CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	214755
Supporting document:	1
Applicant's letter date:	December 15, 2020
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Product:	Lumryz (sodium oxybate oral suspension)
Indication:	Cataplexy or excessive daytime sleepiness (EDS) in patients with narcolepsy
Applicant:	Avadel CNS Pharmaceuticals LLC
Review Division:	Division of Neurology I (DN I)
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1 Executive Summary

1.1 Introduction

Lumryz is an oral suspension of sodium oxybate, developed under the 505(b)(2) pathway by Avadel CNS Pharmaceuticals LLC for the treatment of cataplexy and EDS in patients with narcolepsy. The approved sodium oxybate product (Xyrem) is the Listed Drug. This review focuses on the safety assessment of the excipients present in Lumryz. At the proposed maximum daily dose (MDD) of 9 g, the maximal daily intakes (MDI) of four of the excipients [redacted] mg for povidone [redacted] hydrogenated [redacted] oil, [redacted] and carrageenan, respectively) exceed the inactive ingredient database (IID) limits in the FDA approved drug products with same route of administration.

1.2 Brief Discussion of Nonclinical Findings

See Integrated Summary.

1.3 Recommendations

1.3.1 Approvability

The nonclinical data support approval of Lumryz.

1.3.2 Additional Nonclinical Recommendations

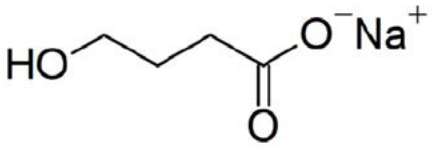
As a post-marketing requirement and based on the results of the data provided, the potential systemic absorption and toxicity of [redacted] should be further evaluated in a relevant species (rat) for a sufficient duration (6 months), at a dose that will support the amount of [redacted] in Lumryz at the proposed MDD of 9 g per day.

2 Drug Information

2.1 Drug

CAS Registry Number:	502-85-2 (Sodium oxybate)
Generic Name:	Lumryz
Code Name:	FT218
Chemical Name:	4-hydroxybutyric acid, sodium salt; 4-Hydroxybutanoic acid monosodium salt; Sodium gamma hydroxybutyrate
Molecular Formula/Molecular Weight:	$C_4H_7NaO_3$, 126.1 g/mol (Sodium oxybate)

Structure or Biochemical Description:



(Sodium oxybate; Sponsor's figure)

Pharmacologic Class (Sodium oxybate): Central nervous system depressant

2.2 Relevant INDs, NDAs, BLAs and DMFs:

NDA 021196 Xyrem (Sodium Oxybate)
LoA to DMF (b) (4) (Sodium Oxybate)
LoA to DMF (b) (4) (Type III (b) (4) Packaging (b) (4)

2.3 Drug Formulation

9 g sodium oxybate suspension with the following excipients:

Component	Maximum Daily Dose (per 9 g Sodium Oxybate)	Basis for Safety Qualification
Microcrystalline cellulose (b) (4)	(b) (4)	IID[1]: 3195 mg (oral capsule)
Povidone (b) (4)		IID: 640 mg; (oral tablet Povidone (b) (4) with additional scientific justification (see below)
Hydrogenated Vegetable (b) (4) Oil (b) (4)		GRAS; used at higher levels in the diet (see below)
Methacrylic acid - (b) (4) copolymer (b) (4) (b) (4)		IID: 400 mg (oral extended -release tablet)
(b) (4)		Publicly available information
Malic acid		IID: 315 mg (oral powder for solution)
Xanthan gum		IID: 360 mg (oral powder for suspension) or 8050 mg/230 mL (oral paste; 1050 mg/30 mL)
Hydroxyethyl cellulose (b) (4)		IID: 150 mg (oral tablet; extended release)
Carrageenan (b) (4)		GRAS (21 CFR 182.7255; used at higher levels in the diet (see below)
Magnesium stearate		IID: 400.75 mg (oral tablet)

[1] Inactive Ingredient Database accessed August 6, 2020
[2] Equivalent to Hydroxyethyl cellulose (b) (4)

(Sponsor's Table)

2.4 Comments on Novel Excipients

Povidone (b) (4) hydrogenated (b) (4) oil, (b) (4) and carrageenan exceed the inactive ingredient database (IID) limits in the FDA approved drug products with same route of administration.

