



Office of Orphan Products Development
Food and Drug Administration
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1501 K Street, N.W.
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Attention: Sean C. Griffin and Kwaku A. Akowuah

Re: Determination that Xywav's (NDA 212690) unexpired orphan-drug exclusivity ("ODE") does not block approval of Lumryz (NDA 214755)

Dear Mr. Griffin and Mr. Akowuah:

We have considered the submissions described in greater detail herein from Jazz Pharmaceuticals, Inc. ("Jazz") and Sidley Austin LLP ("Sidley") as counsel to Jazz. FDA's Office of Orphan Products Development ("OOPD" or "we") provides the response below.

I. Introduction

Herein, this analysis evaluates whether the ODE for Xywav (calcium, magnesium, potassium, and sodium oxybates) blocks the approval of NDA 214755 for Lumryz (sodium oxybate) for extended-release oral suspension submitted by Avadel CNS Pharmaceuticals, LLC ("Avadel") for the treatment of cataplexy or excessive daytime sleepiness ("EDS") in adults with narcolepsy. Xywav became eligible for ODE for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy because its sponsor, Jazz, demonstrated at the time of approval that Xywav was clinically superior to Xyrem, which was previously approved for the same indication. Under section 527(a) of the Federal Food, Drug, & Cosmetic Act ("FD&C Act"), the ODE for Xywav prevents FDA from approving a new drug product that is the "same drug" as Xywav for the same use or indication until its exclusivity expires on July 21, 2027.¹ By regulation, a drug is the "same drug" as Xywav if it contains the same active moiety (oxybate)

¹ Section 527(a) of the FD&C Act; *see also* 21 CFR § 316.31. *See also* FDA, Clarification of Orphan-Drug Exclusivity Following *Catalyst Pharms., Inc. v. Becerra*, 88 Fed. Reg. 4086 (Jan. 24, 2023).

for the same use or indication (the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy)² unless the new drug product is clinically superior to Xywav.³ For the reasons described below, we conclude that Lumryz is clinically superior to Xywav and is thus not considered to be the “same drug” as Xywav within the meaning of 21 CFR § 316.3(b)(14) and section 527(a) of the FD&C Act. Therefore, Xywav’s ODE does not block approval of NDA 214755 for Lumryz for the treatment of cataplexy or EDS in adults with narcolepsy.

We also conclude that Lumryz is eligible for its own term of ODE because it is clinically superior to both Xywav and Xyrem. Under section 527(c)(1) of the FD&C Act, if FDA has previously approved a drug that is otherwise the same drug for the same use or indication, the subsequent drug may be eligible for its own term of ODE if the sponsor demonstrates that its product is clinically superior to every such previously approved drug.⁴ As set forth below, we have determined that Avadel has demonstrated Lumryz’s clinical superiority to every previously approved oxybate drug for the same use or indication, i.e., both Xywav and Xyrem. Therefore, Lumryz is eligible for its own term of ODE for the treatment of cataplexy or EDS in adults with narcolepsy.

OOPD consulted with agency sleep experts and the Division of Neurology 1 (“DN1”) in making this determination,⁵ and their scientific thinking and expert opinions have been integral to this decision. As discussed below, FDA’s determination is based on careful consideration of the relevant scientific, legal, and regulatory issues raised and the materials submitted by outside parties. On December 15, 2020, Avadel submitted to OOPD and to the file for NDA 214755 an “exclusivity claim.”⁶ On July 14, 2021, Avadel submitted to OOPD and to the file for NDA 214755 a supplement to its “exclusivity claim.”⁷ On July 21, 2021, Avadel sent a letter to OOPD and to FDA’s Office of Chief Counsel (“OCC”) presenting arguments why Lumryz’s NDA should be eligible for approval notwithstanding Xywav’s ODE.⁸ On October 25, 2021, Latham & Watkins LLP as counsel to Avadel sent OCC a letter presenting arguments about the approvability of Lumryz’s NDA.⁹ On August 30, 2022, Avadel sent a letter to OOPD with additional arguments about clinical superiority.¹⁰

² The indication for Lumryz is “the treatment of cataplexy or EDS in adults with narcolepsy,” which is not co-extensive with, but falls entirely within, the scope of Xywav’s ODE because Xywav’s ODE includes a broader age range.

³ 21 CFR § 316.3(b)(14).

⁴ Section 527(c)(1) of the FD&C Act; *see also* 21 CFR § 316.34(c).

⁵ *See* Mahadevappa Hunasikatti MD FCCP and Nargues Weir MD FCCP FAASM ATSF, *Consult request on Lumryz* (Apr. 29, 2023) [hereinafter Sleep Expert Consult]; DN1, *Office of Orphan Products Development Consult Request #16-5302* at (May 1, 2023) [hereinafter DN1 Lumryz Consult].

⁶ Avadel, *Exclusivity Claim* (Dec. 15, 2020).

⁷ Avadel, *Exclusivity Claim – Supplemental Information in Demonstration of Clinical Superiority of FT218* (Jul. 14, 2021).

⁸ Letter from Jerad G. Seurer to Nicole Wolanski and Mark Raza, *Approval and Orphan Drug Exclusivity for FT218 (sodium oxybate for extended-release oral suspension)* (Jul. 21, 2021).

⁹ Letter from John R. Manthei to Elizabeth Dickinson, *Lumryz (sodium oxybate) for extended-release oral suspension (NDA 214755)* (Oct. 25, 2021).

¹⁰ Letter from Jennifer Gudeman to Sandra Retzky, *Orphan Drug Considerations for LUMRYZ (sodium oxybate) for Extended-Release Oral Suspension – DRU 2016-5302* (Aug. 30, 2022).

In addition to the submissions OOPD received from Avadel and its counsel, OOPD received submissions from Jazz. On September 16, 2021, Jazz sent a letter to OOPD presenting arguments why Lumryz is not clinically superior to Xywav (“Jazz’s September 2021 Letter”).¹¹ On December 6, 2022, Sidley as counsel to Jazz sent OCC a letter presenting arguments why Lumryz is not clinically superior to Xywav (“Sidley Letter”) and requested a meeting with OCC.¹² On January 18, 2023, FDA met with Sidley during which Sidley presented a slide deck (“Sidley Slides”).¹³ In this analysis, the arguments presented in Jazz’s September 2021 Letter, the Sidley Letter, and the Sidley Slides are collectively referred to as Jazz’s arguments.¹⁴

II. Legal Background

A. Orphan-Drug Designation (“ODD”)

Congress enacted the Orphan Drug Act in 1983 to provide incentives for the development of drugs for rare diseases or conditions that would not otherwise be developed due to the small patient population and lack of profitability of such drugs.¹⁵ Section 526 of the FD&C Act defines a “rare disease or condition,” in relevant part, as any disease or condition that affects less than 200,000 persons in the United States.¹⁶ To be eligible for ODD incentives — including tax credits for qualified clinical testing, exemption from the application user fee, and, potentially, ODE — the sponsor of a drug must request ODD for a rare disease or condition under section 526 of the FD&C Act, and FDA must grant ODD.¹⁷ FDA’s regulations at 21 CFR Part 316 lay out the requirements for an ODD submission.¹⁸ A sponsor of a drug that is “otherwise the same as an already approved drug may seek and obtain ODD for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug.”¹⁹

¹¹ Letter from Dennis Ahern to Sandra Retzky, *Considerations Regarding Clinical Superiority for Oxybate Products* (Sep 16, 2021) [hereinafter Jazz’s September 2021 Letter].

¹² Letter from Sean C. Griffin to Shoshana Hutchinson, *Orphan Drug Exclusivity for NDA 212690* (Dec. 6, 2022) [hereinafter Sidley Letter].

¹³ See Sidley, Presentation to the Office of Chief Counsel of behalf of Jazz Pharmaceuticals, Inc. (Jan. 18, 2023) [hereinafter Sidley Slides]. This meeting was listening only for FDA.

¹⁴ We also note that on November 29, 2022, TREND Community, a patient advocacy organization, sent a letter to OOPD presenting arguments and patient testimonials why there is a need for a once-nightly oxybate therapy. Letter from Maria Picone to FDA (Nov. 29, 2022). Then on January 2, 2023, Clete A. Kushida, M.D., Ph.D. sent a letter to OOPD to present arguments that Lumryz is clinically superior to the existing oxybate therapies, Xyrem and Xywav. Letter from Clete A. Kushida to Sandra Retzky (Jan. 3, 2023). These letters did not serve as a basis for FDA’s decision.

¹⁵ Pub. L. No. 97-414, 96 Stat. 2049 (1983).

¹⁶ See section 526(a)(2)(A) of the FD&C Act.

¹⁷ See section 526(a)(1) of the FD&C Act. A sponsor must request ODD prior to submitting a marketing application for the drug for the relevant disease.

¹⁸ See, e.g., 21 CFR §§ 316.20-21.

¹⁹ 21 CFR § 316.20(a).

B. ODE

One important incentive Congress provided in the Orphan Drug Act for sponsors developing drugs for rare diseases is the potential for a drug to become eligible for ODE. Section 527(a) states, in relevant part:

Except as provided in subsection (b), if the Secretary-

(1) approves an application filed pursuant to section 505, or

(2) issues a license under section 351 of the Public Health Service Act

for a drug designated under section 526 for a rare disease or condition, the Secretary may not approve another application . . . or issue another license . . . for the same drug for the same disease or condition for a person who is not the holder of such approved application or of such license until the expiration of seven years from the date of the approval of the approved application or the issuance of the license. . . .

In short, ODE prevents FDA from approving or licensing the same drug for the same use or indication for a person who is not the holder of such approved application or of such license until the expiration of seven years from the date of approval or licensure.²⁰

The statute provides two exceptions to ODE at section 527(b), under which FDA may approve an application for the same drug as a drug with ODE for the same use or indication. First, FDA may approve such an application if the agency finds that the sponsor of the drug with ODE cannot “ensure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition.”²¹ Second, FDA may also approve such an application if the sponsor of the drug with ODE consents to the approval of the application.²²

As explained below, FDA interprets section 527(a) in two contexts: 1) to determine whether a drug is eligible for ODE and 2) to determine whether certain pending drugs may be approved during an approved drug’s unexpired ODE (i.e., the scope of ODE).

i. Eligibility for ODE

An orphan-designated drug becomes eligible for ODE under section 527(a) of the FD&C Act once FDA approves or licenses it for the designated rare disease or condition, subject to the additional condition of clinical superiority in section 527(c) of the FD&C Act, when applicable. Section 527(c)(1) states:

If a sponsor of a drug that is designated under section 526 and is otherwise the same, as determined by the Secretary, as an already approved or licensed drug is seeking exclusive approval or exclusive licensure described in subsection (a) for the same rare disease or condition as the already approved drug, the Secretary shall require such sponsor, as a

²⁰ See section 527(a) of the FD&C Act; *see also, e.g.*, 21 CFR §§ 316.31, 316.34, 316.3(b)(14).

²¹ Section 527(b)(1) of the FD&C Act.

²² Section 527(b)(2) of the FD&C Act.

condition of such exclusive approval or licensure, to demonstrate that such drug is clinically superior to any already approved or licensed drug that is the same drug.

