- Leave the supplies at bedside and go to bed immediately
- Pour the entire contents of the nightly dose packet into the dosing cup
- Drink the entire contents of the dosing cup

As such, we considered the comprehensive results from both HFVS 1 and the supplemental HFVS 2 and our findings are below in Sections 4.1 and 4.2.

3.2 METHODOLOGY DISCUSSION

Our review of the HF validation study methodology identified a concern that Avadel did not implement our previous recommendation under IND 126321 to evaluate the task to "*wait at least 2 hours after eating before administration*" in the labeling comprehension portion of the HF validation study. In response to our March 23, 2021 Information Request (IR) under this NDA review, Avadel stated[8]:

(b) (4)

On June 1, 2021, we reached out to DN1 and the Division of Neuropsychiatric Pharmacology (DNP) to determine whether they agree with Avadel's above response to our information request. In an internal meeting on August 16, 2021, DN1 and DNP disagreed with Avadel's response. They further state that (b) (4) failure to wait at least 2 hours after eating prior to administration may lead to decreased efficacy. Thus, we disagree with Avadel and maintain this to be a critical task and failure to complete or comprehend this task will result in patient harm or compromised care.

While we disagree with Avadel's decision to exclude evaluation of this important critical task in the HF validation studies, we are aware of labeling mitigations in place on the similar and currently marketed Xyrem product which share the same intended users and same warning of food effect. Specifically, the Xyrem product labeling includes a statement to inform users not to eat within 2 hours of taking the product which we find may be applied in this particular circumstance.

Based on our postmarketing experience with the similar currently marketed product, Xyrem, we expect that users will understand the use instructions if the same labeling mitigations are applied. We provide a recommendation in Table A below. Our recommendation is intended to align the proposed label with similar currently marketed products. As such, and in this

[8] Clinical Information Amendment (NDA 214755 Sodium Oxybate). Chesterfield (MO): Avadel CNS Pharmaceuticals, LLC; 2021 MAR 29. Available from: \\CDSESUB1\evsprod\nda214755\0010\m1\us\111-info-amend\clin-info-amend.pdf

particular instance, we find our recommendation can be implemented without submission of additional HF validation data.

4 RESULTS AND ANALYSES

Section 4.1 describes the analyses of use errors, close calls, and use difficulties identified with critical tasks in the HF validation studies. Section 4.2 describes use errors, close calls and use difficulties with non-critical tasks in the HF validation studies. Lastly, Section 4.3 describes an evaluation of the omission of data for the non-critical task "Fill the dosing cup with water to line B" in HFVS 1.

4.1 ANALYSIS OF CRITICAL TASK ERRORS

Table 3 describes the study results, Avadel's analyses of the results, and DMEPA's analyses and findings for use errors, close calls and use difficulties with critical tasks.

Table 3. Identified Issues and DMEPA's Findings		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the simulated use critical task of "place supplies at bedside" in HFVS 2 which includes the subtasks of preparing and administering the dose at the bedside there were 17 use errors: • 8 participants prepared the dose away from the bedside but successfully administered it at the bedside. • 9 participants prepared the dose and administered it away from the bedside. The subjective data and Avadel's RCA stated: • 12 use errors were attributed to participants who "intentionally violated" the instructions for use (IFU), reflecting an "abnormal use" situation. These participants stated that despite seeing the IFU instructions, they would prepare the dose in the kitchen or bathroom at home. These participants also mentioned factors such as wanting to avoid spills and messes at their bed, having insufficient workspace at their bedside, not wanting the clutter and wanting to keep their supplies out of reach of their children or pets. Avadel noted that this "abnormal use" situation is likely beyond reasonable means of risk mitigation through the design of the user interface. • 3 use errors were attributed to study artifact because the participants misinterpreted the	Per Avadel's URRA, failure to place supplies at bedside can lead to injury from falling. Our review of the HFVS 2 study results identified subjective feedback from participants indicating that the illustration in the "Before each use" section in the IFU is not clear to prepare and take the product at the bedside. However, we note the same participants also stated that the image under the IFU step 15 informed them that the dose should be prepared at bedside. Our review of the IFU notes that the image in step 15 is identical to the illustration in the "Before each use" section. Additionally, we find that the IFU prominently presents the section title "Mix…at your bedside" and multiple steps include the statement "At your bedside,.." (e.g., steps 1 (b) (4) and 15). Thus, based on our review of the labels and labeling, subjective feedback, RCA, and risk mitigations implemented between HFVS 1 and HFVS 2, we agree with Avadel that the residual risk is acceptable for this task. We have no recommendations.

	"kitchen" table where the study supplies were provided as the bedside table as it was a small room and all seemed close together; despite the moderator instructions envision separate rooms. • 2 use errors were attributed to participants relying on the illustrations in the IFU. The participants said the illustrations were not apparent. Both participants eventually realized the dose should be prepared and administered at the beside after referring to IFU step 15 ("Leave the empty cup at your bedside…"). Both participants said if they were to prepare and take another dose, it would be at the bedside. Per Avadel, further risk mitigations were not implemented because the IFU already contains information about gathering supplies at the bedside, preparing the dose at the bedside, and taking the dose at the bedside in multiple locations. Also, Avadel concluded that the IFU provides similar risk controls as with similar currently marketed products that present the same risk with respect to administering the dose at bedside.	
2.	For the simulated-use critical task "pour the entire contents of the nightly dose packet into the dosing cup" in HFVS 2 there was one use error. • 1 participant held the packet horizontally while cutting it open when a small amount of powder spilled out out.	Per the Applicant's URRA, failure to pour the entire contents of the nightly dose packet into the dosing cup can lead to underdose and no change in narcolepsy symptoms. If more than one packet is added, the side effects from an overdose may occur. Our review of the study results identifies subjective feedback from HFVS 2 indicating the IFU should include a warning to hold the

	The subjective data and Avadel's RCA indicated: • The use error was attributed to an action-based error (i.e., slip) in holding the packet horizontally while cutting it open. The participant stated the picture in step 3 of the IFU was clear and common sense to hold the packet upright when opening a packet with powder; however, a warning could be added to that step about keeping the packet upright. • Per Avadel, the amount of powder lost could not be quantified but appeared to be a small amount with a minimal underdose and no clinically meaningful impact. Per Avadel, the IFU illustration for step 3 shows the proper positioning of the packet. Thus, no further mitigation measures were implemented.	packet upright so that product spillage does not occur; however, the participant also stated the picture in step 3 is clear and consistent with common sense. Our review of the IFU step 3 finds the picture shows the packet being held upright while opening. Our review of the IFU step 4 finds that the instructions are clear for pouring the entire contents in the dosing cup. Thus, based on our review of the labels and labeling, subjective feedback, RCA, and risk mitigations implemented between HFVS 1 and HFVS 2, we agree with Avadel the residual risk is acceptable for this task. We have no recommendations.
3.	For the knowledge based assessment (KBA) critical task "Storing the carton" (KBA question: "Sally just brought home her "FT218 (b) (4) from the pharmacy. Where should she store carton?"), there were two use errors in HFVS 2. • One participant (2N10) stated the carton should be stored in a "nice, dry place." • One participant (2N15) was stated she could not find any storage information but then noticed the storage instructions in the IFU when answering subsequent KBA questions. The subjective data and Avadel's RCA stated:	Per Avadel's URRA, failure to store the carton in a secure place can lead to side effects or overdose (if child is able to access the product). Our review of the study results finds that the phrasing of KBA question, "Where should she store carton?," may have contributed to both use errors because there are other storage statements such as "Store…in a clean and dry place", located in the IFU section "How should I store". Our review finds the question was unclear; therefore, these users experienced study artifact. We have no recommendations.

	• 1 participant experienced use error because they expected the target information to be located in the important information section of the IFU. • 1 participant experienced a use error and saw the storage information but did not locate the warning to keep out of the reach of children but she noticed it later during the RCA and thought the IFU instructions were clear. Per Avadel, the user interface provides the warning to keep out of each of children in multiple locations (i.e., container labels, carton labeling, and IFU). Additionally, Avadel states this is a "common requirement" for medicines in general and is not unique to this product. Thus, no further risk mitigations were implemented.	
4.	For the KBA critical task "DO NOT drive or operate heavy machinery within 6 hours of taking the proposed product" (Question: "Sally wakes up a couple of hours after taking her dose and decides to drive to the store. Is that okay?") there was one use difficulty in HFVS 2. • 1 participant initially responded that you should not get out of bed. The subjective data and Avadel's RCA stated: • The bulleted statement, "DO NOT drive or operate heavy machinery…" in the "Important Information" section of the IFU did not initially stand out to the participant. The participant	Per Avadel's URRA, failure to follow the safety precaution to avoid driving or operating heavy machinery within less than 6 hours can lead to accident/injury to user or others. While our review identified subjective feedback indicating the information did not initially stand out to the participant, our review of the IFU finds that the current presentation of the information under "Important information" section, along with the warning on the front of the dose packet and on the side of the carton are acceptable and prominently placed to alert users of the target information. We also note that the participant suggested revising the statement to include bold font or separate the statement from other bullets. Our review of the IFU labeling finds the statement includes a bolded "DO NOT…" precursor and is already separated from other bullets. As such, we do not have recommendations for improvement to the IFU or labeling.