2.4.1 Povidone (b) (4)

Povidone is a linear polymer consisting of 1-vinyl-2-pyrrolidone monomers. The proposed maximal daily intake (MDI) of (b) (4) mg for povidone (b) (4) in FT218 is below the IID limit (b) (4) in the FDA approved oral drugs. The molecular weight (MW) of povidone (b) (4) kDa) is higher than that of povidone (b) (4) kDa). There is an inverse log/log linear relationship between absorption and molecular weight of povidone; therefore, less systemic absorption could be expected with povidone (b) (4) The sponsor used the higher IID limit for povidone (b) (4) to justify the amount of povidone (b) (4) in FT218.

Form	Average Molecular Weight
(b) (4)	

(Sponsor's Table)

2.4.2 Hydrogenated (b) (4) oil

Per 21 CFR 170.30 (c), hydrogenated (b) (4) oil is Generally Recognized as Safe (GRAS) for use in food. The proposed maximal daily intake (MDI) of (b) (4) mg for hydrogenated (b) (4) oil is (b) (4) fold lower than the dietary intake of median saturated fatty acids (15-34 g/day) based on the CSFII 1994-98 data for food consumption. According to the USP-NF, the composition of hydrogenated (b) (4) oil is (b) (4) The proposed MDI levels of each fatty acid present in hydrogenated (b) (4) oil are substantially lower than the typical U.S. dietary intake of these fatty acids based on the 1999-2000 National Health and Nutrition Examination Survey (NHANES). The sponsor used the higher daily consumption for each fatty acid present in hydrogenated (b) (4) oil to justify the amount of hydrogenated (b) (4) oil in FT218.

Fatty Acid	USP-NF (% Composition)	Daily Fatty Acid Intake from (b) (4) g/Day (b) (4) Hydrogenated Oil	Total Daily Dietary Fatty Acid Intake (b) (4)
(b) (4)			

(Sponsor's Table)

2.4.3 (b) (4)

is an anionic copolymer of methacrylic acid (b) (4) The following toxicology studies were based on the (b) (4) study reports provided by the sponsor to support the safety of (b) (4) in FT218.

General Toxicology
The GLP-compliant oral toxicity studies were conducted in mouse (6-week), rat (6-month), and rabbit (6-week).

IBR No. 2-1-772-87: Male mice (12/group) were administered doses of 0, 100, 600 or 1500 mg/kg/day (b) (4) by daily oral gavage for 6 weeks. Clinical signs (rough coat, alopecia) and reduced body weights were observed at the HD. Dose-related activation of the thyroidal epithelium (thyroid structural changes in the thyroidal center including epithelial height, nuclei of epithelial cells, and interfollicular solidification) was observed at MD and HD. The NOAEL was the LD of 100 mg/kg/day.

IBR No. 3-4-242-84: Male and female rats (25/sex/group main, 10/sex/group recovery) were administered doses of 0, 200, 600, or 1500 mg/kg/day (b) (4) by daily oral gavage for 6 months. Dose-related activation of the thyroidal epithelium (thyroid structural changes in the thyroidal periphery and center including follicle diameter, epithelial height, nucleus size, and nuclear stainability) was observed at all doses. Fatty degeneration of peripheral cells of liver was observed at the HD. At the end of recovery, only thyroid activation was observed. A NOAEL was not able to be determined based on thyroid toxicity at all doses.

IBR No. 3-4-120-89: Male and female rats (15/sex/group) were administered doses of 0, 10, 30, or 100 mg/kg/day [redacted] by daily oral gavage for 6 months. No test article-related findings were observed. The NOAEL was the HD of 100 mg/kg/day.

IBR No. 2-3-773-87: Male and female rabbit (6/sex/group) were administered doses of 0, 100, 600 or 1500 mg/kg/day [redacted] by daily oral gavage for 6 weeks. Dose-related activation of the thyroidal epithelium (thyroid structural changes in the thyroidal center including epithelial height, nuclei of epithelial cells, and size of follicles) was observed at MD and HD. The NOAEL in this study was the LD of 100 mg/kg/day.

Reproductive and Developmental Toxicology

Pregnant rats (20/group) were administered doses of 0, 10, or 500 mg/kg/day [redacted] by daily oral gavage from GDs 6 to 16. Cesarean section and necropsy were conducted on GD 20. No test article-related findings in maternal animals or on fetal survival or development were observed.