When applicable, FDA requires the sponsor of a subsequent drug to demonstrate clinical superiority to all (i.e., each and every) previously approved drugs with the same active moiety for the same indication or use to be eligible for its own term of ODE.²³

Section 527(c)(2) of the FD&C Act defines “clinically superior” for the purposes of meeting the condition of clinical superiority in section 527(c)(1) to mean “the drug provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, or by providing a major contribution to patient care.”²⁴ The orphan-drug regulations at 21 CFR § 316.3(b)(3) define “clinically superior” as follows:

Clinically superior means that a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in one or more of the following ways:

- (i) Greater effectiveness than an approved drug (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative effectiveness claim for two different drugs; in most cases, direct comparative clinical trials would be necessary; or
- (ii) Greater safety in a substantial portion of the target populations, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. In some cases, direct comparative clinical trials will be necessary; or
- (iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.²⁵

Section 527(c) of the FD&C Act was enacted by Congress under the FDA Reauthorization Act of 2017 (“FDARA”), and the applicability of the section was clarified in the Consolidated Appropriations Act, 2021 (2020). Prior to FDARA, FDA had relied upon its regulations to require a drug that is otherwise the same drug as a previously approved drug for the same use or indication to demonstrate clinical superiority to the previously approved drug for it to be eligible for ODE. *See, e.g.*, 21 CFR § 316.34(c) stating that “If a drug is otherwise the same drug as a previously approved drug for the same use or indication, FDA will not recognize orphan-drug exclusive approval if the sponsor fails to demonstrate upon approval that the drug is clinically superior to the previously approved drug.” *See also* 21 CFR § 316.3(b)(3) & § 316.3(b)(14). In

²³ 21 CFR § 316.3(b)(14) defines “same drug” to mean, in relevant part, “a drug that contains the same active moiety as a previously approved drug and is intended for the same use . . . except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.” Further discussion of this definition appears in the subsequent subsection.

²⁴ Section 527(c)(2) of the FD&C Act.

²⁵ 21 CFR § 316.3(b)(3).

response to court losses on the specific issue of whether FDA could impose such a clinical superiority requirement as a precondition for eligibility for ODE, Congress amended the statute to give the agency explicit statutory authority to do so.

Section 527(c)(1) states that if a sponsor “is seeking exclusive approval or exclusive licensure described in subsection (a)” for an otherwise same drug that has already been approved or licensed for the same disease or condition, “as a condition of such exclusive approval or licensure,” the sponsor must demonstrate “that such drug is clinically superior to any already approved or licensed drug that is the same drug.” As the text demonstrates, section 527(c) only concerns potential eligibility of a subsequent drug for its own period of ODE and does not address whether a subsequent drug’s approval is blocked by another drug’s ODE even where clinical superiority of the subsequent drug has been shown. As described further below, the blocking effect of ODE of a previously approved drug is instead described in 527(a) of the FD&C Act.

ii. Scope of ODE

As explained above, under section 527(a) of the FD&C Act, ODE prevents FDA from approving or licensing the same drug for the same use or indication for a person who is not the holder of such approved application or of such license until the expiration of seven years from the date of approval or licensure. FDA looks to the definition of “same drug” at 21 CFR § 316.3(b)(14) in determining whether a subsequent drug is the same drug for the same indication or use as a previously approved drug with unexpired ODE. That regulation defines “same drug” to mean, in relevant part, “a drug that contains the same active moiety as a previously approved drug and is intended for the same use . . . except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.”²⁶ Thus, under FDA’s validly promulgated and longstanding regulations, the “same drug” definition has a chemical and clinical component. In the 1992 Final Rule for the orphan-drug regulations, FDA explained that “two drugs would be considered the same drug if the principal, but not necessarily all, structural features of the two drugs were the same, unless the subsequent drug were shown to be clinically superior” and that “either differences in active moiety or clinical superiority will be sufficient to make two micromolecular drugs different.”²⁷ Accordingly, if the sponsor of the subsequent drug for the same indication or use can demonstrate that its drug has a different active moiety²⁸ or is clinically superior²⁹ to the drug with ODE (i.e., the “first drug”), the subsequent drug will not be considered to be the “same drug” as the drug with ODE, and that drug’s ODE will not block approval of the application for the subsequent drug for the same indication or use.³⁰

Interpreting section 527(a) of the FD&C Act in this manner does not create an exception to ODE analogous to those codified at section 527(b) of the FD&C Act that were discussed above; the

²⁶ 21 CFR § 316.3(b)(14).

²⁷ See FDA, *Orphan Drug Regulations, Final Rule*, 57 Fed. Reg. 62076, 62078 (Dec. 29, 1992) [hereinafter 1992 Final Rule].

²⁸ See 21 CFR § 316.3(b)(2) for orphan-drug definition of “active moiety.”

²⁹ See 21 CFR § 316.3(b)(3) defining “clinically superior.”

³⁰ 1992 Final Rule, 57 Fed. Reg. at 62078 (“Assuming that a subsequent drug’s marketing application is otherwise approvable, FDA will not interpret the Orphan Drug Act to block approval of any drug proved to be clinically superior to a drug with currently effective exclusive marketing rights.”).

exceptions at 527(b) concern instances where FDA determines that a drug is the same drug for the same indication or use but is approvable nonetheless despite another same drug's unexpired ODE. Drugs that are approved under the exceptions at section 527(b) would be chemically and clinically the same as the drug with unexpired ODE and would not include clinically superior drugs.

In summary, for a determination under section 527(a) as to whether a drug's unexpired ODE blocks approval of a subsequent drug, FDA compares the subsequent drug to the drug with unexpired ODE. In circumstances in which the subsequent drug contains the same active moiety for the same indication or use as the drug with unexpired ODE, FDA determines whether the subsequent drug is clinically superior to the drug with ODE. If it is clinically superior, the subsequent drug is not considered to be the "same drug," and thus its approval for the same indication or use is not blocked. By contrast, for a determination under section 527(c) of the FD&C Act as to whether a subsequent drug with the same active moiety for the same indication or use as a previously approved drug is eligible under section 527(a) for its own term of ODE, FDA compares the subsequent drug to all such previously approved drugs, even if ODE for those drugs has expired. If the subsequent drug is clinically superior to each, then it is eligible for its own term of ODE.

C. Clinical Superiority

As explained above, section 527(c)(2) of the FD&C Act defines clinically superior to mean that "the drug provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, *or* by providing a [MCTPC]," and 21 CFR § 316.3(b)(3) defines clinically superior to mean that "a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in *one or more* of the following ways:" greater effectiveness, greater safety, or a MCTPC (emphasis added). In both definitions, the subsequent drug must provide a significant therapeutic advantage "over and above" an already approved drug in just one way—greater efficacy, greater safety, *or* by providing a MCTPC—to be considered clinically superior. Neither the plain reading of the statute nor that of the regulation imposes an additional requirement that in order to provide a significant therapeutic advantage in one of the three measures, the drug must also be at least comparable in the other two measures.

There is at least one instance in which FDA determined that a subsequent drug is clinically superior based on greater efficacy even though the drug was less safe in one measure than the previously approved drug with ODE. Specifically, FDA considered whether different interferon beta products for relapsing remitting multiple sclerosis ("RRMS") were clinically superior to one another. This situation involved three interferon beta products for the same use. The first interferon beta for treatment of RRMS, Betaseron, was approved on July 23, 1993, and was eligible for ODE until July 23, 2000. During Betaseron's period of ODE, a different sponsor, Biogen, sought marketing approval for another interferon beta product for RRMS called Avonex. FDA determined that Biogen demonstrated that Avonex was clinically superior to Betaseron because Avonex was safer due to elimination of skin necrosis at injection sites.³¹ As a result,

³¹ FDA, *Memorandum, Clinical Superiority of Biogen's interferon product, Avonex*, DRU-1991-627 (Apr. 16, 1996).

Avonex was a different drug than Betaseron under the orphan-drug regulations, and Betaseron's ODE did not block its approval. On May 17, 1996, FDA approved Avonex for RRMS, and it was eligible for its own term of ODE until May 17, 2003. Subsequently, during Avonex's period of ODE, a third sponsor, Serono, sought approval for an interferon beta product for RRMS called Rebif. Serono demonstrated that Rebif was more effective than Avonex based on a study showing that patients taking Rebif were less likely to experience multiple sclerosis exacerbations than patients taking Avonex.³² However, Rebif patients experienced skin necrosis at injection sites that Avonex patients did not (i.e., the same adverse event that was present with Betaseron that led to the determination that Avonex was clinically superior to Betaseron based on safety).³³

FDA concluded that Rebif was clinically superior to Avonex based on greater effectiveness, and that the safety considerations of Rebif compared to Avonex were "not directly relevant" to the clinical superiority determination.³⁴ In making its decision, FDA explained the following:

[T]he regulations do not state that clinical superiority must be based on overall risk benefit being deemed superior for the subsequent product compared to the prior product. In fact, the regulations indicate that only a selected aspect may constitute a sufficient basis to reach a conclusion of clinical superiority. That is, the aspects not selected by the sponsor for focus (e.g., safety when efficacy is selected; efficacy when safety is selected) do not require a comparative assessment. The regulations require neither that all aspects of known efficacy nor all aspects of safety be shown to be superior. Nor do the regulations indicate that other aspects of safety or efficacy be shown "comparable" when only one specific aspect of safety or efficacy is shown to be superior.³⁵

FDA also stated:

There is no additional requirement that the subsequent product, although clinically superior in one parameter, must also be shown to be at least equal in all others. This would set an inappropriate and nearly impossible burden (in terms of clinical trial design) on the sponsor of a second product. A more meaningful standard is a significant therapeutic benefit in terms of increased effectiveness and adequate safety, or increased safety and adequate effectiveness. The balancing of risks and benefits embodied in a drug product as a whole is done when the agency determines whether the drug may be approved for the particular use.³⁶

D. MCTPC

³² See FDA, *BLA STN 103780/0 Comparative Study of Rebif to Avonex and Orphan Exclusivity* at 20 (Mar. 7, 2002) [hereinafter CBER Rebif memo].

³³ *Id.*

³⁴ *Id.*

³⁵ *Id.* at 3-4. See also *id.* at 10-11 ("Orphan drug regulations do not state that all known clinical actions of a product must be shown superior to the competitor."); *id.* at 20 ("[T]he orphan drug regulations do not require that safety be superior or even identical between two drugs when a clinical efficacy comparison is employed for the demonstration of being not the 'same drug.'").

³⁶ FDA, *Memorandum, OOPD Analysis of Exclusivity Issues Raised in the Serono BLA for Rebif* at 3 (Mar. 7, 2002) [hereinafter OOPD Rebif memo].

Because of the diverse ways in which drugs may qualify as clinically superior (and therefore not the “same drug”) under the law, FDA evaluates clinical superiority on a case-by-case basis.³⁷ Specifically, with respect to MCTPC, to preserve the statutory incentive to develop orphan drugs, the agency has stated that MCTPC is “intended to constitute a narrow category.”³⁸ Regarding how to demonstrate a MCTPC, the agency has also stated:

- “There is no way to quantify such superiority in a general way. The amount and kind of superiority needed would vary depending on many factors, including the nature and severity of the disease or condition, the quality of the evidence presented, and diverse other factors.”³⁹
- “The following factors, when applicable to severe or life-threatening diseases, may in appropriate cases be taken into consideration when determining whether a drug makes a major contribution to patient care: convenient treatment location; duration of treatment; patient comfort; reduced treatment burden; advances in ease and comfort of drug administration; longer periods between doses; and potential for self-administration.”⁴⁰
- MCTPC “determinations can be complex and encompass consideration of a number of factors that potentially implicate safety and effectiveness, which are evaluated on a case-by-case basis for each drug product.”⁴¹

Relative effectiveness and safety of the drug may be relevant in assessing whether a drug makes a MCTPC, and a drug must meet FDA’s safety and effectiveness standards to obtain approval, but, as explained above, nothing in the statute or regulation requires comparable effectiveness and safety. In the Rebif example noted above, FDA stated with respect to MCTPC:

This analysis may involve multiple aspects of the drug product, since the benefit to the patient is likely to be greater convenience or less discomfort, and the very term “major contribution to patient care” implies a more global assessment. So, for example, an assessment of the safety or effectiveness of the new form of the subsequent product might be considered in determining whether the drug made a major contribution to patient care. However, even in this instance, there can not [sic] be an infinite number of comparison criteria if this provision of the regulation is to be meaningful.⁴²

For example, if the administration of a drug were changed from intravenous (IV) to oral, FDA would consider, if appropriate, whether any adverse events diminished the advantage of the

³⁷ See FDA, *Orphan Drug Regulations, Proposed Rule*, 56 Fed. Reg. 3338, 3340 (Jan. 29, 1991) [hereinafter 1991 Proposed Rule] (“The content of this evidence [needed for a demonstration of clinical superiority] will depend on the nature of the superiority claimed.”); see also 1992 Final Rule, 57 Fed. Reg. at 62079 (stating that a major contribution to patient care “determination will have to be made on a case-by-case basis.”).