	suggested revising statement to include bold font or separate the statement from other bullets. Per Avadel, the information to not drive or operate heavy machinery within 6 hours of taking the proposed product is included in the "Important Information" section of the IFU, and on carton labels and container labeling. Additionally, Avadel stated that ultimately, all participants answered correctly. Thus, no further risk mitigations were implemented.	Thus, based on our review of the labels and labeling, subjective feedback, RCA, and risk mitigations implemented between HFVS 1 and HFVS 2, we agree with Avadel that the residual risk is acceptable for this task. We have no recommendations.
5.	For the KBA critical task "Disposing unused drug" (Question: "John is preparing to throw away a used nightly dose packet when he notices there is still some drug powder in it. How should he dispose of the packet?") , there was 1 use error and 1 use difficulty in HFVS 1. • The participant who experienced the use error stated, "I would wrap it up into another bag and throw it into the trash." • The participant who experienced the use difficulty struggled to locate the target information in the IFU the participant commented she had seen the information somewhere during the simulated use portion of the session. After searching for a while, she eventually found the information in the correct location of the IFU. The subjective data and RCA feedback stated: • The participant who experienced a use error started by reading the beginning of the IFU to find	Per Avadel's URRA, failure to properly dispose of the empty nightly dose packet can lead to drug product being accessible to non-patients which can cause side effects/overdose. Our review of the study results identified subjective feedback indicating that the target information for disposing the drug product could be overlooked because it is located on the back of the IFU; however, our review of the IFU Steps 16 and 17 finds that the instructions are in the IFU and in sequential order. Additionally, similar marketed products have the disposal information also located at the end of the IFU. As such, we do not find the task failure supports additional changes to this step and thus we do not have recommendations for revision to the IFU. Thus, based on our review of the labels and labeling, subjective feedback, RCA, and risk mitigations implemented between HFVS 1 and HFVS 2, we agree with Avadel that the residual risk is acceptable for this task. We have no recommendations.

	the information; while searching, she only looked at one side of the IFU and was not able to find the answer (located on page 4). She then made the comment "I would wrap it up into another bag and throw it into the trash.". • The participant who experienced a use difficulty started reading the beginning of the IFU to find the information. While searching, she made the comment that she had seen the information somewhere during the simulated use portion of the session. After searching for a while, she eventually found the information on page 4. • Per Avadel, the location of the disposal instructions on the last page of the IFU did not meet the participants expectations as both participants searched the beginning of the IFU. Avadel noted that no other suggestions were offered of where the information should be from these participants. Avadel concluded the information on proper disposal is (i.e. to rinse any unused powder and reconstituted drug down the sink) is presented in the IFU. Ultimately all except for 1 participant answered correctly for this task. Although she stated she would dispose of it in the trash, she stated she would attempt to secure/seal the drug material by putting it into a bag before disposing of it. Lastly, Avadel noted the instructions are intentionally on page 4 (the last page) of the IFU, after the administration steps, to avoid users trying to complete another task away from the bedside; meaning, the product should be	

	disposed of the next day. Thus, no further risk mitigations were implemented.	
6.	For the KBA critical task "taking the dose with medicines that cause sleepiness" (Question: "John caught a cold and wonders if he can take nighttime cold medicine before taking his dose of FT218. Is that okay?"), there was 1 use error and 1 use difficulty in HFVS 1. • 1 participant experienced use error and was unable to find the intended information about not taking medicines that cause sleepiness when using the proposed product. After not being able to find the information, she stated that she would assume one would talk to their doctor, which is what it says in the instructions. • 1 participant experienced use difficulty was able to eventually locate it. The subjective data and RCA stated: • The participant who experienced use error and was unable to locate the target information commented that not all nighttime medicines cause sleepiness, indicating that she was looking for the specific language from the task question about nighttime cold medicine. She also mentioned talking to her doctor about this topic. • Avadel interpreted this use error as potential study artifact associated with the question design. Avadel also noted the participant said she would	Per Avadel's URRA, taking this medication with other medications that cause sleepiness can lead to a drug-drug interaction with side effects or overdose. Our review of the study results finds that the phrasing of KBA question, "John caught a cold and wonders if he can take nighttime cold medicine before taking his dose of FT218. Is that okay?" may have contributed to the use error one participant experienced due to study artifact. Our review finds the question was unclear and brought attention to cold medicine and therefore, users experienced study artifact. We have no recommendations.

	seek guidance from her doctor, which implies she would not be likely to commit the use error of taking medicines that cause sleepiness with the proposed product. • The participant with use difficulty said he initially glossed over the beginning of the IFU (i.e. "Important Information section) and therefore, did not see the information at first. He did not provide suggestions to make the content more noticeable. Avadel concluded the target statement "Medicines that cause sleepiness should not be used while taking Lumryz (sodium oxybate)" is included in the "Important Information" section of the IFU and the one use error that occurred related to this question appears to be related to study artifact rather than a usability issue with the product materials. Thus, no further risk mitigations were implemented.	
7.	For the KBA critical task "disposing used dosing cup" (Question: "Sally has finished the last nightly dose packet in her kit. What should she do with the used cup?") there was 1 use error and 1 use difficulty in HFVS 1. • 1 participant experienced use error stated the cup should be kept since it's the only one in the kit. • 1 participant experienced use difficulty and struggled to locate the target information in the IFU to throw away the rinsed dosing cup in the trash after finishing the last nightly dose packet in the kit.	Per Avadel's URRA, failure to dispose of the rinsed dosing cup at the end of the pack can lead to marginal overdose (less than 2% drug residue). However, per the medical officer assigned to this drug product, Lumryz has not been studied in children less than 7 years of age. Thus, data to support the sponsor's assertion that 2% residue left in the cup is marginal is unavailable. Our review of the study results did not identify subjective feedback relevant to mitigate this potential use error. Our review of the IFU "how do I throw away (dispose) of Lumryz (sodium oxybate)?" finds that the instructions on disposal are in sequential order and we find the presentation of the information

	The subjective data and Avadel's RCA stated: • The participant with the use error stated that it makes sense that he would get a new cup with a new kit but he could not find the information when being asked; and he was not sure where or how that information could be presented in the IFU or carton. • The participant with the use difficulty only read one side of the IFU. She stated she initially skimmed the IFU to find the answer; when asked follow-up questions, the information on the other side of the IFU was pointed out to her. Once she noticed the other side of the IFU, she was able to locate the answer. • Per Avadel, the location of the disposal instructions did not meet participants expectations about where to find this information in the IFU. Avadel concluded the residual material in the cup would not represent more than 2% of the dose per assay testing at the manufacturing site and the possible harm of the non-patient ingesting the drug residue is anticipated to entail a non-critical marginal overdose. Thus, no further risk mitigations were implemented.	acceptable. We note step 9 and step 14 of the IFU both state "make sure to drink all of the mixed solution in the dosing cup" in bold prominent text. Further the disposal section provides clear instructions to rinse the cup. As such, we do not find the task failure supports additional changes to this step and thus we do not have recommendations for improvement to the IFU or labeling. Thus, based on our review of the labels and labeling, subjective feedback, RCA, and risk mitigations in place, we agree with Avadel that the residual risk is acceptable for this task. We have no recommendations.

8.	For the KBA critical task "using only one packet" (Question: "Sally is used to taking another medication for her condition and wants to prepare two doses of FT218 to take for the night. Is that okay?") , there were two use difficulties in HFVS 2. • 2 participants struggled to locate the relevant content in the product materials about taking only one nightly dose packet per day but were able to eventually answer correctly. The subjective data and Avadel's RCA stated: • The experienced participant said she remembered seeing this information in the instructions during the preceding study activities. She referred to the "Before each use" section of the IFU to infer the correct answer as it mentions getting one nightly dose packet when gathering supplies. She suggested that the relevant statement in the "Important Information" section of the IFU would be easier to see if it were bolded. • The naïve participant inferred the correct response from the steps in the IFU, as he said they only show one dose packet as being used, as well as the title box of the IFU which states "1 packet per dose". However, he had trouble locating the target content in the IFU. He said he focused on the bullets with the bold "DO NOT" at the beginning of them. Avadel noted the target information "Take only one nightly dose packet per day at bedtime" in the first bullet	Per Avadel's URRA, failure to take only one packet (i.e. take more than one packet) can lead to side effects or overdose. We reached out to DN1 to determine the harm to patients for using more than one packet. DN1 stated taking more than one packet is potentially serious and could lead to central nervous system depression and adverse events such as drowsiness, deeper stages of unconsciousness, respiratory depression, etc. Our review of the study results identified subjective feedback stating the target information was initially difficult to locate in the IFU. However, all participants provided the correct response. Additionally, our review of the simulated-use data of the HF validation study finds that there were no user errors attributed to users adding more than one dose packet. Our review of the IFU "Important information" section and Step 10 finds that warnings are in place to use only one packet nightly. Additionally, the target information is located on the nightly dose packet and on the side carton panel labeling. As such, we do not find the task failure supports additional changes to this step and thus we do not have recommendations for improvement to the IFU or labeling. Thus, based on our review of the labels and labeling, subjective feedback, RCA, and risk mitigations implemented between HFVS 1 and HFVS 2, we agree with Avadel that the residual risk is acceptable for this task. We have no recommendations.