Genetic Toxicology

[redacted] was negative in the Ames assay, in vitro mouse lymphoma cell forward mutation assay, and in vivo mouse bone marrow micronucleus assay.

Risk Assessment

Based on a mg/m^2 comparison at the NOAEL (100 mg/kg/day) in mouse, rat, and rabbit, the sponsor will not have a 10-fold safety margin for the proposed MDI of [redacted] mg for [redacted] in FT218 as a result of dose-related activation of the thyroidal epithelium.

Maximum Daily Intake (MDI)	Margin (based on mg/m^2)		
mg	Mouse NOAEL (100 mg/kg/day)	Rat NOAEL (100 mg/kg/day)	Rabbit NOAEL (100 mg/kg/day)
[redacted]			

2.4.4 Carrageenan

Per 21 CFR 182.7255, carrageenan is Generally Recognized as Safe (GRAS) for use in food. The proposed maximal daily intake (MDI) of [redacted] mg for carrageenan is [redacted] fold lower than the dietary intake of carrageenan [redacted] g/day) based on a dietary survey conducted in South Florida (Shah and Huffman, 2003, Ecology of Food and Nutrition).

Carrageenan is a sulfated polygalactan with an average molecular weight (MW) of approximately 100-150 kDa. The following toxicology studies were based on the review paper (Weiner, 2014, Critical Reviews in Toxicology) provided by the sponsor to support the safety of carrageenan in FT218.

Monkeys (19 males and 21 females) receiving 0, 50, 200, or 500 mg/kg/day of carrageenan orally for 7.5 years showed no evidence of accumulation in the liver, lymph nodes, small intestine, colon, or cecum. Diarrhea and fecal occult blood were observed in a dose-related manner throughout the study. In a GLP-compliant toxicity study, male and female rats (20/sex/group) were administered doses of 0, 2.5, or 5% of

carrageenan in the diet for 90 days. No test article-related findings were observed. The NOAEL in rat was 5% in the diet (3630.5 mg/kg/day). In a three-generation reproduction study, male and female rats (40 males and 40 females) were administered doses of 0, 0.5, 1, 2.5, or 5% of carrageenan in the diet. Dose-related decrease in the weights of offspring at weaning and diarrhea at 2.5% and 5% were observed. Carrageenan was negative in the Ames assay, in vitro chromosomal aberration assay in rat bone marrow cells, and in vivo mouse bone marrow micronucleus assay.

Risk Assessment
Based on a mg/m^2 comparison at the NOAEL in rat, the sponsor will have a (b) (4)-fold safety margin for the proposed MDI of (b) (4) mg for carrageenan in FT218.

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Lumryz is intended to be used for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients with narcolepsy. Dosing is to be 6 g to 9 g per night taken orally.

11 Integrated Summary and Safety Evaluation

Lumryz is an oral suspension of sodium oxybate, developed under the 505(b)(2) pathway by Avadel CNS Pharmaceuticals LLC for the treatment of cataplexy and EDS in patients with narcolepsy. The approved sodium oxybate product (Xyrem) is the Listed Drug.

This nonclinical review focused on the safety assessment of four excipients (povidone (b) (4) hydrogenated (b) (4) oil, (b) (4) and carrageenan) that exceed the inactive ingredient database (IID) limits in the FDA approved drug products with same route of administration. The proposed maximum daily dose (MDD) for Lumryz is 9 g, which would result in maximal daily intakes (MDI) of (b) (4) mg for povidone (b) (4) hydrogenated (b) (4) oil, (b) (4) and carrageenan, respectively.

Povidone (b) (4)
The proposed maximal daily intake (MDI) of povidone (b) (4) in FT218 is below the inactive ingredient database (IID) limit of povidone (b) (4) in the FDA approved oral drugs. Based on different molecular weights (MWs) of povidone (b) (4) ((b) (4) kDa) and (b) (4) (b) (4) kDa), less systemic absorption could be expected with povidone (b) (4) The proposed levels of povidone (b) (4) in FT218 are not toxicologic concern.