³⁸ 1991 Proposed Rule, 56 Fed. Reg. at 3343.

³⁹ 1992 Final Rule, 57 Fed. Reg. at 62078.

⁴⁰ FDA, *Orphan Drug Regulations, Final Rule*, 78 Fed. Reg. 35117, 35125 (Jun. 12, 2013) [hereinafter 2013 Final Rule].

⁴¹ *Id.* at 35124.

⁴² CBER Rebif memo, *supra* note 32, at 3.

change in administration from IV or oral. In that respect, safety concerns could inform the MCTPC analysis, but a safety concern present in a subsequent drug that was not present in the previous drug would not automatically defeat a MCTPC finding. That determination would be made on a case-by-case basis and depend upon the nature of the safety concern weighed against the benefits of the MCTPC.

III. Factual Background

This matter involves three different drug products that contain the same active moiety (oxybate)⁴³ for the treatment of cataplexy or EDS in patients with narcolepsy. Jazz is the current sponsor of Xyrem (sodium oxybate) and Xywav (calcium, magnesium, potassium, and sodium oxybates). Avadel is the sponsor of Lumryz (sodium oxybate).

A. Normal Sleep and Narcolepsy

The following background concerning normal sleep and narcolepsy is based on OOPD's consultation with two board certified sleep experts in FDA ("Sleep Expert Consult").⁴⁴

Adequate sleep is essential for humans as it physically and psychologically restores bodily functions.⁴⁵ Without adequate sleep, humans function poorly and may die prematurely.⁴⁶ Chronic sleep loss, sometimes called sleep debt, is well known to cause reduced performance, increased risk for accidents and death, and detrimental effects on both psychological and physical health.⁴⁷

Normal sleep architecture is characterized in adults as a progression of 90 to 120 minute sleep cycles starting with non-REM Stage 1 sleep (NREM or N1 sleep), then non-REM Stage 2 (NREM or N2) sleep, then non-REM Stage 3 (NREM or N3) sleep, and ending in Rapid Eye Movement (REM or Stage R) sleep.⁴⁸ Rapid eye movements and dreaming occur during Stage R.⁴⁹ After Stage R, the normal adult has a very brief return to Stage Wake (Stage W), in the transition of going from cycle to cycle, though this awakening is not typically remembered, is normal and does not contribute to sleep fragmentation, sleep loss, or daytime sleepiness.⁵⁰ The

⁴³ The active moiety oxybate may also be referred to as gamma-hydroxybutyrate (GHB).

⁴⁴ Sleep Expert Consult, *supra* note 5. These physicians are boarded in (1) internal medicine; (2) pulmonology; (3) critical care medicine; (4) and sleep. One of the consultants continues to see patients in a sleep clinic. Statements in this subsection of the document are based on statements in this consult.

⁴⁵ Kiran Maski, *Insufficient sleep: Evaluation and management*, UpToDate (May 23, 2022), <https://www.uptodate.com/contents/insufficient-sleep-evaluation-and-management>.

⁴⁶ Chiara Cirelli, *Insufficient sleep: Definition, epidemiology, and adverse outcomes*, UpToDate (Oct 10, 2022), <https://www.uptodate.com/contents/insufficient-sleep-definition-epidemiology-and-adverse-outcomes>.

⁴⁷ *Id.*

⁴⁸ Douglas Kirsch, *Stages and architecture of normal sleep*, UpToDate (Sep 12, 2022), <https://www.uptodate.com/contents/stages-and-architecture-of-normal-sleep>.

⁴⁹ James A. Rowley & M. Safwan Badr, *Chapter 1: Normal Sleep*, in *Essentials of Sleep Medicine* 3, at 5 (M. Safwan Badr & Jennifer L. Martin eds., 2nd ed. 2022).

⁵⁰ Mary A. Carskadon & William C. Dement, *Monitoring and staging human sleep, Chapter 2—Normal Human Sleep: An Overview*, in *Principles and practice of sleep medicine* at 12 (M.H. Kryger et al., eds., 5th ed. 2011); *see also* Rowley, *supra* note 49, at 5 (Fig. 1.2).

normal sleep cyclical pattern typically repeats four to five times per night.⁵¹ Cycling progression through these stages is the basic structural organization of normal sleep and is called “sleep architecture.”⁵²

Each sleep stage has unique features. Stage N1 sleep is light sleep (easily arousable), Stage N2 sleep is intermediate in depth (less light sleep), and Stage N3 is deep sleep, otherwise known as restorative sleep, slow-wave sleep (SWS), or delta sleep.⁵³ Brain activity is low during Stage N3 sleep, and importantly, many recovery functions in the body occur only in this stage of sleep.⁵⁴ Normally, the sleep cycles progress through the night with increasing time in Stage N3 during initial sleep cycles and increasing REM sleep in each later sleep cycle during the night.⁵⁵

Stage N3 sleep has a unique and important role in restoring the mind and body.⁵⁶ With sleep loss or deprivation or interruption, one enters Stage N3 sleep earlier and with increased quantity during the night.⁵⁷ Thus, the body attempts to achieve sleep equilibrium by rapidly restoring this critical stage of sleep.⁵⁸ On polysomnography (PSG)—a diagnostic full sleep study with an electroencephalogram (EEG)—REM sleep is a time of active brain EEG waves and physiological instability characterized by somewhat irregular heart rate and breathing patterns.⁵⁹ REM is associated with paralysis of all muscles except the essential respiratory muscles (e.g., the diaphragm).⁶⁰

When an arousal occurs (e.g., when waking up to take medication during the night after falling asleep), there is a shift in an EEG pattern—one that leads to a longer Stage W with alertness or consciousness, even if not remembered.⁶¹ That duration of time in Stage W is prolonged and will adversely impact a clinical measure called Wake After Sleep Onset (WASO)—a metric of how much wakefulness happens in a night of sleep.⁶² In treating sleep disorders, including narcolepsy, the goal is to maximize the time in sleep and minimize wake time (i.e., minimize WASO).⁶³ Disruption of sleep leads to the inability to enter Stage N3, or disruption of N3, and such individuals will revert back to Stage W and subsequently progress to Stage N1 sleep and so

⁵¹ Kirsch, *supra* note 48.

⁵² Rowley, *supra* note 49, at 5.

⁵³ Carskadon, *supra* note 50, at 11.

⁵⁴ Derk-Jan Dijk, *Regulation and Functional Correlates of Slow Wave Sleep*, Supp. To Vol. 5 No. 2 Journal of Clinical Sleep Medicine, S6, at S6 (2009).

⁵⁵ Carskadon, *supra* note 50, at 11.

⁵⁶ Lixia Chen et al., *The association between sleep architecture, quality of life, and hypertension in patients with obstructive sleep apnea*, 27 Sleep and Breathing 191, at 192 (2023).

⁵⁷ Kirsch, *supra* note 48; *see also* Carskadon, *supra* note 50, at 15.

⁵⁸ *See* Sleep Expert Consult, *supra* note 5, at 4.

⁵⁹ Ye Zhang et al., *Polysomnographic nighttime features of narcolepsy: A systematic review and meta-analysis*, 58 Sleep Medicine Reviews at 1 (2021); *see also* David W. Carley & Sarah S. Farabi, *Physiology of Sleep*, 29 Diabetes Spectr. 5, at 6; *see also* Kirsch, *supra* note 48; *see also* Carskadon, *supra* note 50, at 3-4.

⁶⁰ Rowley, *supra* note 49 at 5.

⁶¹ Kirsch, *supra* note 48; *see also* Pierre Philip et al., *Sleep Fragmentation in Normals: A Model for Sleepiness Associated with Upper Airway Resistance Syndrome*, 17 Sleep 242, at 244-245 (1994).

⁶² Eric Suni, *Wakefulness After Sleep Onset*, Sleep Foundation (updated Jan. 18, 2023), <https://www.sleepfoundation.org/sleep-studies/wakefulness-after-sleep-onset>.

⁶³ *See* Sleep Expert Consult, *supra* note 5, at 5.

forth.⁶⁴ The disruption changes sleep architecture and will increase WASO.⁶⁵ This disruption is something to be avoided in the narcoleptic patient, if possible.⁶⁶

Narcolepsy is a disorder of REM intrusion into wakefulness.⁶⁷ Sudden REM sleep onset during wakefulness causes loss of motor tone (i.e., sleep paralysis) along with a dream like state called cataplexy.⁶⁸ REM intrusion can also occur during sleep, disrupting the normal sleep architecture described above.⁶⁹ Individuals with narcolepsy “generally fall asleep rapidly but can spontaneously awaken several times during the night and have difficulty returning to sleep. This sleep maintenance insomnia seems paradoxical in a disorder characterized by daytime sleepiness, and it may reflect a low threshold to transition from sleep to wakefulness.”⁷⁰ REM intrusion in sleep shifts sleep stages and prevents sleep continuity (also called sleep consolidation), fragments normal sleep architecture, and prevents sufficient deep sleep (i.e., prevents N3 restorative sleep from occurring because the sleep stages keep shifting to lighter sleep).⁷¹ Often Stage N1 increases at the debt of Stage N3 sleep given the increased number of shifts between sleep stages.⁷² This results in daytime sleepiness with the consequences of sleep fragmentation or sleep deprivation (i.e., altered sleep architecture which may affect daytime performance).⁷³

EDS is the most common and chronic symptom of narcolepsy.⁷⁴ Per Scammell: “[t]he sleepiness may be so severe that patients with narcolepsy can rapidly doze off with little warning; these episodes are commonly referred to as ‘sleep attacks.’”⁷⁵ Another symptom of narcolepsy, cataplexy, is an “emotionally-triggered transient muscle weakness” that can cause a patient to collapse.⁷⁶

For narcolepsy, the goals of therapy are “to achieve ‘normal’ alertness during conventional waking hours or to maximize alertness at important times of the day, (e.g., during work, school, or while driving),” and to the extent possible, promote normal sleep at night.⁷⁷ Management of narcolepsy is multimodal and includes non-pharmacologic and pharmacologic treatment.⁷⁸ Non-pharmacologic care, including “sleep hygiene,” is “critical to obtaining adequate, quality sleep

⁶⁴ Richard Berry et al., *The AASM Manual for the Scoring of Sleep and Associated Events, Rules, Terminology and Technical Specifications*, American Academy of Sleep Medicine (AASM) (2020), version 2.6 at 22-33.

⁶⁵ See Sleep Expert Consult, *supra* note 5, at 6.

⁶⁶ *Id.*

⁶⁷ Thomas E Scammell, *Clinical features and diagnosis of narcolepsy in adults*, UpToDate (Jul. 12, 2022), <https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-narcolepsy-in-adults>.