	of the "Important information" section of the IFU did not stand out to the participants. Per Avadel, all participants answered correctly and the warning was already in the IFU, on the dose packets, and in the warning section of the side panel of the carton. Thus, no further risk mitigations were implemented.	
9.	For the KBA critical task "taking the dose at bedtime" (Question: "Sally is ready to take her first dose but is unsure when to take it. When should she take her dose?", there was one use difficulty in HFVS 2. • 1 participant struggled to locate the target information in the IFU to take only one nightly dose packet per day at bedtime. The subjective data and Avadel's RCA stated: • The participant looked at the "Important information" section of the IFU but did not initially notice the relevant content. He later reread the section and correctly answered the task question. He stated if the information is important, then it should be bolded or in red text. He added that he would expect his doctor to provide this information to him. • Avadel identified the warning did not stand out to the participant; however, Avadel stated the target information is in the IFU under "Important information", in step 10, and a warning is located	Per Avadel's URRA, failure to take this medication at bedtime can lead to accident while performing dangerous activities such as driving/injury to others. We note the participant suggested the warning should be either bolded or in red text to show it is important. Our concern with this approach is that the overly prominence of this statement may take away from the other important information. Our review of the labeling finds the statement is located under the section called "Important Information" along with other statements. In addition, our review of the labeling indicates the IFU, carton and container labels all provide warnings related to taking the packet at bedtime and to prepare the product at the bedside. Thus, based on our review of the labels and labeling, subjective feedback, RCA, and risk mitigations implemented between HFVS 1 and HFVS 2, we agree with Avadel that the residual risk is acceptable for this task. We have no recommendations.

	on the front of each nightly dose packet and the side panel of the carton. Avadel concluded that ultimately all participants answered correctly, and the aforementioned warnings are in place. Thus, no further risk mitigations were implemented.	
10.	For the KBA critical labeling comprehension task "taking the dose at bedside"(Question: "John is lying in bed after taking his dose. He decides to get up to brush his teeth in the bathroom. Is that okay?"), there was 1 use difficulty in HFVS 2. • 1 participant conveyed the proper response; however, he had trouble locating the target content in the IFU to avoid getting out of bed after taking the proposed product. The subjective data and Avadel's RCA stated: • The statement initially did not stand out to the participant because he focused on the bullets with the bold "DO NOT" at the beginning of them. He stated it should be bolded to grab his attention and his doctor should tell him. Per Avadel, the information regarding administering at bedside is included in the IFU "Important Information" section and under Step 15. Per Avadel, all participants answered correctly. Thus, no further risk mitigations were implemented.	Per Avadel's URRA, failure to take the dose at the bedside can lead to injury from falling. Our review of the subjective feedback identified the participant stated the information should be bolded to grab his attention and his doctor should tell him. Our concern with the bolding approach is that the overly prominence of this statement may take away from the other important information. Our review of the labeling finds the statement is located under the section called "Important Information" along with other important statements. Our review of the IFU also identified instructions to take the dose at the bedside under "Important Information" and in Step 15, which states "avoid getting out of your bed after your dose" in bold prominent text. We note the participant did successfully find the information in the Important Information section. Thus, based on our review of the labels and labeling, subjective feedback, RCA, and risk mitigations implemented between HFVS 1 and HFVS 2, we agree with Avadel that the residual risk is acceptable for this task. We have no recommendations.

4.2 ANALYSIS OF NON-CRITICAL TASK ERRORS

The HF validation study results for HFVS 1 and HFVS 2 showed use errors, (e.g. failures, difficulties, and close calls) with the following three non-critical tasks; however, based on our review of the available participants' subjective feedback, Avadel's root cause analysis, and Avadel's proposed risk mitigation strategy we determined the residual risk is acceptable. Specifically, we find that the labeling mitigations in place include information that is prominently placed within the labels and labeling and in alignment with best labeling practices. In addition, we considered the use tasks of the proposed product as compared with the use tasks in similar marketed products with the same user groups to determine if there are any known concerns of vulnerability to use error and did not identify any concern. Subsequently, we did not identify further need for risk mitigation strategies at this time to address the use errors related to the following use tasks:

- Break open the tamper-evident seal on the carton lid
- Open the nightly dose packet
- Fill the dosing cup to line B (for rinsing step)

4.3 ANALYSIS OF THE OMISSION OF NON-CRITICAL RINSING TASKS DATA

Per Avadel, in HFVS 1, five participants did not perform the non-critical task "Fill the dosing cup with water to line B"; which precluded participant completion of the subsequent rinsing tasks listed below. As such, Avadel categorized observed performance for the following four rinsing tasks for these five participants as "no data".

- Close the dosing cup by twisting the cap on clockwise
- Shake the closed dosing cup for greater than 5 seconds
- Open the dosing cup by twisting the cap counterclockwise
- Drink the entire contents of the dosing cup

As part of our review, we considered if the omission of these non-critical use tasks could have a negative clinical impact on the use of the proposed product.

Per Avadel's Use Failure Modes and Effect Analysis (uFMEA), failure to fill the dosing cup with water to line B and subsequently perform the four rinsing tasks listed above could result in a marginal underdose (less than 2% drug residue not consumed). Thus, we e-mailed our colleagues in DN1 on June 01, 2021 for input regarding whether a 2% underdose would have significant clinical impact and DN1 agreed with Avadel's finding.

Thus, based on our assessment of the information submitted and in consideration of the discussions with the DN1, we find the omission of data from these non-critical use tasks is acceptable.

4.4 LABELS AND LABELING

Table 4 and Table A below include the identified medication error issues with the product samples, packaging, label and labeling submitted on December 15, 2020 and March 10, 2021, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table A was conveyed to the Applicant in the September 13, 2021 IR (see Appendix E) and in light of this, the Applicant submitted revised container labels, carton labeling, and the IFU on September 16, 2021. Our review of the revised labels and labeling determined that the revised labels and labeling were generally acceptable from a medication error perspective with the exception of the Recommended Dosage statement. We acknowledge the Applicant implemented our recommendation to include the Recommended Dosage statement on the container labels but was not carried forth on the carton labeling. We provide letter ready language for the Sponsor in section 5 below.

Table 4: Identified Issues and Recommendations for Division of Neurology 1			
	Identified Issue	Rationale for Concern	Recommendation
Prescribing Information- General Issues			
1.	As proposed, the package type term is presented as, "(b) (4) packets."	We are unclear if the package type term, "(b) (4) packets" is considered an appropriate package type term for the proposed product.	We defer to the Office of Pharmaceutical Quality (OPQ) to determine the appropriate package type term. We recommend that the package type term be presented consistently throughout all labels and labeling.
2.	The presentation of the established name and dosage form is presented as "(sodium oxybate for extended-release oral suspension)".	It is unclear if the term "for extended-release oral suspension" is the dosage form and thus, should be presented outside of the parenthesis following the established name.	We defer OPQ to determine the appropriate presentation of the established name and dosage form. We recommend the established name and dosage form be presented consistently throughout all labels and labeling.
Highlights of Prescribing Information and Full Prescribing Information Section 2.2: Important Administration Instructions			
1.	The PI instructs users to prepare the dose with approximately 80 mL (approximately 1/3 cup) of water; however, the co-packaged dosing cup includes line A and line B markings (i.e., no mL or cup markings).	Lack of clarity regarding regarding the volume of water required to prepare a dose may lead to wrong technique medication errors.	We recommend revising section 2.2 to refer to the IFU for additional preparation instructions.
Full Prescribing Information Section 2.1: Dosing Information			
1.	The dosing information in subsection 2.1 could be improved to clarify that your product is administered once per night as a single dose.	Lack of clarity regarding the frequency of administration may lead to wrong dose medication errors.	We recommend revising subsection 2.1 to ensure that the word "once" precedes the term "per night."

<table>
<tr><td colspan="4">Full Prescribing Information Section 2.2: Important Administration Instructions</td></tr>
<tr><td>1.</td><td>The statement “suspensions should be consumed within 30 minutes” is presented in subsection 16.1; however, we would expect important information related to administration to be in subsection 2.2 “Important Administration Instructions.”</td><td>We are concerned that this statement may be overlooked, which may pose risk of administration of degraded drug product.</td><td>Relocate the statement “suspensions should be consumed within 30 minutes” from section 16.1 to subsection 2.2.</td></tr>
<tr><td>2.</td><td>Subsection 2.2 lacks the route of administration.</td><td>We are concerned that not stating the route of administration may cause confusion and lead to medication errors.</td><td>Revise the statement “LUMRYZ is taken as a single dose at bedtime.” to “LUMRYZ is taken orally as a single dose at bedtime.”</td></tr>
<tr><td colspan="4">Full Prescribing Information Section 16.1: How Supplied</td></tr>
<tr><td>1.</td><td>As currently presented, the package configuration and NDC number for each strength is not provided.</td><td>The packaging configuration is required to appear in Section 16 in accordance with 21 CFR 201.57(c)(17).</td><td>We recommend revising subsection 16.1 to include each packaging presentation and NDC number. Consider providing this information in table format similar to the example below.
<table>
<tr><th>Strength</th><th>Package Size</th><th>NDC Number</th></tr>
<tr><td rowspan="2">4.5 g</td><td>7 single-dose packets</td><td>NDC XXXXX-XXX-XX</td></tr>
<tr><td>30 single-dose packets</td><td>NDC XXXXX-XXX-XX</td></tr>
<tr><td rowspan="2">6 g</td><td>7 single-dose packets</td><td>NDC XXXXX-XXX-XX</td></tr>
<tr><td>30 single-dose packets</td><td>NDC XXXXX-XXX-XX</td></tr>
<tr><td>7.5 g</td><td>7 single-dose packets</td><td>NDC XXXXX-XXX-XX</td></tr>
</table></td></tr>
</table>

				30 single-dose packets	NDC XXXXX-XXX-XX
			9 g	7 single-dose packets	NDC XXXXX-XXX-XX
				30 single-dose packets	NDC XXXXX-XXX-XX
2.	The term "(b) (4)" in the statement "Each (b) (4) includes nightly dose packets…" could be improved to better describe how your product is supplied.	Lack of clarity of your proposed product packaging may lead to confusion for users.	Revise the statement in section 16.1 from "Each (b) (4) includes nightly dose packets…" to "Each carton includes single-dose packets…".		
Full Prescribing Information Section 16.2: Storage					
1.	Subsection 16.2 of the PI states "LUMRYZ should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)."; however, the recommended storage temperature should be provided as a range.	Lack of clarity and consistency regarding the storage condition might contribute to confusion and deteriorated drug medication errors.	We defer to OPQ to determine the appropriate storage statement. We recommend including the term "at room temperature" for clarity and including a range. We also recommend ensuring all storage statements are consistent throughout all labels and labeling.		