Hydrogenated (b) (4) oil
Hydrogenated (b) (4) oil is Generally Recognized as Safe (GRAS) for use in food. The proposed maximal daily intake (MDI) of hydrogenated (b) (4) oil is lower than the dietary intake of median saturated fatty acids based on the CSFII 1994-98 data for food consumption. The proposed MDI levels of each fatty acid present in hydrogenated

(b) (4) oil are substantially lower than the typical U.S. dietary intake of these fatty acids based on the 1999-2000 National Health and Nutrition Examination Survey (NHANES). The proposed levels of hydrogenated (b) (4) oil in FT218 are not toxicologic concern.

(b) (4)

The GLP oral toxicity studies were conducted in mouse (6-week), rat (6-month), and rabbit (6-week). In all species, the primary finding was dose-related activation of the thyroidal epithelium as evidenced by thyroid structural changes. These studies (conducted prior to 1990) suggest the potential for systemic toxicity. This is unexpected because of the high molecular weight of the excipient (b) (4) da). An additional finding in the 6-month rat study (0, 200, 600, or 1500 mg/kg/day) included fatty degeneration of peripheral cells of liver at HD. There were no test article-related effects on offspring in an embryofetal development study in rats administered up to 500 mg/kg/day test (b) (4) by oral gavage from GDs 6 to 16. (b) (4) was negative in the Ames assay, in vitro mouse lymphoma cell forward mutation assay, and in vivo mouse bone marrow micronucleus assay.

Based on a mg/m^2 comparison at the NOAEL (100 mg/kg/day) in mouse, rat, and rabbit, the sponsor will not have a (b) (4) fold safety margin for the proposed maximal daily intake (MDI) of (b) (4) mg for (b) (4) in FT218. Given the findings in the thyroid in multiple animal species (which suggests the potential for systemic toxicity), an additional nonclinical study is needed to study oral absorption of radiolabeled (b) (4) in rat. If oral absorption of (b) (4) is demonstrated in rat, then a 6-month oral toxicology study of (b) (4) in rat will be needed in order to identify an unexpected serious risk of adverse effects of FT218. Although the above additional data are needed to ensure the safety of this excipient, at this time, no potential toxicities associated with (b) (4) at the doses of sodium oxybate proposed, have been identified that would preclude approval.

Carrageenan

Carrageenan is Generally Recognized as Safe (GRAS) for use in food. The proposed maximal daily intake (MDI) of carrageenan is lower than the dietary intake of carrageenan based on a dietary survey conducted in South Florida. The nonclinical information provided in the published review paper (Weiner, 2014, Critical Reviews in Toxicology) included general toxicity studies in monkey and rat, reproduction study in rat, and genotoxicity studies. Monkeys receiving up to 500 mg/kg/day carrageenan orally for 7.5 years showed no tissue storage of carrageenan. The only effects observed were diarrhea and fecal occult blood, which were commonly seen with high levels of dietary fibers. In the 90-day GLP dietary rat study, no adverse test article-related effects were observed following administration of up to 5% (3630.5 mg/kg/day) of carrageenan in the diet. In the three-generation reproduction study in rat (0, 0.5, 1, 2.5, or 5%), the only effects observed were dose-related decrease in the weights of offspring at weaning and diarrhea at 2.5% and 5%. Carrageenan was negative in the Ames assay, in vitro chromosome aberration assay in rat bone marrow cells, and in vivo mouse bone marrow micronucleus assay.

Based on a mg/m^2 comparison at the NOAEL (3630.5 mg/kg/day) in rat, the sponsor will have a [(b) (4)]-fold safety margin for the proposed MDI of [(b) (4)] mg for carrageenan in FT218. The proposed levels of carrageenan in FT218 are not toxicologic concern.

12 Recommendations

Lumryz is approvable from a nonclinical perspective; however, previous studies of [(b) (4)] in multiple species suggest the potential for systemic toxicity that warrants further assessment as a post-marketing required study. The sponsor will be required to conduct an oral absorption study of radiolabeled [(b) (4)] in rat. If oral absorption of [(b) (4)] is demonstrated in rat, then a 6-month oral toxicology study of [(b) (4)] in rat will be needed, at a dose that will support the amount of [(b) (4)] in Lumryz at the maximum dose described in the proposed product label, 9 g Lumryz per day.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHUN TING LEE
06/17/2022 04:05:31 PM

LOIS M FREED
06/17/2022 04:16:14 PM
I concur.