⁶⁸ *Id.*

⁶⁹ Imran Ahmed & Michael Thorpy, *Chapter 15: Narcolepsy and Idiopathic Hypersomnia*, in *Essentials of Sleep Medicine* 327, at 328 (M. Safwan Badr & Jennifer L. Martin eds., 2nd ed. 2022).

⁷⁰ Scammell, *Clinical*, *supra* note 67.

⁷¹ Michelle T. Cao & Christian Guilleminault, *Chapter 90: Narcolepsy: Diagnosis and Management*, in *Neurologic Disorders* 873, at 873; see also Zhang, *supra* note 59 at 11.

⁷² Sleep Expert Consult, *supra* note 5, at 6.

⁷³ *Id.* at 6-7.

⁷⁴ Scammell, *Clinical*, *supra* note 67; see also Cao, *supra* note 71, at 873.

⁷⁵ Scammell, *Clinical*, *supra* note 67.

⁷⁶ *Id.*

⁷⁷ Thomas E Scammell, *Treatment of narcolepsy in adults*, UpToDate (Nov. 14, 2022), <https://www.uptodate.com/contents/treatment-of-narcolepsy-in-adults>.

⁷⁸ Kiran Maski et al., *Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline*, 17 *Journal of Clinical Sleep Medicine* 1881, at 1892 (2021).

on an ongoing basis.”⁷⁹ Sleep hygiene means consistent sleep scheduling, a bedtime routine of personal care, napping, daily exercise, and a sleep environment conducive to sleep without interruptions.⁸⁰

In addition to behavioral changes promoting good sleep hygiene, most patients with narcolepsy also require pharmacotherapy.⁸¹ Oxybate salts are one class of drugs that improves symptoms of EDS and decreases episodes of cataplexy.⁸² Per Scammell, especially for patients with severe and disabling sleepiness:

Oxybates have a different mechanism of action than other narcolepsy medications and act primarily through *consolidating nighttime sleep*. Although risks and side effects, as well as cost, may be higher with oxybates, they can offer the best chance of optimal symptom control with monotherapy. For patients with a good response to oxybates, other wake-promoting medications may be able to be tapered.⁸³

As explained above, “consolidating nighttime sleep” means ensuring sleep continuity through the normal stages of sleep architecture. Therefore, oxybate products are intended to decrease nocturnal arousals (also known as nighttime or nocturnal awakenings) to decrease sleep fragmentation that leads to poor quality sleep. Importantly, as explained in more detail below, the effectiveness of Xyrem and Xywav wanes during the night, so their labeling recommends that patients awaken for a second dose. Lumryz, as a once nightly formulation, will eliminate such nocturnal arousal, thus minimizing disturbances and decreasing sleep fragmentation.

B. Regulatory History of Oxybate Products for Narcolepsy

On November 7, 1994, FDA granted ODD to Jazz’s predecessor Orphan Medical, Inc. for oxybate⁸⁴ for the treatment of narcolepsy. On July 17, 2002, FDA approved Xyrem for the treatment of cataplexy associated with narcolepsy, and Xyrem was eligible for ODE for the treatment of cataplexy associated with narcolepsy until July 17, 2009. On November 18, 2005, FDA approved Xyrem for a new indication, the treatment of EDS in patients with narcolepsy, and Xyrem was eligible for a new term of ODE for the treatment of EDS in patients with narcolepsy until November 18, 2012. Both of those periods of ODE have since expired. Finally, on October 26, 2018, FDA approved Xyrem for the treatment of cataplexy or EDS in pediatric patients 7 years of age and older with narcolepsy. Prior to this approval, the safety and effectiveness of Xyrem in pediatric patients had not been established, and therefore this approval

⁷⁹ Maski, *Insufficient*, *supra* note 45.

⁸⁰ See National Sleep Foundation, *10 Tips for a Better Night’s Sleep*, <https://www.thensf.org/sleep-tips/>; see also American Academy of Sleep Medicine, *How to sleep better*, https://aasm.org/resources/pdf/products/howtosleepbetter_web.pdf; see also Ahmed, *supra* note 69 at 340.

⁸¹ Timothy I. Morgenthaler et al., *Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin*, 30 *Sleep* 1705 at 1705-1711 (2007).

⁸² Scammell, *Treatment*, *supra* note 77.

⁸³ *Id.* (emphasis added).

⁸⁴ We note that ODD letters and the ODD database often refer to the generic name of the drug the sponsor uses in its request for designation rather than the active moiety, but the ODD applies to the active moiety (here, oxybate for the treatment of narcolepsy).

expanded the indication to a new patient population. Xyrem was eligible for ODE for the treatment of cataplexy or EDS in pediatric patients 7 years of age and older with narcolepsy, which will run until October 26, 2025.⁸⁵

Xyrem has a concentration of 0.5 grams (g)/milliliter (mL) of sodium oxybate, equivalent to 0.413 g/mL of oxybate.⁸⁶ Xyrem is taken in 2 doses at night, the first dose at bedtime with the second dose taken 2.5 to 4 hours later.⁸⁷ For adults, the initial starting dose is 4.5 g per night, which can be increased in increments of 1.5 g per night at weekly intervals to a maximum of 9 g per night.⁸⁸ The maximum dose of 9 g contains approximately 1,640 milligrams (mg) of sodium.⁸⁹ This amount can make up a large portion of the maximum daily recommended sodium (for example, CDC guidelines recommend less than 2,300 mg of sodium each day as part of a healthy eating pattern).⁹⁰ Due to its high sodium content, Xyrem's labeling includes a Warning and Precaution on use of the drug in patients sensitive to high sodium intake and recommends consideration of the amount of daily sodium intake in each dose of Xyrem for patients sensitive to sodium intake (e.g., those with heart failure, hypertension, or renal impairment).⁹¹ The sodium warning is listed last of eight warnings, and warnings are listed in order of relative clinical significance.⁹²

Subsequently, Jazz developed a low-sodium alternative to Xyrem called Xywav. Xywav consists of 4 active ingredients, all of which have oxybate as the active moiety: calcium oxybate (0.234 g/mL), potassium oxybate (0.130 g/mL), magnesium oxybate (0.096 g/mL), and sodium oxybate (0.040 g/mL) — equivalent to 0.413 g/mL of oxybate, the same as Xyrem.⁹³ The total salt concentration is 0.5 g/mL.⁹⁴ Also like Xyrem, the recommended starting dosage for Xywav in adults is 4.5 g per night administered orally, divided into two doses, one at bedtime with the second dose to be taken 2.5 to 4 hours later.⁹⁵ Xywav can be titrated by increments of up to 1.5 g per night per week to the recommended maximum dosage of 9 g per night.⁹⁶ At the maximum

⁸⁵ Pediatric exclusivity extends Xyrem's ODE until April 26, 2026.

⁸⁶ Xyrem FDA-Approved Labeling at Section 3 (Apr. 2023), available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021196s042lbl.pdf [hereinafter Xyrem 2023 Labeling].

⁸⁷ *Id.* at section 2.1. Note that the labeling describes dosage “per night” regardless of whether the patient primarily sleeps during the day or night. This analysis will also use the word “night” to refer to the patient's bedtime.

⁸⁸ *Id.* at section 2.1.

⁸⁹ *Id.* at section 5.8.

⁹⁰ See CDC, *About Sodium*, available at: <https://www.cdc.gov/salt/food.htm>.

⁹¹ Xyrem 2023 Labeling, *supra* note 86, at section 5.8. The warning states, “Xyrem has a high salt content. In patients sensitive to salt intake (e.g., those with heart failure, hypertension, or renal impairment), consider the amount of daily sodium intake in each dose of Xyrem. Table 3 provides the approximate sodium content per Xyrem dose.”

⁹² See FDA, *Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* at 7 (Oct. 2011) (available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/warnings-and-precautions-contraindications-and-boxed-warning-sections-labeling-human-prescription>) (“The order in which adverse reactions are presented in the WARNINGS AND PRECAUTIONS section should reflect the relative clinical significance of the adverse reactions”).

⁹³ Xywav FDA-Approved Labeling at section 3 (Apr. 2023), available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/212690s011lbl.pdf [hereinafter Xywav 2023 Labeling].

⁹⁴ *Id.*

⁹⁵ *Id.* at section 2.1.

⁹⁶ *Id.*

dose for adults, the sodium content of Xywav is 131 mg.⁹⁷ Therefore, unlike Xyrem, there are no Warnings and Precautions in Xywav’s labeling related to that drug’s use in patients sensitive to high sodium intake.

Because the active moiety in Xywav is also oxybate, Xywav is covered by Jazz’s ODD for oxybate for the treatment of narcolepsy. On July 21, 2020, FDA approved Xywav for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy. In order for Xywav to be eligible for ODE, Jazz was required to demonstrate that Xywav was clinically superior to Xyrem.⁹⁸ OOPD determined that Xywav was clinically superior to Xyrem because the reduced sodium in Xywav provides greater safety in a substantial portion of the target population.⁹⁹ Specifically, at the effective daily dose of 6 g to 9 g, Xyrem adds approximately 1,100 mg to 1,640 mg of sodium to each patient’s daily sodium intake, compared to Xywav, which adds only 87 to 131 mg of sodium to each patient’s daily sodium intake for the same recommended daily dose.¹⁰⁰ OOPD concluded, “the differences in the sodium content of the two products at the recommended doses will be clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated.”¹⁰¹ OOPD noted that whether sodium content of Xyrem increases cardiovascular risks in patients with narcolepsy has never been specifically or adequately investigated; however, the general base of knowledge about the effects of sodium support that the amount of sodium in Xyrem would increase cardiovascular risks in patients with narcolepsy.¹⁰²

Because FDA found Xywav to be clinically superior to Xyrem, Xywav was eligible for ODE.¹⁰³ On June 24, 2021, OOPD sent a letter to Jazz stating that it is eligible for ODE for Xywav for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy, effective as of the July 21, 2020, approval of NDA 212690.¹⁰⁴ Xywav’s ODE for this indication will run until July 21, 2027.

⁹⁷ NDA 212690 Clinical Review at 7 (available at:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212690Orig1s000MedR.pdf).

⁹⁸ Section 527(c)(1) of the FD&C Act.

⁹⁹ See FDA, *Exclusivity Memorandum DRU-1994-858, Xywav (calcium, magnesium, potassium, and sodium oxybates)* at 6 (Sep. 30, 2021) [hereinafter Xywav Exclusivity Memo]. During OOPD’s assessment of Xywav’s clinical superiority over Xyrem, OOPD received and considered two letters from Jazz containing arguments why Xywav is clinically superior to Xyrem. See letter from Arthur Merlin d’Estreux to Janet Maynard, *Orphan Drug Exclusivity for JZP-258, NDA No. 212690* (Apr. 24, 2020); see also letter from Robert Iannone to Janey Maynard, *Request to Expedite Recognition of Orphan Drug Exclusivity for XYWAV (NDA 212690)* (Apr. 19, 2021). Additionally, OOPD received and considered a letter from Avadel providing arguments why Xywav is not clinically superior to Xyrem. See letter from Jennifer Gudeman to Janet Maynard, *Sodium Oxybate for the Treatment of Narcolepsy* (Dec. 8, 2020). OOPD also consulted with the Division of Neurology 1 (“DN1”) in the Center for Drug Evaluation and Research (“CDER”). See DN1, *Consult Request NDA 212690 Xywav* (Nov. 27, 2020) [hereinafter DN1 2020 Xywav Consult]; See also DN1, *Consult Request NDA 212690 Xywav* (Mar. 8, 2021).

¹⁰⁰ Xywav Exclusivity Memo, *supra* note 99, at 3.

¹⁰¹ FDA, *Clinical Superiority Findings*, available at <https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings>.

¹⁰² Xywav Exclusivity Memo, *supra* note 99, at 5.