Table A: Identified Issues and Recommendations for Avadel CNS Pharmaceuticals LLC			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use			
1.	Step 3 of the Instructions For Use (IFU) lacks instructions to tap or shake down the packet before opening.	Based on information you provide in your submission, failure to complete this step may result in product loss and result in an underdose. medication error.	Consider revising Step 3 to include instructions for users tap or shake the packet prior to opening.
2.	The IFU does not provide instructions on what to do if the dose is not consumed within 30 minutes of mixing.	Lack of instructions for this step may cause confusion and result in deteriorated drug medication errors.	Revise the IFU "Important Information" section to include instructions regarding what to do if the dose has not been consumed within 30 minutes of mixing (e.g., discard the mixed dose and prepare a new dose).
3.	The IFU can be improved to provide information regarding the timing of the onset of effect to align with subsection 2.2 of the Prescribing Information (PI).	While we acknowledge that you inform users to avoid "getting out of your bed after taking…", we find that informing users how quickly the medication may take effect may further minimize patient harm as a result from falling.	Revise the Important information section of the IFU to include information regarding the timing of the onset of effect in alignment with subsection 2.2 of the PI.
4.	The graphical description in the section titled "FT218 (b) (4) on page 1 of the IFU shows two single-dose packets as part of the contents (i.e. front and back); however, this	We are concerned that users may misinterpret the front and back images of the same packet as two separate packets, which may lead to overdose errors if two packets are	Consider revising the graphical description of your user interface (i.e., the graphic under "FT218 (b) (4) on page 1 of the IFU) to include only one image of the single-dose packet.

	product is intended to be administered as one packet nightly.	administered. We are particularly concerned with the higher risk of negative transfer due to previous experience with similar marketed products that are administered twice nightly.	
5.	The placeholder "FT218", is used throughout the IFU.	The proposed proprietary name, Lumryz, was found conditionally acceptable on March 12, 2021.	Replace "FT218" with the conditionally approved proprietary name, "Lumryz", throughout the IFU.
6.	The IFU describes your proposed product as a (b) (4); however, the term is not included in section 16 of the PI.	The use of inconsistent terminology in the labeling may lead to confusion.	Revise your IFU to remove the term (b) (4)
Container Labels and Carton Labeling			
1.	Each strength statement lacks adequate spacing between the numerical dose and unit of measure.	Lack of adequate spacing may impact readability and result in wrong strength medication errors.	Revise your container labels and carton labeling to place adequate space between the numerical dose and unit of measure (e.g. [4.5 g instead of 4.5g]), for each strength, to improve readability.
2.	There is inadequate differentiation between the (b) (4) color schemes for the tradedress of your 6 g and 7.5 g container labels and carton labeling.	Lack of adequate differentiation may contribute to product selection medication errors.	Revise the color scheme used for either the 6 g strength or the 7.5 g strength so that the colors are better differentiated. In addition, ensure the color selected is differentiated from your 9 g and 4.5 g strengths.
3.	For the 4.5 g strength, the color contrast of the (b) (4) color font used for	Insufficient color contrast can contribute to medication errors by	We recommend revising the background color and/or the proprietary name font color to improve the contrast and readability of the proprietary

	the proprietary name against the gray background can be improved to allow adequate readability of the proprietary name.	making it difficult for healthcare professionals, caregivers, and/or patients to readily identify important product information. See *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (*April 2013).[9]	name for the 4.5 g container label and carton labeling.
4.	The header and format for the expiration date is presented inconsistently. For example, your carton labeling uses the format and header "EXP M YYYY" and the container label uses the format "EXPIRY: XXXX".	Lack of clarity and consistency regarding the expiration date might contribute to confusion and deteriorated drug medication errors.	FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. Lastly, revise your expiration date header to ensure a consistent format (i.e., either "EXP" or "EXPIRY"). See *Draft Guidance for Industry: Product*

			Identifiers under the Drug Supply Chain Security Act - Questions and Answers (September 2018).[9]
5.	As currently presented, the first letter of the proprietary name, Lumryz, is not capitalized.	We are concerned that not capitalizing the first letter of the proprietary name "L" may lead to product selection medication error should the first letter be misinterpreted as the letter "I" .	We recommend you consider capitalizing the first letter of the proprietary name or modifying the font style improve readability and minimize misinterpretation.Error! Bookmark not defined.
6.	The (b) (4) statement is inconsistent with the terminology in the PI.	Per 21 CFR 201.55, labels for prescription drugs should bear a statement of the recommended dosage. Additionally, we are concerned that inconsistent terminology may lead to confusion.	Revise the statement (b) (4) to read as: "Recommended Dosage: see prescribing information."
7.	The linear barcode has been omitted.	The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2).	Add the product's linear barcode to each individual container label and carton labeling. The barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

[9] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

8.	The strength statement on your container label does not align with the carton labeling. For example, the carton labeling states "4.5 g per packet", while the container label states [redacted]".	We are concerned that inconsistent terminology may cause confusion for users and lead to medication errors.	Revise your container labels for each strength to state "per packet" after the strength (i.e. 4.5 g per packet, 6 g per packet, etc.), to be aligned with the carton labeling.
Carton Labeling			
1.	As currently presented, the carton labeling does not state all of the contents in the carton on the Principal Display Panel (PDP).	Lack of clarity regarding the carton contents may lead to confusion.	Revise your carton labeling to provide the carton contents on the PDP. For example, add a statement similar to "This carton contains:…" followed by a list of the carton contents.
2.	The statement "Must be Prepared per the Instructions for Use (See [redacted])" is inconsistent with the terminology in the PI.	We are concerned that inconsistent terminology may lead to confusion.	Revise the statement to state: "Must be prepared per the Instructions for Use (see prescribing information)".
3.	The medication guide (MG) statement "Dispense the enclosed Medication Guide to each patient" is missing from the PDP of the carton labeling.	Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a MG is required under this part shall instruct the authorized dispenser to provide a MG to each	Add the MG statement "Dispense the enclosed Medication Guide to each patient" on the PDP.

		patient to whom the drug product is dispensed and shall state how the MG is provided. These statements shall appear on the label in a prominent and conspicuous manner.	

5 CONCLUSION AND RECOMMENDATIONS

Our review of the results of the human factors (HF) validation studies (HFVS 1 and supplemental HFVS 2) identified use errors with critical tasks. However, taking into consideration the review of the subjective feedback, root cause analysis, our independent review of the proposed user interface, the risk mitigations implemented, and our postmarketing experience with similar currently approved products, we find residual risks associated with these use errors acceptable. Thus, in this specific instance, we accept the simulated HF validation study results.

The revised container labels and IFU received on September 16, 2021 are acceptable from a medication error perspective. The revised carton labeling can be improved to include the recommendation dosage statement. Thus, we provide this recommedantion for the Applicant in section 5.1 below.

5.1 RECOMMENDATIONS FOR AVADEL

We find the results of your human factors (HF) validation study to be acceptable.

We acknowledge you added the Recommended Dosage statement (i.e., “Recommended Dosage: see prescribing information”) to the container labels; however, this statement is missing from your carton labeling. Per 21 CFR 201.55, labels for prescription drugs should bear a statement of the recommended dosage. Add the statement, “Recommended Dosage: see prescribing information” to your carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Lumryz (sodium oxybate) that Avadel submitted on March 10, 2021.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class	CNS agent
Active Ingredient	sodium oxybate
Indication	Treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy
Route of Administration	Oral
Dosage Form	for extended-release oral suspension
Strength	4.5 g, 6 g, 7.5 g, 9 g
Dose and Frequency	The recommended starting dosage is 4.5 grams (g) per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the effective dosage range of 6 g to 9 g per night orally. The dosage may be gradually titrated based on efficacy and tolerability. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.
How Supplied	LUMRYZ is a blend of white to off-white granules for oral suspension in water. Each carton includes either 7 packets or 30 packets of LUMRYZ, one Instructions for use, and one dosing cup.

	(b) (4)
Storage	LUMRYZ should be stored at 20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).
Container Closure/Device Constituent(s)	Dosing cup
Intended Users	Adult patients
Intended Use Environment(s)	Home

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On March 01, 2021, we searched the L:drive and AIMS using the terms, sodium oxybate, NDA 214755 and IND 126321 to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified three previous reviews[10,11,12] and we considered our previous recommendations to see if they are applicable for this current review.

[10] Stewart, J. Human Factors Validation Protocol for sodium oxybate (IND 126321). Silver Spring (MD): FDA CDER, OSE, DMEPA (US); 2018 JUL 12. RCM No.: 2018-813

[11] White, L. Human Factors Validation Protocol for sodium oxybate (IND 126321). Silver Spring (MD): FDA, CDER OSE, DMEPA (US); 2020 MAR 26. RCM No.: 2020-215

[12] Purcell, J. Review of Response to HF Advice for sodium oxybate (IND 126321). Silver Spring (MD): FDA CDER, OSE, DMEPA (US); 2020 APR 21. RCM No.: 2020-215-1

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information for HFVS 1 submitted 12/15/20 can be accessible in EDR via: \\CDSESUB1\evsprod\nda214755\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\eds\5354-other-stud-rep\hfft218-1801\hfft218-1801-usability-engr-summ-rpt.pdf

The background information for HFVS 2 submitted 2/1/21 can be accessible in EDR via: \\CDSESUB1\evsprod\nda214755\0004\m5\53-clin-stud-rep\535-rep-effic-safety-stud\eds\5354-other-stud-rep\hfft218-1801\hfft218-1801-usability-engr-summ-rpt.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HFVS 1study results report submitted 12/15/20 can be accessible in EDR via: \\CDSESUB1\evsprod\nda214755\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\eds\5354-other-stud-rep\hfft218-1801\hfft218-1801-summative-report.pdf.