¹⁰³ See section 527(c) of the FD&C Act.

¹⁰⁴ Letter from Nicole Wolanski to Jazz Pharmaceuticals, Inc., *Orphan-Drug Exclusivity Letter DRU-1994-858* (June 24, 2021). OOPD also responded to Avadel’s letter to explain that we considered their arguments before concluding that Xywav was eligible for ODE. See letter from Nicole Wolanski to Jennifer Gudeman, *Sodium Oxybate for the Treatment of Narcolepsy* (Jun. 24, 2021).

Concurrently, Avadel developed Lumryz, an extended-release oral suspension version of sodium oxybate for the treatment of narcolepsy. The active moiety in Lumryz, like both Xyrem and Xywav, is oxybate. While Xyrem and Xywav are both dosed twice per night, with the patient instructed to wake from sleep to take the second dose, Lumryz is dosed once per night before sleep. Therefore, Lumryz’s labeling does not advise an awakening to take a second dose for proper administration.¹⁰⁵ At the recommended daily dose of 6 g to 9 g, Xyrem and Lumryz both have the same sodium content (approximately 1,100 mg to 1,640 mg). As explained above, at the same recommended daily dose of 6 g to 9 g, Xywav has a lower sodium content of 87 mg to 131 mg. See Table 1 for a summary of the differences among the drugs.

Table 1: Comparison of Xyrem, Xywav, and Lumryz Dosing and Sodium Content per Daily Dose

Drug	Dosing	Amount of sodium at the recommended daily dose of 6 g to 9 g
Xyrem	Twice-per-night	1,100 mg to 1,640 mg
Xywav	Twice-per-night	87 mg to 131 mg
Lumryz	Once-per-night	1,100 mg to 1,640 mg

On April 20, 2016, Avadel¹⁰⁶ requested ODD for oxybate¹⁰⁷ for the treatment of narcolepsy. At the time of the request for designation, Xyrem was already approved for a narcolepsy indication, but Xywav was not yet approved. Because Avadel was seeking ODD for oxybate for the same disease for which Xyrem was approved, Avadel was required to provide a plausible hypothesis that its drug was clinically superior to Xyrem to be eligible for ODD.¹⁰⁸

Upon review of the initial request for designation, OOPD asked Avadel to provide additional support for its hypothesis for clinical superiority.¹⁰⁹ Avadel submitted an amendment to its request for designation on October 13, 2017. At that time, to determine whether the plausible hypothesis standard for ODD had been met, OOPD consulted with clinical experts in the Division of Neurology Products (DNP) regarding the benefit of Lumryz’s once-per-night dosing over Xyrem’s twice-per-night dosing.¹¹⁰ DNP stated that if a formulation of sodium oxybate can be administered only once each night, it would have advantages over a sodium oxybate drug administered twice-per-night, like Xyrem.¹¹¹ DNP cited several reasons such a formulation could be clinically superior, including that a drug administered once per night would be much more convenient and less disruptive for patients, and that a drug administered once-per-night may present less risk to patients, for example risks from falls when waking up to take the second

¹⁰⁵ Lumryz, FDA-Approved Labeling (May 2023) [hereinafter Lumryz Labeling].

¹⁰⁶ Avadel submitted the request for designation under the name Flamel Ireland Limited. In 2017, there was a cross-border merger of Flamel and Avadel; the latter entity survived the merger as the public holding company.

¹⁰⁷ At the time, Avadel referred to its product as FT218 or sodium oxybate for extended-release oral suspension. See also *supra* note 84.

¹⁰⁸ 21 CFR § 316.20(a).

¹⁰⁹ FDA, *Review of Request for ODD for sodium oxybate, DRU-2016-5302* at 5 (Jul. 28, 2016); see also Letter from Gayatri R. Rao to The Weinberg Group, Inc., *Deficiency Letter, DRU-2016-5302* (Aug. 23, 2016).

¹¹⁰ As the result of a reorganization of the CDER, the review division responsible for oxybate drug products for the treatment of narcolepsy is now called the Division of Neurology 1 (DN1).

¹¹¹ Division of Neurology Products, *Sodium Oxybate Consultation Request* at 9 (Nov. 24, 2017).

dose.¹¹² DNP’s response supported OOPD’s conclusion that there was a plausible hypothesis that Lumryz may be clinically superior to Xyrem based on providing greater safety or by making a MCTPC over Xyrem.¹¹³ Therefore, on January 8, 2018, FDA granted Avadel’s request for ODD for oxybate for treatment of narcolepsy.¹¹⁴

On December 15, 2020, Avadel submitted NDA 214755 for Lumryz. On July 18, 2022, FDA tentatively approved Lumryz for the treatment of cataplexy or EDS in adults with narcolepsy. The Tentative Approval Letter stated, “This letter does not address whether any orphan drug exclusivity (ODE) recognized for Xyrem under NDA 021196 or for Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution under NDA 212690 affects the approvability of Avadel’s application.”¹¹⁵ On March 1, 2023, Avadel submitted an amendment to NDA 214755 requesting final approval.

IV. Discussion

A. Applicability of the Clinical Superiority Standard

Xywav currently has ODE for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy, and as such, FDA may not approve another sponsor’s marketing application for the same drug for the same use or indication until its exclusivity expires on July 21, 2027.¹¹⁶ Lumryz contains the same active moiety as Xywav (oxybate), and Avadel is seeking approval for Lumryz for an indication covered by Xywav’s unexpired ODE (the treatment of cataplexy or EDS in adults with narcolepsy). Under the orphan-drug regulations, Lumryz is the “same drug” as Xywav unless Lumryz is clinically superior to Xywav.¹¹⁷ If Lumryz is clinically superior to Xywav, then it is not the “same drug” as Xywav, and Xywav’s ODE will not block Lumryz’s approval.¹¹⁸

¹¹² *Id.* at 8-9.

¹¹³ FDA, *Review of Amended Request for Orphan Drug Designation for sodium oxybate, DRU-2016-5302* at 4-6 (Dec. 21, 2017). The standard for ODD is a “plausible hypothesis” that the subsequent drug may be clinically superior to the first drug. When FDA grants ODD to a drug that is otherwise the same drug as a previously approved drug for the same rare disease or condition based on a plausible hypothesis of clinical superiority, that means FDA agrees that the sponsor “may be able to produce a clinically superior drug,” not that the sponsor has provided evidence that its drug in fact would be clinically superior. *See* 1991 Proposed Rule, 56 Fed. Reg. at 3340. This is a lower standard than is required to demonstrate clinical superiority for the purposes of determining whether a drug’s ODE blocks approval of another drug or determining eligibility for ODE.

¹¹⁴ Letter from Debra Y. Lewis to The Weinberg Group Inc., *Designation letter for sodium oxybate, DRU-2016-5302* (Jan. 8, 2018). *See also supra* note 84.

¹¹⁵ Letter from Teresa Buracchio to Marla E. Scarola, *Tentative Approval Letter* (Jul. 18, 2022).

¹¹⁶ Section 527(a) of the FD&C Act; 21 CFR §§ 316.31 & 316.3(b)(14).

¹¹⁷ 21 CFR § 316.3(b)(14).

¹¹⁸ Jazz asserts that for FDA to approve Lumryz, Lumryz must be clinically superior to Xywav. *See* Sidley Letter, *supra* note 12, at 5-8. We agree with this conclusion but note that Jazz at one point appears to arrive at this conclusion based on an incorrect interpretation of the law, citing to section 527(c) of the FD&C Act (the condition of clinical superiority to be eligible for ODE) as an exception to ODE. *See, e.g., id.* at 7 (“Thus, section 527(c)(1) provides that a later-in-time applicant can break through unexpired exclusivity (or obtain new exclusivity) only by demonstrating that its proposed drug will be ‘clinically superior to *any already approved or licensed drug that is the same drug.*’ 21 U.S.C. § 360cc(c)(1) . . .”). Later, Jazz changed its position during the meeting between Sidley and OCC. *See* Sidley Slides, *supra* note 13, at 10 (stating that section 527(c) cannot be read as a third exception to ODE

Avadel is not seeking approval for Lumryz for an indication covered by Xyrem’s unexpired ODE.¹¹⁹ Upon approval, in order to be eligible for its own term of ODE, an orphan-designated drug must be clinically superior to all otherwise same drugs previously approved for the same use or indication.¹²⁰ Accordingly, if Lumryz is clinically superior to Xywav and Xyrem, then it will be eligible for its own term of ODE.

i. Clinical superiority can overcome ODE

As explained above, the definition of “same drug” in the orphan-drug regulations states that if a subsequent drug that has the same active moiety and is for the same use as a previously approved drug “can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.”¹²¹ Accordingly, if a subsequent drug is clinically superior to a drug with ODE that has the same active moiety and is for the same indication or use, approval of the subsequent drug is not blocked by that drug’s ODE. Jazz provides three arguments why FDA cannot apply the definition of “same drug” here to determine that Lumryz is a different drug than Xywav, and thus not blocked by Xywav’s ODE.

First, Jazz argues that *Depomed* and *Eagle* struck down FDA’s definition of “same drug.”¹²² As a threshold matter, *Depomed* and *Eagle* concerned a different set of facts and a distinct legal issue. Those cases addressed FDA’s authority to require a demonstration of clinical superiority as a condition for eligibility for ODE prior to the addition of section 527(c) to the FD&C Act. Jazz acknowledges this, stating, “Section 527(c) thus addresses the specific factual scenario at issue in *Depomed*, *Eagle*, and *United Therapeutics* by providing that subsequent periods of ODE cannot be obtained without proof of clinical superiority.”¹²³ Thus, the holdings of these cases concern eligibility for ODE, not the scope of ODE (i.e., what ODE blocks). The district court in *Eagle Pharms* explicitly stated: “[t]he scope of Bendeka’s exclusivity is an issue that the FDA must determine in the first instance.”¹²⁴

and that section 527(c) addresses only serial grants of exclusivity). Section 527(c) only concerns potential eligibility of a subsequent drug (like Lumryz) for its own period of ODE; it does not address whether a subsequent drug’s (Lumryz’s) approval is blocked by Xywav’s ODE. See section II.B of document for further explanation.

¹¹⁹ Avadel is only seeking approval for the treatment of cataplexy or EDS in the adult population with narcolepsy, and Xyrem’s ODE only blocks approval of the same drug for the treatment of cataplexy or EDS in the pediatric population. Jazz acknowledges that “[. . .] the unexpired ODE for XYREM is not at issue (because Avadel’s proposed labeling omits pediatric use).” Sidley Slides, *supra* note 13, at 7.

¹²⁰ Section 527(c)(1) of the FD&C Act.

¹²¹ 21 CFR § 316.3(b)(14)(i); *see also* similar language in 316.3(b)(14)(ii).

¹²² Sidley Letter, *supra* note 12, at 6; *see also* Sidley Slides, *supra* note 13, at 14.

¹²³ Sidley Slides, *supra* note 13, at 10.