The HFVS 2 study results report submitted 2/1/21 can be accessible in EDR via: \\CDSESUB1\evsprod\nda214755\0004\m5\53-clin-stud-rep\535-rep-effic-safety-stud\eds\5354-other-stud-rep\hfft218-1801\hfft218-1801-d9721-037-r2-stdy-rpt.pdf.

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

We issued an information request (IR) on March 23, 2021 to request: a copy of the Investigator's Guide used in the validation studies, root cause analysis and proposed risk mitigations for tasks with use errors, close calls and use difficulties. The Applicant responded on March 29, 2021 and the response can be accessible via EDR: \\CDSESUB1\evsprod\nda214755\0010\m1\us\111-info-amend\clin-info-amend.pdf.

We issued an IR on April 20, 2021 to request a description of the changes made to the HF protocol under IND 126321 related to remote testing, and to identify the participants that participated in remote testing. The Applicant responded to the IR on April 23, 2021 and the response can be accessible via EDR: \\CDSESUB1\evsprod\nda214755\0015\m1\us\111-info-amend\clin-info-amend.pdf.

We issued an IR on September 13, 2021 to request revisions to the container labels, carton labeling, and IFU. On September 16, 2021, the Applicant responded and the response can be accessible via EDR: \\CDSESUB1\evsprod\nda214755\0032\m1\us\111-info-amend\info-req-label.pdf.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[13] along with postmarket medication error data, we reviewed the following Lumryz (sodium oxybate) labels and labeling submitted by Avadel.

- Container label received on December 15, 2020 and September 16, 2021
- Carton labeling received on December 15, 2020 and September 16, 2021
- Packaging received on December 15, 2020 and September 16, 2021
- Instructions for Use received on December 15, 2020
    - Available from: \\CDSESUB1\evsprod\nda214755\0001\m1\us\114-label\1141-draft-label\proposed-ifu.pdf
- Instructions for Use received September 16, 2021
    - \\CDSESUB1\evsprod\nda214755\0032\m1\us\114-label\1141-draft-label\lumryz-ifu.pdf
- Medication Guide received on March 10, 2021. Available from:
    - \\CDSESUB1\evsprod\nda214755\0007\m1\us\114-label\1141-draft-label\proposed.docx
- Prescribing Information received on March 10, 2021. Available from:
    - \\CDSESUB1\evsprod\nda214755\0007\m1\us\114-label\1141-draft-label\proposed.docx

F.2 Label and Labeling Images received on December 15, 2020

Container Label

4.5 g

[13] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

ANKARA N YOKUM
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COLLEEN L LITTLE
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LOLITA G WHITE
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DANIELLE M HARRIS
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M E M O R A N D U M

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

DATE: September 23, 2021

TO: Partha Roy, Ph.D.
Director
Office of Bioequivalence
Office of Generic Drugs

Eric Bastings, M.D.
Director
Division of Neurology I
Office of Neuroscience
Office of New Drugs

FROM: Makini Cobourne-Duval, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Director (Acting)
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Remote record review (RRR) of (b) (4) (b) (4)

1. RRR Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote record review (RRR) of (b) (4) (b) (4) and the analytical portion of Study 20-277 (sponsor reference – PKFT218-1801) under NDA 214755 for FT218(sodium oxybate or GHB) conducted at (b) (4) (b) (4) An onsite inspection was not possible due to the disruption of inspectional activities by COVID-19 global pandemic.

I observed the following objectionable conditions during the RRR: (b) (4), the lack of documented sample collection times at the designated timepoints throughout study conduct and during method validation. And for Study 20-277 (sodium oxybate), the lack of validation assessments for matrix effect of lipemic samples and the lack documentation of whether collected subject samples were lipemic.

1.1. Recommendation

After my review of the objectionable conditions observed during the RRR and the firm's response to the RRR observations, I conclude there was an observation that impacts the reliability of data from one of the audited studies. Non-responsive
Non-responsive

However, regarding Study 20-277 (sponsor reference – PKFT218-1801) for FT218 (sodium oxybate or GHB), additional study documents and data provided as part of the firm's response indicates that the objectionable conditions did not impact the reliability of the studies. Therefore, I conclude that the data from Study 20-277 (sponsor reference – PKFT218-1801) for FT218 (sodium oxybate or GHB) are reliable, given that review division confirms the summary results after review of the amended validation data.

2. Reviewed Studies

Non-responsive

Study 20-277 (NDA 214755) (sponsor reference - Study PKFT218-1801) "A Comparative, Open-Label, 2 Period, Randomized 2-Sequence, Crossover Study to determine the relative bioavailability of FT218 (Single Dose Administered at a dose of 6 g) when compared with the reference listed product, US Xyrem® in Healthy Volunteers"

Sample Analysis Period: 9/3/2020 – 10/8/2020

3. Scope of RRR

OSIS scientist Makini Cobourne-Duval, Ph.D., Pharmacologist, reviewed Non-responsive and the analytical portion of Study 20-277 conducted at (b) (4)
(b) (4)

The RRR included an examination of study records, method validatio and reference drug product reserves [redacted] Non-responsive and interviews with the firm's management and staff. In addition, we conducted a live interactive, virtual tour via ZoomGov of the relevant facilities with live Q&A through tour.

4. RRR Observations

At the conclusion of the RRR, I observed objectionable conditions and discussed these observations with the firm's management during the RRR close-out meeting.

My evaluation of the discussed observations (and the firm's response dated 9/13/2021 (**Attachment 1**)) are presented below.

4.1. Observations discussed at the close-out of RRR

[redacted] (b) (4)

[redacted] (b) (4)

Since the summary of validation results for this partial validation indicates that the objectionable conditions did not

impact the reliability of the studies, I conclude that the data from Study 20-277 (sponsor reference - PKFT218-1801) for FT218 (sodium oxybate or GHB) are reliable, given that review division confirms the summary results after review of the amended validation data.

4.1.2 Item 2

Non-responsive

OSIS Evaluation:

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Edit: SA 9/15/2021, 9/16/2021, 9/20/2021, 9/21/2021, 9/22/2021,9/23/2021; AD 09/22/2021

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(b) (4)

OSIS File #: BE 9075 (NDA 214755) (b) (4)

Attachments

Attachment 1 – (b) (4)

Attachment 2 –

Attachment 3 –

Attachment 4 –

Attachment 5 –

Attachment 6 –

Attachment 7 –

Attachment 8 –

Attachment 9 –

Attachment 10 –

Attachment 11 –

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/s/

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MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 25, 2021

To: Eric Bastings, M.D., Acting Director
Division of Neurology 1

Through: Dominic Chiapperino, Ph.D., Director
Joshua Lloyd, M.D., Medical Officer Team Leader
Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff

From: James Tolliver, Ph.D., Senior Pharmacologist
Controlled Substance Staff

Subject: Lumryz (Sodium Oxybate Extended-Release Oral Suspension), Code Name FT218, NDA 214755
Dosages, formulations, routes: Extended-release oral suspension manufactured and packaged in (b) (4) packs in unit dosage strengths of 4.5 g, 6 g, 7.5 g, and 9 g sodium oxybate
IND Number: 126,321
Indication(s): Treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy
Sponsor: Avadel CNS Pharmaceuticals, LLC
PDUFA Goal Date: October 15, 2021

Materials Reviewed:

- Preclinical and clinical data submitted in support of NDA 214755 and pertinent to examining FT218 from an abuse potential perspective

Table of Contents

I. SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Neurology I dated January 5, 2021, for CSS to review and provide any comments from an abuse potential perspective concerning NDA 214-755 for Sodium Oxybate Extended-Release Oral Suspension, code name FT218, intended for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy. NDA 214-755, submitted to the Agency by Avadel CNS Pharmaceuticals, LLC, on December 15, 2020, is utilizing the 505(b)(2) regulatory pathway with Xyrem (sodium oxybate) oral solution (NDA 021196) by Jazz Pharmaceuticals as the listed drug.

FT218 is intended to provide a formulation of sodium oxybate that is dosed once at bedtime rather than the required twice-nightly dosing regimen of the currently approved sodium oxybate formulation (i.e., Xyrem), which is taken at bedtime and then again 2.5 to 4 hours later for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy. Dosage strengths will include 4.5, 6, 7.5 and 9 grams of sodium oxybate per night.

Sodium oxybate is a central nervous system depressant in Schedule I of the Federal Controlled Substances Act (CSA). Drug products containing sodium oxybate and approved for medical use in the United States, such as Xyrem and XYWAV, are in Schedule III of the CSA. If approved, FT218 will also be in Schedule III of the CSA.

In response to a request dated December 15, 2020, the Agency has reviewed and deemed conditionally acceptable the proposed proprietary name, Lumryz (DARRTS, NDA 214-755, March 12, 2021) for Sodium Oxybate Extended-Release Suspension. Considering that the nonclinical as well as clinical studies utilize the code name FT218, this review will also use the name FT218

2. Conclusions

1. Sodium Oxybate Extended-Release Oral Suspension, code name FT218, tradename Lumryz, is under development for the treatment of excessive daytime sleepiness and cataplexy in adults with narcolepsy. It is intended to provide a formulation of sodium oxybate that is dosed once at

bedtime rather than the required twice-nightly dosing regimen of the currently approved sodium oxybate formulation (i.e., Xyrem), which is taken at bedtime and then again 2.5 to 4 hours later for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy.