¹²⁴ *Eagle Pharms., Inc. v. Azar*, No. CV 16-790 (TJK), 2018 WL 3838223, at *3 (D.D.C. Aug. 1, 2018). *See also id.* at *2 (“But the Order did not adopt Eagle’s (or any other party’s) interpretation of the scope of Bendeka’s exclusivity.”); *id.* (“And as Defendants repeatedly and correctly assert, the scope of Bendeka’s exclusivity was not before the Court in this litigation. *See, e.g.,* Defs.’ Mot. at 7 (‘Eagle repeatedly emphasized that the scope of exclusivity for Bendeka was a separate issue from the existence of any such exclusivity, indicating that only the latter was properly before this Court.’). Rather, the issue was whether Bendeka should enjoy orphan-drug exclusivity at all. Accordingly, that was the only issue that the Court’s Opinion and Order addressed, as Defendants acknowledge. *See id.* at 2, 9; Defs.’ Reply at 2. And doing so did not require the Court to address whether Bendeka is the same drug as Treanda under either the FDA’s regulations or the statute.”). *See also* FDA, *Dear Applicants for*

Jazz nonetheless points to several quotations from the cases in looking for support, but these quotations do not speak directly to the situation at issue with Lumryz. The first quotation,¹²⁵ from the background section of the *Depomed* decision, simply describes how the definition of “same drug” “effectively limits the scope of exclusivity,” but neither *Depomed* nor *Eagle* addressed the scope of the plaintiffs’ exclusivity (i.e., whether approval of another sponsor’s drug was blocked by the plaintiffs’ exclusivity).¹²⁶ Jazz also quotes language in the *Depomed* decision stating, “This Court will not impute to Congress an intention to authorize an exception that Congress itself did not think worth enacting.”¹²⁷ However, the regulatory definition of “same drug” does not create an extra-statutory “exception” to ODE. As explained in section II.B above, under section 527(a), FDA may not approve another sponsor’s application for the same drug for the same use or indication as a drug with ODE.¹²⁸ Exceptions to ODE describe situations where FDA can nevertheless approve another sponsor’s application for the same drug for the same use or indication during a period of unexpired ODE.¹²⁹ Instead of creating such an exception to ODE where same drugs for the same indications or uses can be approved despite a drug’s unexpired ODE, the definition of “same drug” identifies certain drugs that are not the same (e.g., clinically superior drugs) and, in this context, helps clarify the scope of ODE once it has attached. When a subsequent drug that is otherwise the same drug (i.e., contains the same active moiety and is for the same use or indication) as a drug with unexpired ODE and is found to be clinically superior to that drug with unexpired ODE, then the subsequent drug is not the “same drug,” and the unexpired ODE cannot block approval of that drug under section 527(a) of the FD&C Act (because such ODE can only block same drugs for the same uses or indications).¹³⁰ That section 527(b) enumerates two exceptions to ODE does not undermine the

Certain Products Containing Bendamustine Letter, Docket No. FDA-2018-N-3773 (Feb. 20, 2019) (“FDA has . . . determined that the agency will continue to apply its existing ‘same drug’ regulation when determining the scope of Bendeka’s exclusivity (i.e., exclusivity prevents the approval of any other drug with the same active moiety (here, bendamustine) for the exclusivity-protected indications.”).

¹²⁵ Sidley Slides, *supra* note 13, at 14 (quoting *Depomed v. HHS*, 66 F. Supp. 3d 217 (D.D.C. 2014) (“FDA’s ‘insertion of the ‘same drug’ concept . . . effectively limits the scope of exclusivity protection because under the regulations, only if a new drug uses the same [active moiety] to treat the same disease or condition . . . and the new drug is also not found to be ‘clinically superior’ to the existing orphan drug will the FDA . . . forbid its marketing within the exclusivity period.”).

¹²⁶ *Depomed v. HHS*, 66 F. Supp. 3d 217 (D.D.C. 2014); *see also Eagle Pharms., Inc. v. Azar*, 952 F.3d 323 (D.C. Cir. 2020).

¹²⁷ Sidley Letter, *supra* note 12, at 6; *see also* Sidley Slides, *supra* note 13, at 14. Similarly, the Sidley Letter also later quotes from *Depomed*, “Where Congress explicitly enumerates certain exceptions to a general prohibition, additional exceptions are not to be implied.” Sidley Letter, *supra* note 12, at 8.

¹²⁸ Section 527(a) of the FD&C Act.

¹²⁹ The exceptions to 527(a) of the FD&C Act are enumerated in section 527(b).

¹³⁰ This distinction between an exception to ODE and a definitional exclusion from the term “same drug” is a meaningful one. The exceptions to ODE under section 527(b) set forth the circumstances under which FDA may approve an application even though it is for the same drug for the same indication or use as the drug that has ODE. Meanwhile, a subsequent drug that is clinically superior to the drug with ODE is simply not the same drug as the drug that has ODE and is therefore excluded from the scope of subsequent drugs that are blocked by that ODE. A standard illustration of this distinction, familiar to most law students, is the evidentiary rule against hearsay. Federal Rule of Evidence 802 provides that hearsay is generally inadmissible. Rules 801(c)-(d) exclude certain statements from the definition of hearsay: 801(c) limits hearsay to out-of-court statements offered for their truth, while 801(d) further specifies certain statements that are “not hearsay.” Meanwhile, Rules 803, 804, and 807 provide for certain exceptions to the rule against hearsay—statements that meet the definition of hearsay, but that are nevertheless not

agency's conclusion that a clinically superior drug is definitionally not the "same drug," and therefore its approval is not blocked by ODE.

Jazz also cites quotations from *Eagle* critiquing "FDA's imposition of its clinical-superiority requirement" and that FDA's "interpretation reads a limitation into the text that is not there."¹³¹ Again, *Eagle* concerned FDA's imposition of the condition of clinical superiority for a sponsor to be eligible for its own period of ODE, which is not at issue here. We have already recognized that Xywav is eligible for ODE. Xywav's ODE, however, only blocks approval of the same drug for the same indication or use.

Second, Jazz argues that the enactment of section 527(c) of the FD&C Act superseded and invalidated the regulatory definition of "same drug." Specifically, Jazz argues that the regulatory definition of "same drug" is inconsistent with section 527(c)(1), because the statute does not contain what Jazz refers to as the "'not-the-same' fiction."¹³² However, Jazz ignores crucial words in the statute. As explained above, Section 527(c)(1) requires a demonstration of clinical superiority when the sponsor of a drug is seeking ODE for "a drug that is designated under section 526 and *is otherwise the same*, as determined by the Secretary, as an already approved or licensed drug" for the same use or indication.¹³³ The orphan-drug regulations, which predate section 527(c)(1), use this same phrase; *see, e.g.*, 21 CFR § 316.3(b)(3) (stating "that a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is *otherwise the same drug*)" (emphasis added)); 21 CFR § 316.34(c) ("If a drug is *otherwise the same drug* as a previously approved drug for the same use or indication, FDA will not recognize orphan-drug exclusive approval if the sponsor fails to demonstrate upon approval that the drug is clinically superior to the previously approved drug." (emphasis added)); Congress legislated against this backdrop. Black's Law Dictionary defines "otherwise" as:

otherwise *adv.* (bef. 12c) **1.** In a different way; in another manner <David Berkowitz, otherwise known as Son of Sam>. **2.** By other causes or means <to succeed by hard work and otherwise>. **3.** In other conditions or circumstances <to know him otherwise than through law practice>. **4.** Except for what has just been mentioned <page 99 was illegible; otherwise, the records were easy to decipher>. **5.** Busy doing something else <she was otherwise engaged that day>. **6.** To the contrary; differently <although the economists say that legal markets are soft, many law-firm leaders think otherwise>. • The term *otherwise* tends to be quite broad in scope.

subject to the rule against hearsay. Exceptions to the rule against hearsay and exclusions from its definition are therefore addressed separately. The same is true here.

¹³¹ Sidley Letter, *supra* note 12, at 6; see also Sidley Slides, *supra* note 13, at 14.

¹³² Sidley Slides, *supra* note 13, at 15-16. *Id.* at 15 (arguing that "[t]he statute does not rely on any legal fiction and does not pretend that a clinically superior product is no longer 'the same' as prior drugs that contain the same active moiety; that '[i]nstead, the statute created a clinical superiority requirement that embraces 'sameness;' that "[p]ursuant to section 527(c)(1), a second or further period of ODE is conditioned on a demonstration that the proposed drug is 'clinically superior to any already approved or licensed drug that is the same drug;' and that "[p]er the statute XYWAV remains 'the same drug' as other oxybates even though it is clinically superior").

¹³³ Section 527(c)(1) of the FD&C Act (emphasis added).

These dictionary definitions make clear that “otherwise” connotes difference. By using the phrase “otherwise the same” the statute (and regulations) acknowledges that a clinically superior drug is not, in fact, considered to be the same as a previously approved drug. The orphan-drug regulations defining “same drug” state that “if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug,” which is entirely consistent with section 527(c)’s description of a clinical superior drug as one that is “otherwise the same” as (i.e., different than) a previously approved drug. FDA has previously considered whether the enactment of the FDARA provisions at section 527 conflicted with its regulations and concluded that “FDA’s current regulations are consistent with FDARA.”¹³⁴

Third, Jazz argues that allowing a clinically superior drug to overcome the ODE of an otherwise same drug goes against the intent of Congress and renders ODE meaningless.¹³⁵ FDA disagrees. As Jazz itself acknowledges, Congress expressed an interest in incentivizing the development of clinically superior products.¹³⁶ The ODE framework executes that intention in two ways: first, clinically superior drugs can be eligible for their own terms of ODE; second, clinically superior drugs can be approved during the ODE period for a drug that is otherwise the same as the clinically superior drug because they fall outside the scope of that drug’s ODE. Although ODE does not block as much as Jazz would prefer in this instance, that does not render ODE “meaningless.” Xywav’s ODE blocks FDA approval of all applications from other sponsors for the same drug for the same use or indication for seven years (subject to the exceptions in section 527(b)), a valuable benefit that is not just limited to blocking FDA’s approval of generic drugs referencing Xywav.

ii. MCTPC in Relation to Safety

As explained above, Lumryz may demonstrate clinical superiority to Xywav by showing that it provides a significant therapeutic advantage through greater effectiveness, greater safety, or by making a MCTPC. Doing so would render Lumryz a different drug than Xywav such that Xywav’s ODE would not block Lumryz’s approval. Importantly, as explained above, one drug can demonstrate a MCTPC over a previously approved drug even if the drug is not as effective or safe in every respect as the previously approved drug. Jazz tries to argue otherwise. Jazz claims that “longstanding FDA policy requires the second-in-time drug to achieve at least comparable safety as the earlier drug” in order to be clinically superior.¹³⁷ Additionally, Jazz claims that “to be eligible for clinical superiority a drug must also provide safety at least comparable to the approved drug” and that “a new drug that is less safe than an already approved orphan drug cannot be considered ‘clinically superior’ to the first drug.”¹³⁸ The same argument is also made in the Sidley Letter, which states, “clinical superiority cannot be demonstrated through tradeoffs—a later drug is not clinically superior if it sacrifices the safety or efficacy

¹³⁴ *Dear Applicants for Certain Products Containing Bendamustine Letter*, *supra* note 124. Jazz points to section 527(d) of the FD&C Act to suggest that the agency cannot apply its definition of “same drug” to interpret the statute and its regulations at Subpart D of Part 316. As noted here, FDA has previously considered this issue and concluded that FDA’s current regulations are consistent with FDARA.

¹³⁵ Sidley Letter, *supra* note 12, at 8; *see also* Sidley Slides, *supra* note 13, at 17.

¹³⁶ Sidley Slides, *supra* note 13, at 17.

¹³⁷ Jazz’s September 2021 Letter, *supra* note 11, at 1.

¹³⁸ *Id.* at 2.

achieved by its predecessors.”¹³⁹ In the Sidley Slides, Jazz relies on the words “over and above” in section 527(c)(2) to argue that clinical superiority requires “progress” and thus a drug cannot be clinically superior to a previously approved drug if it is also less safe than the previously approved drug. These assertions are not correct.

First, the words “over and above,” in the context of the statute and regulation at 21 CFR § 316.3(b)(3), cannot be read to mean a drug must be as safe as a previously approved drug to make a MCTPC. As explained in section II.C above, section 527(c)(2) of the FD&C Act defines clinically superior to mean that “the drug provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, *or* by providing a [MCTPC],” and 21 CFR § 316.3(b)(3) defines clinically superior to mean that “a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in *one or more* of the following ways:” greater effectiveness, greater safety, or a MCTPC (emphasis added). Jazz conveniently ignores the italicized statutory and regulatory language in these definitions. In both definitions, the subsequent drug must provide a significant therapeutic advantage “over and above” an already approved drug in just one way—greater efficacy, greater safety, *or* by providing a MCTPC—to be considered clinically superior. The plain reading of both the statute and the regulation does not impose an additional requirement that in order to provide a significant therapeutic advantage in one of the three measures, the drug must also be at least comparable in the other two measures. The relative effectiveness and safety of the drug may be relevant in assessing whether a drug makes a MCTPC, and a drug must meet FDA’s fundamental safety and effectiveness thresholds to obtain approval (see section II.D above), but nothing in the statute or regulation requires comparable effectiveness and safety in every respect.

In fact, in the 2011 proposed rule for amending the orphan-drug regulations, FDA proposed adding such a requirement to the regulation.¹⁴⁰ Specifically, FDA proposed adding that a demonstration of MCTPC must also include “a demonstration that the drug provides safety and effectiveness comparable to the approved drug.”¹⁴¹ In the 2013 final rule, however, FDA did not adopt that proposed change, so as not to create “a new standard” for MCTPC.¹⁴² Instead, FDA stated that MCTPC “determinations can be complex and encompass consideration of a number of factors that potentially implicate safety and effectiveness, which are evaluated on a case-by-case basis for each drug product.”¹⁴³

Jazz points to the 2011 proposed rule to argue that a “comparable safety showing” is “consistent with longstanding FDA policy.”¹⁴⁴ To the contrary, as discussed above, the final rule makes clear that requiring a showing of comparable safety and effectiveness for a MCTPC would create a “new standard.”¹⁴⁵ Jazz also claims that it “could find no precedent where FDA has endorsed a

¹³⁹ Sidley Letter, *supra* note 12, at 8-9; *see also* Sidley Slides, *supra* note 13, at 29.

¹⁴⁰ FDA, *Orphan Drug Regulations, Proposed Rule*, 76 Fed. Reg. 64868, 64871 (Oct. 19, 2011) [hereinafter 2011 Proposed Rule].

¹⁴¹ *Id.* at 64878.

¹⁴² 2013 Final Rule, 78 Fed. Reg. at 35124.

¹⁴³ *Id.*

¹⁴⁴ Jazz’s September 2021 Letter, *supra* note 11, at 2 footnote 4 (referencing 2011 Proposed Rule, 76 Fed. Reg. at 64876).

¹⁴⁵ 2013 Final Rule, 78 Fed. Reg. at 35124.

comparably effective but less safe product as clinically superior.”¹⁴⁶ However, more importantly, based on our review, agency precedent is devoid of instances in which we refused to find a MCTPC for a drug based on a failure to show comparable safety or efficacy.¹⁴⁷ As explained above, safety concerns could inform a MCTPC analysis, but a safety concern present in a subsequent drug that was not present in the previous drug would not automatically defeat a finding of MCTPC. That determination would be made on a case-by-case basis and depend upon the nature of the safety concern weighed against the benefits of the MCTPC. As described in detail in section II.C, FDA’s ODE determination regarding Rebif provides at least one instance where we found a drug to be clinically superior based on greater efficacy even though the drug was less safe in one measure than the previously approved drug with ODE. As noted above, Rebif patients experienced skin necrosis at injection sites that patients on a previously approved drug (Avonex) did not (i.e., the same adverse event that was present with the previously approved drug Betaseron that led to the determination that Avonex was clinically superior to Betaseron based on safety).¹⁴⁸ While this clinical superiority determination was not based on a MCTPC finding, the example nonetheless demonstrates that the agency does not require comparable safety and efficacy to be considered clinically superior.

Jazz claims that FDA’s clinical superiority analyses include an assessment of whether the subsequent drug is at least “not less safe than” the previously approved drug to support its assertion that “a new drug that is less safe than an already approved orphan drug cannot be considered ‘clinically superior’ to the first drug.”¹⁴⁹ To support these claims, Jazz cites examples where FDA considered whether a previously approved drug is at least not less safe.¹⁵⁰ As discussed below, although these examples discuss the relative safety of two drugs, they do not support a conclusion that a drug *must* be at least “not less safe” than an already approved drug to be clinically superior to that drug. FDA has considered whether a subsequent drug has comparable safety and efficacy to the previously approved drug as part of an overall assessment of whether the subsequent drug makes a MCTPC. For example, to reiterate what we said above, where certain adverse events associated with a change in administration raise safety concerns for a subsequent drug that are not present for a previous drug, FDA could consider such information to determine whether the safety concerns affect the agency’s finding that certain benefits of the drug create a MCTPC, but such safety concerns would not automatically lead FDA to deny the drug approval or exclusivity based on a finding that the drug was not clinically superior.

The specific examples provided by Jazz do not counsel otherwise. First, Jazz cites to OOPD’s statements, in determining that Revcovi (elapegademase-lvlr) is clinically superior to Adagen (pegademase bovine), that “OOPD does not need to determine whether Revcovi is in fact more safe than Adagen. Clinical superiority based on effectiveness has been demonstrated, and

¹⁴⁶ Jazz’s September 2021 Letter, *supra* note 11, at 1.

¹⁴⁷ We are aware of certain language in agency documents that could be interpreted as suggesting FDA has such a policy. As described further below, despite these statements, none of FDA’s past precedents that OOPD reviewed manifest application of such a policy upon approval when FDA is determining eligibility for ODE or when it is considering whether a drug may be approved in light of another sponsor’s ODE. Given the quantum of information suggesting otherwise, it is clear that those statements do not reflect such an agency policy.

¹⁴⁸ CBER Rebif memo, *supra* note 32, at 20.

¹⁴⁹ Jazz’s September 2021 Letter, *supra* note 11, at 2.

¹⁵⁰ *Id.* at 2 footnote 4; *see also* Sidley Slides, *supra* note 13, at 30.

Revcovi is at least not less safe than Adagen.”¹⁵¹ Revcovi and Adagen are both enzyme replacement therapies used to treat adenosine deaminase (“ADA”) deficiency in patients with severe combined immunodeficiency. Adagen is derived from a bovine source, while Revcovi is recombinant (i.e., made in a laboratory). OOPD determined that Revcovi is clinically superior to Adagen based on a consult with expert clinicians in the review division, who found that Revcovi is more effective as it provides more stable plasma ADA activity, more consistently above the therapeutic threshold associated with clinical benefit associated with long term survival.¹⁵² Because OOPD found Revcovi to be clinically superior based on greater efficacy, it did not need to determine if Revcovi also provided greater safety. Efficacy and safety are alternative prongs for clinical superiority. Nothing in OOPD’s reasoning suggests that the fact that Revcovi was “not less safe than Adagen” was a factor in OOPD’s finding of clinical superiority based on greater effectiveness or that if Revcovi had been less safe, then Revcovi could not have been found to be clinically superior. Nor do OOPD’s statements mean that FDA has a policy that in order to be clinically superior based on efficacy, a subsequent drug must also provide safety at least comparable to the previously approved drug.

Second, Jazz cites an ODD memo regarding a potential plausible hypothesis of clinical superiority of enteric-coated cysteamine (later named Procysbi (cysteamine bitartrate)) over another cysteamine product for the treatment of cystinosis.¹⁵³ Enteric-coated cysteamine had ODD for the treatment of cystinosis based on a plausible hypothesis that enteric-coated cysteamine may be clinically superior to the previously approved cysteamine product for the same disease based on safety by causing less nausea and vomiting.¹⁵⁴ Note that at the time of the cited memo, OOPD was not conducting an analysis of whether the sponsor had, in fact, demonstrated clinical superiority. The memo responded to a June 23, 2008, letter from the sponsor asking to update the hypothesis that was the basis of the ODD.¹⁵⁵ OOPD reviewed this request, and in the memo cited by Jazz, explained that OOPD assesses MCTPC “individually” (on a case-by-case basis) and considers factors including “the nature of the orphan indication, course of treatment for the indication, and benefits that could be obtained from the new product.”¹⁵⁶ The memo then states, as cited by Jazz, “Inherent in this analysis is the general assumption that changes in drug administration would maintain a similar or improved adverse event profile and similar efficacy.”¹⁵⁷ As explained below, this statement is consistent with and reflects the MCTPC standard we described above.

At the ODD stage, as is the case in the Procysbi memo, FDA does not have full safety, efficacy, and other data for the drug necessary to make a definitive determination about clinical

¹⁵¹ Jazz’s September 2021 Letter, *supra* note 11, at 2 footnote 4.

¹⁵² FDA, *Exclusivity Memorandum, DRU-2014-4675, Revcovi (elapegademase-lvlr)* at 3 (Oct. 14, 2020).

¹⁵³ Jazz’s September 2021 Letter, *supra* note 11, at 2 footnote 4; *see also* Sidley Slides, *supra* note 13, at 30.

¹⁵⁴ FDA, Review of Request for ODD for enteric-coated cysteamine, DRU-2006-2310 (Oct. 10, 2006) [hereinafter Procysbi Designation Memo].

¹⁵⁵ Letter from Ted Daley to Timothy Cote, *Orphan Drug Exclusivity Determination for Delayed-release Cysteamine Bitartrate Capsules (i.e., enteric-coated beads) for Treatment of Cystinosis, DRU-2006-2310* (Jun. 23, 2008). Note that there is no requirement for a sponsor to update the hypothesis of clinical superiority upon which an ODD is based. This sponsor seemingly wanted to know if OOPD would accept the hypothesis for clinical superiority as it anticipated later submitting a marketing application for which it wanted ODE.

¹⁵⁶ FDA, *Memorandum, Request for OOPD Opinion, DRU-2006-2310* (Mar. 3, 2009) [hereinafter Procysbi 2009 memo].

¹⁵⁷ *Id.*

superiority; therefore, for the plausible hypothesis analysis at the ODD stage, unless a safety or efficacy concern is readily apparent to the agency absent receipt of safety and efficacy data in the sponsor's application for approval, we generally assume that the drug provides comparable safety and efficacy.¹⁵⁸ At the approval stage, once such safety and efficacy data about the drug has been submitted in an application for marketing approval, that general assumption may or may not still apply, depending on what the submitted data shows. As we stated above, FDA may consider whether, for example, any adverse events documented within the drug's safety data submitted in its application for approval diminish the advantages of, for example, a change in route or frequency of administration. In that respect, as explained above, safety concerns could inform the MCTPC analysis, but a safety concern present in a subsequent drug that was not present in the previous drug would not automatically disqualify the drug from obtaining a MCTPC finding. As stated above, clinical superiority analyses can "vary depending on many factors"¹⁵⁹ and MCTPC "implies a more global assessment."¹⁶⁰

In the case of Procysbi, upon approval, FDA found that Procysbi was clinically superior to the previously approved cysteamine product Cystagon based upon a MCTPC finding. The reviewer noted that the safety profile for Procysbi and Cystagon were similar "although a higher incidence of GI AEs were observed in the pivotal trial with delayed-release cysteamine in comparison to Cystagon."¹⁶¹ If anything, this example shows that FDA has made a MCTPC finding upon approval where a drug was potentially less safe in at least one respect than the previously approved drug.