2. As a product containing sodium oxybate, FT218, once approved will be in Schedule III of the federal Controlled Substances Act (CSA).

3. FT218 is formulated in dosage strengths of 4.5 g, 6 g, 7.5 g, and 9 g sodium oxybate. FT218 contains both immediate-release (IR) pellets as well as controlled-release (CR) coated pellets, (b) (4). Each dose is contained within (b) (4) packs, consisting of foil folded and sealed vertically at the back, as well as sealed at the top and bottom. At dosing, the contents of a (b) (4) pack are poured into 80 mL of (b) (4) for oral administration. Sponsor recommends tap water. (See Table 1 of Discussion for Dosage Composition)

4. The controlled-release pellets contain excipients intended to delay the release of sodium oxybate in the presence of (b) (4) tap water. In vitro extraction studies (ETD 218-005) demonstrated that the controlled-release properties are maintained using water of pH 5.6 to 5.8, as well as by such acidic solutions as Coca-Cola and Crystal Light. The release properties were compromised with water having a pH of 6.6. It should be noted that the water tested was that found in Europe or North Africa. According to the proposed label, FT218 should be reconstituted in water. In the United States, the federal Environmental Protection Agency (EPA) recommends that "public water systems" which would include tap water be in a range of pH 6.5 to 8.5.[1] As such most tap water, if used as a reconstitution liquid, might possibly compromise the controlled-release properties of sodium oxybate particularly if not quickly consumed.

5. Alkaline liquids are expected to compromise the controlled release of sodium oxybate. Milk products, including almond milk, as well as most herbal and green teas, and selected fruit and vegetable juices are basic liquids.

6. Hot solutions as well as alcohol containing solutions (20% and 40% ethanol) also result in a more rapid release of sodium oxybate, indicating compromise of the controlled-release properties of the CR pellets.

7. The clinical development program consists of 10 phase 1 studies, one completed phase 3 efficacy study (CLFT218-1501), and 1 ongoing phase 3 efficacy study (Protocol CLFT218-1901). (See **Table 2** of the Discussion) Nine of the ten phase 1 studies utilized the to-be-marketed formulation for FT218. All studies excluded subjects with a history of drug or alcohol abuse.

8. In six of the nine phase 1 studies using the to-be-marketed formulation for FT218, the incidence of adverse events indicative of abuse potential was low. (See **Table** 4 of the Discussion) Such adverse events included "feeling drunk", "euphoric mood", "feeling high", "feeling of relaxation", "mood altered", and "feeling abnormal." In all phase 1 studies, dosing was

[1]https://www.watersystemscouncil.org/download/wellcare_information_sheets/potential_groundwater_contaminant_information_sheets/9709284pH_Update_September_2007.pdf

administered in the clinical setting under investigator supervision, thereby significantly reducing the risk of abuse, misuse, diversion, or compliance issues.

9. Phase 3 efficacy study CLFT218-1501 utilized a parallel design comparing FT218 to placebo and using FT218 doses of 4.5 g, 6 g, 7.5 g, and 9 g of sodium oxybate. Adverse events indicative of possible abuse potential were not reported in this study. Six instances of "medication errors," in which subjects did not take the current doses, were documented, but none involved suspected abuse or diversion. Death, overdose, abuse, and misuse were otherwise not found in the study.

10. Distribution of FT218 will be regulated under a LUMRYZ REMS Program that will require patient and prescriber enrollment, as well as use of certified specialty pharmacies for dispensing. Details are still being worked out between the Agency and Sponsor (REMS Correspondence, April 13, 2021, NDA 214755, SN0016; DARRTS - REMs Review – Interim Report, NDA 214755, July 20, 2021).

3. Recommendations

Based on our findings, as captured in the Conclusions section, we recommend the following:

1. Upon receiving marketing approval, FT218 will meet criteria to be in Schedule III of the federal Controlled Substances Act [21 CFR § 1308.13 (c) (6)].[2]

2. Sodium oxybate is a well-known drug of abuse. As such, CSS believes that a comprehensive LUMRYZ REMS Program should be put in place for the distribution of FT218.

II. DISCUSSION

1. Chemistry

1.1 Substance Information

FT218 is formulated for dosage strengths of 4.5 g, 6 g, 7.5 g, and 9 g sodium oxybate for single nighttime administration. FT218 contains both immediate-release (IR) pellets as well as controlled-release (CR) coated pellets, (b) (4). The CR coated pellets are designed to provide a delayed release after oral administration. (b) (4)

[2] 21 CFR § 1308.13 (c) (6) Any drug product containing gamma hydroxybutyric acid, including its salts, isomers, and salts of isomers, for which an application is approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

(b) (4) The drug product also contains (b) (4) Malic acid (b) (4) The detailed unit composition of the to-be-marketed FT218 product is provided in **Table 1** below.

Table 1. Unit Composition of To-Be-Marketed Sodium Oxybate ER Oral Suspension (FT218) – 4.5 g, 6 g, 7.5 g, and 9 g. (Source: Table 1 of Module 2.3.P Drug Product)

Component	Function	Quantity (g) per 4.5 g Dose Unit	Quantity (g) per 6 g Dose Unit	Quantity (g) per 7.5 g Dose Unit	Quantity (g) per 9 g Dose Unit
(b) (4)					
Sodium Oxybate					
Microcrystalline Cellulose (b) (4)					
Povidone (b) (4)					
Hydrogenated Vegetable Oil (b) (4)					
Methacrylic Acid Copolymer (b) (4)					
(b) (4)					
Malic Acid					
Carrageenan (b) (4)					
Hydroxyethyl Cellulose (b) (4)					
Xanthan Gum (b) (4)					
Magnesium Stearate					
Total Weight		7.115	9.489	11.858	14.230

(b) (4). Dissolution studies in 0.1N HCl media demonstrated the biphasic release of sodium oxybate from the FT218, thereby demonstrating the maintenance of the controlled-release properties of the formation. However, when FT218 granules were

placed in a pH 6.8 solution, then the biphasic release was lost, resulting in immediate release of all the sodium oxybate within an approximately 15 to 30 minutes. (b) (4)

The closure system for the FT218 registration batches and commercial product is a (b) (4) pack. For (b) (4)-packs, consists of foil folded and sealed vertically at the back, as well as sealed at the top and bottom. (b) (4) packs are filled with FT218 at dosage strengths of 4.5 g, 6 g, 7.5 g, or 9 g of sodium oxybate. Prior to ingestion, the content of a (b) (4) pack is poured into approximately 1/3 (approximately 80 mL) of water in the dosing cup provided with each prescription. Patients ingest the resulting solution at bedtime preferably within a 30-minute time window following reconstitution. At the time of reconstitution, tap water can be room temperature or warm, but not hot, as hot water causes rapid release of sodium oxybate from the controlled-release pellets (see below).

The recommended starting dose is 4.5 g per night orally. Based upon efficacy and safety, the dose can be titrated up by 1.5 g per night at weekly intervals. Maximum recommended nightly dose is 9 g.

In Vitro Dissolution Studies

In vitro dissolution studies were conducted to examine the effect of selected liquids and temperature on the controlled release of sodium oxybate from CR granules.

- Examining Selected Solvents for Reconstitution of FT218 – Impact on Controlled-Release Properties

Noting that patients might utilize other solvents besides tap water for reconstitution of FT218, Sponsor conducted study ETD 218-005 entitled "Sodium Oxybate CR Granules for Oral Suspension: Study of the Impact of Beverages Used for Reconstitution on the Dissolution Profile." In this study, the dissolution prolife of sodium oxybate CR granules were determined when the granules were placed in selected media. Both 3 grams and 9 grams dosage units were examined using 50 mL of drinking liquid for reconstitution. Time points examined were at 5-minute intervals out to 20 hours. The following solvents were examined:

- Tap Water as Control
- "Glacier Isle" Mineral Water
- "St-Yorre Water" containing bicarbonate ions
- "Badoit Water" containing bicarbonate ions.
- Coca-Cola
- Crystal Light (2 grams per 50 ml of water)

Coca-Cola was selected as a typical soft drink. Crystal Light was selected based on internet discussion forums indicating its use to mask Xyrem's taste. The water liquids utilized came from Europe and not the United States.

At 5 minutes following the mixing of FT218 in tap water, the pH was 5.8 and the subsequent dissolution profile was the typical biphasic release consistent with a sustained controlled-release component. At 5 minutes following reconstitution of FT218 in "Glacier Isle Mineral Water and "Badoit Water," pH of solutions was 5.7 and 5.9, respectively with a subsequent dissolution profile similar that of tap water. With use of "St-Yorre" water, the resulting pH was higher at 6.6 with the subsequent dissolution profile indicating some limited compromise of the controlled-release of sodium oxybate. The dissolution profiles following reconstitution using Coca-Cola, an acidic liquid, and of Crystal Light, did not vary from that produced by tap water. Increasing the dissolution time from 5 minutes to 30 minutes prior to dissolution testing, caused small leftward shifts in the dissolution curves for the controlled-release component when tap water and "Glacier Isle Mineral Water" were used for reconstitution. A greater leftward shift, indicative of a compromise of the controlled-release of sodium oxybate was observed using "Badoit Water" and "St-Yorre" water with reconstitution over 30 minutes. These latter two liquids, following reconstitution, as noted above, had higher pH values of 5.9 and 6.6, respectively.

Consideration should be given to the fact that the "water" samples examined appear to have been, based on the methodology, obtained from European sources. As such the "tap water" was not from the United States. In the United States, the federal Environmental Protection Agency (EPA) recommends that "public water systems" which would include tap water be in a range of pH 6.5 to 8.5. As such most tap water, if used as a reconstitution liquid, might possibly compromise the controlled-release properties of sodium oxybate particularly if not quickly consumed.

- Examining Effect of Water Temperature During Reconstitution on Controlled-Release Properties of FT218

Under Study Report ETD 218-005, Sponsor also examined the effects of temperature of tap water used for reconstitution on the release of sodium oxybate. In this study, the dissolution profile out to 20 hours was determined using tap water at room temperature, compared to tap water held at either 50 °C or 90 °C. Using tap water held at 50 °C, the dissolution profile was only about 10% increased across time points. However, when using hot tap water (90 °C), the dissolution profile revealed rapid and complete release of sodium oxybate within the first approximately 10 to 15 minutes. According to the study report, this rapid release was due to (b) (4) the coating of the controlled-release pellets.

In summary, the results of study ETD 218-005 indicate that the controlled-release of sodium oxybate from FT218 can be compromised by using reconstitution liquids that are either in the high neutral or alkaline pH range or that are held at elevated temperature. Under such conditions, both the IR as well as the controlled-release components are released within the first 15 to 30 minutes. Tap water with a lower pH and held at room temperature is a suitable liquid for reconstitution of FT218. (b) (4)

– Examining Effects of Ethanol on Controlled-Release Properties of FT218

Study report RT 218-37, entitled "FT218- Alcohol Dose Dumping Study", examined the effects of increasing ethanol concentrations on the dissolution of sodium oxybate from reconstituted FT218. To determine these effects, the dissolution profiles were generated in 0.1 N HCl medium with 0, 5, 10, 20, and 40% of ethanol present.

In the presence of HCl 0.1N without ethanol, a normal biphasic dissolution profile over 18 yours of observation was observed. This profile reflected both the immediate-release as well as the delayed controlled-release of sodium oxybate. This same profile as observed in the presence of 5% ethanol. With increasing ethanol concentrations of 10%, 20%, and 40%, a progressive shift in the dissolution curve occurred reflecting an increasing compromise of the controlled-release properties for sodium oxybate. At the higher ethanol level of 40%, both the immediate- and controlled-release sodium oxybate were released within 1 hour.

In summary, with increasing concentrations of ethanol (10 % up to 40%), there is increasing dose dumping of sodium oxybate, due to compromise of the controlled-release properties of FT218.

4. Clinical Studies

No human abuse potential studies were submitted in support of NDA 214655, as they were not requested during the IND stage.

The clinical development program for FT281 consisted of ten Phase 1 studies and one completed Phase 3 efficacy study. A second Phase 3 efficacy study was still in progress upon filing the NDA. Studies constituting the clinical development program are found in **Table 2,** below. All clinical studies, except study PKFT218-1301, used the final to-be-marketed formulation (**Table 1** above) either manufactured at intermediate or commercial scale. For all clinical studies (Phase 1 and 3), subjects reporting a history of drug or alcohol abuse were excluded from participation in the study.

Table 2. Phase 1 and 3 Studies Conducted Under the Clinical Development Program for FT218.

Study Designation	Title
Phase 1 Studies	
PKFT218-1603	An Open-Label, Randomized, Single Dose, Two-Treatment (Fed vs Fasting), Two-Period, Two-Sequence Crossover Study to Assess the Effect of Food on Sodium Oxybate for Extended-Release Oral Suspension (FT218) Formulation Administered at 6 G in Healthy Volunteers
PKFT218-1301*	Single-Dose, Open-Label, Randomized Study in Healthy Volunteers to Assess the Pharmacokinetic Profile of 3 Sodium Oxybate Controlled Release Formulations Based on Micropump Technology and Marketed Reference Xyrem.
PKFT218-1602	A Comparative, Open-Label, Randomized, 2 Periods, 2 Sequences Crossover Study to Assess the Relative Bioavailability of Sodium Oxybate for Extended-Release Oral Suspension (FT218) Formulation (Single Dose Administered at the Dose of 5 G)

	Versus the Marketed Reference Xyrem (At the dose of 2.3 g) in Healthy Volunteers.
PKFT218-1701	A Comparative, Open-Label, Randomized, 2-Stage Sequential Design, 2 Periods, Crossover Study to Demonstrate the Bioequivalence of 2 FT218 Batches (Single Dose of 4.5 Grams) in Healthy Volunteers
PKFT218-1801	A Comparative, Open-Label, 2 Period, Randomized, 2-Sequence, Crossover Study to Determine the Relative Bioavailability of FT218 (Single Dose Administered at a Dose of 6 g) When Compared with the Reference Listed Product, U.S. Xyrem in Healthy Volunteers.
PKFT218-1802	An Exploratory, Open-Label, Randomized, 2 Treatments, 2 Periods, 2 Sequences Crossover Study to Assess the Pharmacokinetics of Two FT218 Batches (Single Dose Administered at the dose of 6 G) in Healthy Volunteers.
PKFT218-1902	An Open-Label, Randomized, 4 Treatments, 4 Periods, 4 Sequence Crossover Study to ASSESS the Pharmacokinetics of Four 6 G Single-Doses of Once-Nightly Sodium Oxybate (FT218) Formulations with Varying Release Rates in Healthy Volunteers.
PKFT218 – 1702	An Open-Label, Sequential Study to Assess the Drug-Drug Interaction of Bivalproex Sodium Extended-Release (ER at Steady State on FT218 Formulation Administer at a Single 6-G Dose in Healthy Volunteers
PKFT218-1901	An Open-Label, Sequential Study to Assess the Drug-Drug Interaction of Divalproex Sodium Extended Release (ER) At Steady-State on FT218 Formulation Administered at a Single 6G Evening Dose in Healthy Male Volunteers.
PKFT218-1601	An Open-Label, 3-Period, Study to Assess the Pharmacokinetics and Safety for Sodium Oxybate for Extended-Release Oral Suspension (FT218) Formulation after Single Dose Administration at Doses of 4.5, 7.5, and 9g in Healthy Volunteers
Phase 3 Efficacy Studies	
CLFT218-1501	A Double-Blind, Randomized, Placebo Controlled, Two Arm Multi-Center Study to Assess the Efficacy and Safety of a Once Nightly Formulation of Sodium Oxybate for Extended-Release Oral Suspension (FT218) for the Treatment of Excessive Daytime Sleepiness and Cataplexy in Subjects with Narcolepsy.
CLFT218-1901 Protocol v2.0 31 Jul 2020 (ONGOING STUDY)	An Open Label Study to Evaluate Long-Term Safety and Tolerability of a Once Nightly Formulation of Sodium Oxybate for Extended-Release Oral Suspension (FT218) and the Ability to Switch from Twice-Nightly Immediate Release Sodium Oxybate to Once-Nightly FT218 for the Treatment of Excessive Daytime Sleepiness and Cataplexy in Subjects with Narcolepsy

*Study did not use the to-be-marketed product formulation.

4.2 Adverse Event Profile Through all Phases of Development

As requested by the Agency under IND 126,321, the Sponsor looked for and documented adverse events potentially associated with abuse potential throughout the clinical development program. Possible adverse events looked for included: euphoric mood; elevated mood; feeling high; feeling abnormal; feeling drunk; feeling of relaxation; thinking abnormal; hallucination; inappropriate affect; mood disorders and disturbances; psychosis; aggression; confusion; disorientation; drug tolerance; habituation; drug withdrawal; substance-use disorder. For all studies, subjects reporting any history of drug or alcohol abuse were excluded from participation. For purposes of this review, the adverse events potentially indicative of abuse potential were documented for nine Phase 1 studies and the single completed Phase 3 efficacy study. Phase 1 study PKFT218-1301 was not evaluated for adverse events, as it did not involve the to-be-marketed formulation. For all studies, adverse events were documented

for the safety population ("safety set"), defined as all subjects who received at least one dose of stud medication in treatment phase.

Phase 1 Clinical Studies Where No Adverse Effects Indicative of Abuse Potential Were Found.

In phase 1 clinical studies PKFT218–1701, PKFT218-1801, and PKFT218-1902, no adverse events indicative of possible abuse potential were documented for any treatments given. As seen in **Table 3** below, these studies collectively resulted in 24 and 64 subjects receiving single oral doses of 4.5 g of FT218 and 6 g of FT218, respectively. In one study (PKFT218-1801), 28 of the subjects also received 6 g Xyrem (2 x 3 g, 4 hours apart).

Table 3. Three Phase 1 Studies Involving To-Be-Marketed FT218 in Which Adverse Events Indicative of Abuse Potential Were Not Observed.

Study Designation	Study Type	Study Design	Safety Set	Oral Treatments
PKFT218-1701	Bioequivalence	Open Label, 2-Period, Randomized, Crossover	24	• 4.5 g FT218 batch MP2 • 4.5 g FT218 batch MP4
PKFT218-1801	Relative Bioavailability	Open Label, 2-Period, 2-Sequence, Crossover	28	• 6.0 g FT218, single oral • 3 g Xyrem 2 x Oral, 4 hrs apart
PKFT218-1902	Bioequivalence	Open Label, 4-Period, 4-Sequence, Crossover	36	• (b)(4)% IR/(b)(4)% CR Particles with lagphase of 4 hours – 6 g • (b)(4)% IR/(b)(4)% CR Particles with lagphase of 2 hours – 6 g • (b)(4)% IR (b)(4)% CR Particles with lagphase of 2 hours – 6 g • (b)(4)% IR/(b)(4)% CR Particles with lagphase of 6 hours – 6 g

Phase 1 Clinical Studies Where Adverse Effects Indicative of Abuse Potential Were Documented.

In phase 1 clinical studies PKFT218-1601, PKFT218-1602, PKFT218–1603, PKFT218-1802, PKFT218-1702, and PKFT218-1901, adverse events indicative of possible abuse potential were documented (see **Table 4** below). Overall, the number of abuse potential related adverse events were limited. These adverse events were not unexpected considering that sodium oxybate is a scheduled drug with abuse potential.

Table 4. Adverse Events Documented in Phase 1 Studies Conducted as Part of the Clinical Development Program for FT218.

Study Designation (Type)	Crossover Design	Oral Treatment	Safety Set No. of Subjects	Adverse Events Indicative of Possible Abuse Potential (No. of Subjects)
PKFT218-1601	Open Label, Single Dose, 3-Period	-4.5 g FT218 -7.5 g FT218 -9.0 g FT218	20 – 4.5 g 20 – 7.5 g 12 – 9.0 g	• "Feeling Drunk" – 1 subject – 7.5 g FT218

PKFT218-1602 (Relative Bioavailability)	Open Label, Randomized, 2-Peroids, 2 Sequences	-6 g FT218 (single dose) -3 g Xyrem (2 x, 4 hrs apart)	27	• "Feeling Drunk" – (3) – 6 g FT218 • "Feeling Drunk" – (2) – 6 g Xyrem • "Euphoric Mood" – (1) – 6 g FT218 • "Euphoric Mood" – (1) – 6 g Xyrem • "Feeling High" – (1) – 6 g FT218
PKFT218-1603 (Food Effect)	Open Label, Randomized, 2-Period, 2-Sequence	-6 g FT218 Fasted -6 g FT218 Fed	16 – Fasted 15 - Fed	• "Euphoric Mood – (1) – FT218 Fasted • "Feeling Drunk" – (4) – FT218 Fasted • "Feeling Drunk" – (4) – FT218 Fed • "Mood Altered" – (1) – FT218 Fed
PKFT218-1702 (Drug-Drug Interaction)	Open Label, Sequential	-6 g FT218 (Day 1) -1250 mg Divalproex Sodium ER (Days 2 to 11) -6 g FT218 + 1250 mg Divalproex Sodium ER (Day 12)	24	• "Feeling Drunk" – (1) – FT218 Alone • "Feeling Drunk" – (1) – Divalprex Alone • "Feeling Abnormal" – (1) – FT218 Alone
PKFT218-1802	Exploratory, Open-Label, Randomized, 2-Perioids, 2-Sequences	-6 g FT218 MP4 Batch A (single dose) -6 g FT218 MP4 Batch B (single dose)	20	• "Feeling Drunk" – (1) – MP4 Batch A
PKFT218-1901 (Drug-Drug Interaction)	Open Label, Sequential	-6 g FT218 (Day 1) -1250 mg Divalproex Sodium ER (Days 2 to 11) -6 g FT218 + 1250 mg Divalproex Sodium ER (Day 12)	24	• "Feeling of Relaxation" – (2) – FT218 Alone • "Feeling of Relaxation" – (1) – FT218 + Divalproex Sodium • "Feeling Drunk" – (1) – FT218 + Divalproex Sodium

Phase 3 Clinical Studies – Adverse Effects Indicative of Abuse Potential

Efficacy Study CLFT218-1501

Completed study CLFT218-151 was a Phase 3, randomized, double-blind, placebo-controlled, 2-arm, multicenter (Canada, U.S., United Kingdom, Australia) study. The purpose of the study was to assess the efficacy and safety of a once-nightly formulation of sodium oxybate (FT218) for the treatment excessive daytime sleepiness (EDS) and cataplexy in subjects with narcolepsy. Subjects with a history of drug or alcohol use that, in the opinion of the investigator, would have interfered with study subject safety and adherence to study requirements were excluded from the study. An initial three-week washout period allowed for screening and baseline measures. Narcoleptic subjects were then divided into two populations (NT1 and NT2) for study in a single parallel-group design with one group receiving placebo and the other FT218. The duration of the study (screening to follow-up) was approximately 17 weeks. A 13-week treatment period was followed by a 1-week follow-up period. The maximum

treatment duration was 13 weeks (8-week up-titration period followed by five weeks on stable dosing at 9 g/night or placebo).

Therapeutic doses were tested starting at 4.5 g followed by forced up-titration (6, 7.5, and 9 g) with 1.5 g/night increments followed by a final stabilization period for 5 weeks at the 9 g dose. With increasing dosage some subjects dropped out of the study. Subjects remained on the 4.5 g dose for 1 week, the 6 g dose for 2 weeks, the 7.5 g dose for 5 weeks, and the 9 g dose for 5 weeks, with safety and efficacy evaluations conducted over a 12-week period (total of 13 weeks on study drug).

A total of 413 patients were enrolled, with 222 randomized and 212 receiving study drug (107 subjects receiving FT218 and 105 subjects receiving placebo = overall safety population). Within the group receiving FT218, 107, 97, 88, and 77 subjects received 4.5 g, 6 g, 7.5 g, and 9 grams of FT218, respectively. Within the placebo group, 105, 97, 88, and 80 received placebo treatments matching the 4.5 g, 6 g, 7.5 g and 9 g FT218).

An examination of the AEs recorded via organ classification did not reveal any instances of abuse-related AEs such as euphoric mood, elevated mood, feeling high, feeling abnormal, feeling drunk, feeling of relaxation, or mood disorders.

Efficacy Study CLFT218-1901

Efficacy study CLFT218-1901 is ongoing. The purpose of the study is to examine the ability to switch from twice-nightly immediate-release sodium oxybate to once nightly FT218 for the treatment of excessive daytime sleepiness and cataplexy in subjects with narcolepsy. The study enrolled the first subject on July 7, 2020, with up to 250 subjects expected to be enrolled. In agreement with the Agency, safety data from subjects enrolled in this study were not presented in the original NDA submission. Rather, to-date safety information would be provided to reviewers in the 120-day safety update. This update was submitted to NDA 214755 (SN 0013) on April 13, 2021. An examination of the adverse events documented so far in the study did not reveal any associated with possible abuse potential.

4.3 Safety Profile

The active pharmaceutical ingredient in FT218 is the same as that found in Xyrem, namely sodium oxybate. FT218 is under development using the 505(b)(2) pathway with Xyrem as the reference drug. As such, FT218 relies upon the findings of safety for Xyrem. Additionally, safety data were obtained from the clinical development program (10 phase 1 studies and 2 phase 3 efficacy studies). In addition, there is a significant scientific and medical literature published regarding sodium oxybate. Collectively, these data indicate that sodium oxybate is associated with an abuse potential. As with Xyrem, FT218 is expected to have an abuse potential. This is supported by the adverse events indicative of abuse potential documented in Phase 1 studies.

Throughout the clinical development program for FT218, there were no deaths, overdoses, or reported unintended pediatric exposures. In efficacy study CLFT218-1501, there was one subject who

experienced “suicidal ideation” while taking 9 g per day of FT218. This adverse effect was deemed related to study drug and resulted in the discontinuation of the subject from the study.

4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials

Ten Phase 1 studies and one completed Phase 3 efficacy study comprise the clinical development program for FT218.

All Phase 1 studies were conducted within the clinical setting with dosage administration monitored by research staff. As such, there was no evidence of abuse or diversion, including drug accountability issues during these studies.

In phase 3 efficacy study CLFT218-1501, there were no reports of abuse, misuse, or diversion. There were six instances of “medication errors”; however, none of these suggested abuse or diversion. No drug accountability issues were reported.

5. Regulatory Issues and Assessment

At such a time as FT218 receives marketing approval, it will be placed in Schedule III of the CSA just as Xyrem and XYWAV are scheduled. Sponsor has accepted Schedule III control.

In the Sponsor-proposed label, FT218 is noted to be in Schedule III. A black box warning is provided regarding central nervous system depression and the potential for abuse and misuse as well mention of the LUMRYZ REMS Program using certified pharmacies for distribution of FT218. Potential for abuse and misuse are addressed in Sections 5 and 9 of the label.

Distribution of FT218 will be regulated under a LUMRYZ REMS Program, which will require patient and prescriber enrollment as well as use of certified specialty pharmacies for dispensing. Details are being worked out between Division and Sponsor (REMS Correspondence, April 13, 2021, NDA 214755, SN0016)

6. Other Relevant Information

FT218 is a new drug product that has not been approved in other countries. It has not been reported in the scientific and medical literature. Sodium oxybate, the active component of FT218, is a known drug of abuse with numerous references in the scientific and medical literature to that effect.

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/s/

JAMES M TOLLIVER
08/25/2021 04:18:28 PM

SILVIA N CALDERON
08/25/2021 04:19:51 PM

DOMINIC CHIAPPERINO
08/25/2021 04:44:54 PM

M E M O R A N D U M

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

DATE: 5/3/2021

TO: Division of Neurology I (DN I)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 214755

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the site in June 2019, which falls within the surveillance interval. The inspection was conducted under the following submissions: Non-responsive Non-responsive.

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observation:

- For Non-responsive, the site did not possess the blinding codes from the end of study (b) (4) (b) (4) through the inspection. Therefore, the accuracy of the dosing with the blinded products could not be verified and OSIS recommended that the data not be accepted for Agency review.

After review of the inspectional findings, OSIS recommended that data from Non-responsive and Non-repsonsive be accepted for Agency review and that data from Non-responsive be rejected. (OSIS Final EIR Review – June 2019).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Celerion	2420 West Baseline Road, Tempe, AZ

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/s/

JAMES J LUMALCURI
05/03/2021 04:27:23 PM