Third, Jazz cites to a memo about the clinical superiority of BeneFix (coagulation factor IX (recombinant)) based on safety to previously approved factor IX products for the prevention of bleeding in hemophilia B.¹⁶² The memo considers whether a demonstration of greater safety under 21 CFR § 316.3(b)(3)(ii) requires a demonstration of a single safety advantage without regard for other safety considerations, or a demonstration of an overall increase in safety considering all aspects of safety.¹⁶³ The memo does not conclude which standard is applicable, but finds that BeneFix provides greater safety under both standards.¹⁶⁴ Each of the quotations

¹⁵⁸ Jazz also cites to FDA's review of a request for ODD for Ravicti as another example of a requirement for comparable safety. See Sidley Slides, *supra* note 13, at 30. This is another example of FDA considering whether there is a plausible hypothesis of clinical superiority, not a demonstration of clinical superiority. In this example, FDA was concerned that the sponsor did not adequately explain why the new dosage form would represent a significant advantage over the previous dosage form, and FDA was concerned that the new dosage form could introduce new safety risks that were not accounted for in the sponsor's hypothesis. See FDA, *Review of Request for Orphan-Drug Designation*, 05-2035, Glycerol tri(4-phenylbutyrate) at 4 (Sep. 2, 2005) ("[I]t is unclear whether the glycerol byproduct of GT4P metabolism would pose its own safety risk in chronic use of the drug."). Thus, a safety concern was readily apparent to the agency at the designation stage absent receipt of safety data in the sponsor's application for approval. Without additional information about the potential safety of the drug and without additional information about the advantages of the drug, FDA was unable to determine there was a plausibly hypothesis of clinical superiority that would warrant ODE.

¹⁵⁹ 1992 Final Rule, 57 Fed. Reg. at 62078.

¹⁶⁰ OOPD Rebif memo, *supra* note 36, at 3.

¹⁶¹ FDA, *Review of an Amended Request for Orphan Drug Designation, 2006-2310, Procysbi (enteric-coated cysteamine)* at 6 (May 28, 2013) [hereinafter Procysbi Exclusivity Memo].

¹⁶² Jazz's September 2021 Letter, *supra* note 11, at 2 footnote 4.

¹⁶³ FDA, *Memorandum, Orphan Product Status of BeneFix Coagulation Factor IX (Recombinant)* (Jan. 21, 1997) [hereinafter "BeneFix memo"].

¹⁶⁴ *Id.*

that Jazz cites are in the context of considering whether one safety advantage needs to be compared to safety concerns in order to make an assessment about greater safety under 21 CFR § 316.3(b)(3)(ii). This is a different question than whether a drug can be clinically superior overall if it is less safe in one respect than the previously approved drug. The first quotation (i.e., “A significant risk associated with the new drug, that is not shared by the approved orphan, would likely render the new drug unapprovable”) is making the obvious point that significant new safety risks inform FDA’s evaluation of the fundamental safety of a drug for marketing approval under section 505 of the FD&C Act. The other two quotations (i.e., “it would be unreasonable to ignore an apparent risk that may outweigh the purported advantage of a new drug,” and “[s]ince there is no established risk to ‘outweigh’ the enhanced viral safety of BeneFix, the significant therapeutic advantage of BeneFix has not been outweighed by anything”) describe a situation where a safety risk associated with the subsequent drug would need to be considered in an overall assessment of safety, but not necessarily prevent a finding of greater safety. These quotations do not support Jazz’s position.

Fourth, Jazz cites FDA’s determination that Signifor LAR (pasireotide)—a “long-acting release” formulation—made a MCTPC by providing once-per-month dosing as compared to twice-per-day pasireotide to treat Cushing’s disease.¹⁶⁵ Specifically, Jazz cites to the statement that “[t]here are no notable differences in the safety and efficacy profiles between the immediate release and long-acting formulations.”¹⁶⁶ Again, stating that there are no notable differences in safety is not the same as stating that if Signifor LAR were less safe then it could not make a MCTPC. The exclusivity memorandum for Signifor LAR does not state that having comparable safety was a requirement to finding a MCTPC.¹⁶⁷

Overall, none of these examples support that FDA will consider a new drug to be clinically superior to a previously approved drug only if the new drug is at least as safe as the previously approved drug.

Finally, Jazz tries to argue from a policy perspective that finding clinical superiority based on one significant advantage to patients even if the drug is less safe in some other measure would undermine the value of the ODE incentive.¹⁶⁸ FDA disagrees. FDA interprets the purpose of the Orphan Drug Act to incentivize the development of better versions of drugs for the treatment or prevention of rare diseases or conditions. FDA believes that a drug may provide a significant therapeutic advantage to patients over a previously approved drug even if, for example, it is less safe in one measure than the previously approved drug. If new drugs were required to be at least as safe as the previously approved drugs, that would prevent a drug that provides a significant therapeutic advantage and otherwise meets FDA’s approval standard from coming to the market during the duration of the previously approved drug’s ODE. Implementing ODE requires balancing the need to incentivize the development of drugs for rare diseases or conditions and the need for patients to access better versions of such drugs. Requiring comparable safety on

¹⁶⁵ Sidley Slides, *supra* note 13, at 30.

¹⁶⁶ *Id.* (quoting clinical superiority findings available at <https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings>).

¹⁶⁷ FDA, *Exclusivity Memorandum*, 09-2887 Signifor LAR (Apr. 3, 2019) [*hereinafter* Signifor Exclusivity Memo].

¹⁶⁸ Jazz’s September 2021 Letter, *supra* note 11, at 20. *See also id.* at 1 (“Because the concept of clinical superiority does not include regression, longstanding FDA policy requires the second-in-time drug to achieve at least comparable safety as the earlier drug”).

every measure before a drug can be found to be clinically superior would be an arbitrarily rigid requirement that would significantly delay approval of drugs with important therapeutic advantages for patients with rare diseases.

FDA has adopted a more nuanced approach to clinical superiority, where a potential MCTPC is considered in the overall context of the safety, efficacy, and other features of the drug to determine if there is an overall significant therapeutic advantage of the new drug. As FDA has stated, MCTPC “determinations can be complex and encompass consideration of a number of factors that potentially implicate safety and effectiveness, which are evaluated on a case-by-case basis for each drug product.”¹⁶⁹ Improvements to drugs are not necessarily linear, where every version of a drug builds off and is better in every respect than the one that came before. An improvement in one respect may benefit patients, even if there is a disadvantage in another aspect of the drug. As FDA has stated, “there can not [sic] be an infinite number of comparison criteria if this provision of the regulation is to be meaningful.”¹⁷⁰ That is not to say that a small advantage provided by a new drug should overcome a large disadvantage also introduced by the drug; however, it would not serve the purpose of the Orphan Drug Act—and public health—if a drug were automatically disqualified from being clinically superior if it were less safe in one regard, while still meeting FDA’s approval standards for safety.

B. Lumryz is Clinically Superior to Xyrem and Xywav

Avadel has not contended that Lumryz has greater effectiveness than Xyrem and Xywav, and DN1 has concluded that “[t]here is no evidence suggesting that the efficacy of Lumryz is different from that of Xyrem or Xywav.”¹⁷¹ Avadel did present arguments why it believes that Lumryz provides greater safety than Xyrem and Xywav,¹⁷² but OOPD concludes that Avadel has not demonstrated that Lumryz provides greater safety than either Xyrem or Xywav.¹⁷³ DN1 has also concluded that Avadel’s arguments do not support a finding of greater safety of Lumryz over either Xyrem or Xywav.¹⁷⁴ Because Avadel has not demonstrated either greater effectiveness or greater safety, Lumryz can be deemed to be clinically superior over Xyrem and Xywav only if Lumryz makes a MCTPC over the previously approved drugs.¹⁷⁵ As explained below, FDA concludes that Lumryz makes a MCTPC over Xyrem and Xywav.

Based on a review of the arguments submitted by Avadel and Jazz, consultation with DN1,¹⁷⁶ and consultation with two board certified sleep experts in FDA,¹⁷⁷ OOPD finds that Lumryz makes a MCTPC over Xyrem and Xywav by providing a once-nightly dosing regimen that

¹⁶⁹ 2013 Final Rule, 78 Fed. Reg. at 35124.

¹⁷⁰ See OOPD Rebif memo, *supra* note 36, at 3 (emphasis added).

¹⁷¹ DN1 Lumryz Consult, *supra* note 5, at 3. There has been no head-to-head study to directly compare Lumryz to Xyrem or Xywav.

¹⁷² See Avadel’s Exclusivity Claim, *supra* note 6; see also Avadel’s Exclusivity Claim Supplement, *supra* note 7.

¹⁷³ For the purposes of this analysis, OOPD will not include a response to each of Avadel’s claims of greater safety. OOPD ultimately finds Lumryz to be clinically superior to Xyrem and Xywav based on making a MCTPC, and Avadel’s arguments about greater safety do not factor into the MCTPC finding.

¹⁷⁴ DN1 Lumryz Consult, *supra* note 5, at 3.

¹⁷⁵ 21 CFR § 316.3(b)(3)(iii).

¹⁷⁶ DN1 Lumryz Consult, *supra* note 5.

¹⁷⁷ See Sleep Expert Consult, *supra* note 5.

avoids a nocturnal arousal to take a second dose. Crucial to this finding is that the three oxybate products are for the treatment of symptoms of narcolepsy—a chronic sleep disorder. The purpose of oxybate treatment is to consolidate a narcoleptic’s sleep to improve daytime symptoms of EDS and cataplexy.¹⁷⁸ As explained in more detail below, waking up to take a second dose of Xyrem and Xywav is antithetical to the goal of improving sleep. This is compounded by the fact that narcolepsy is a chronic condition and patients may need treatment for the remainder of their lives.

As explained by FDA’s sleep experts in greater detail in their consult, even with a single nocturnal arousal, there can be impairment of alertness and decline in cognitive performance the following day.¹⁷⁹ It is known that disrupting sleep, even briefly, changes sleep architecture—the normal pattern of NREM and REM cycles requisite for daily restoration.¹⁸⁰ As explained in section III.A of this document and by FDA’s sleep experts, when an arousal occurs (e.g., when waking up to take medication during the night after falling asleep), there is a shift in an EEG pattern—one that leads to a longer Stage W with alertness or consciousness, even if not remembered.¹⁸¹ The duration of time in Stage W necessary to take the second dose and fall back asleep is prolonged and will adversely impact WASO.¹⁸² In treating sleep disorders, including narcolepsy, the goal is to maximize the time in sleep and minimize wake time (i.e., minimize WASO).¹⁸³ Hence, nocturnal arousals should be avoided—especially in those with sleep disorders—as the goal of treatment is to restore normal sleep architecture.¹⁸⁴

Xyrem and Xywav are administered in two divided doses, with the first dose taken at bedtime and second dose taken 2.5 to 4 hours later. FDA’s sleep experts have concluded that awakening to take a second dose of Xyrem or Xywav is not optimally supportive of the continual sleep necessary for narcolepsy patients to restore sleep architecture and daytime alertness with more normal functioning.¹⁸⁵ Such dosing necessitates awakening from sleep, prompting a nocturnal arousal.¹⁸⁶ Both Xyrem and Xywav labeling explain that after a dose, it usually takes at least 5 to 15 minutes to fall asleep, which means it usually takes at least 5 to 15 minutes to fall back asleep after taking the second dose.¹⁸⁷ Awakening to take a second dose necessarily disrupts sleep and causes fragmented sleep.¹⁸⁸ A person with disrupted sleep cannot simply return to sleep and resume their normal sleep cycle.¹⁸⁹ Disruption of sleep leads to the inability to enter Stage N3, or disruption of N3, and such individuals will revert back to Stage W and subsequently progress to Stage N1 sleep and so forth.¹⁹⁰ So, upon taking a second dose of Xyrem or Xywav,

¹⁷⁸ Scammell, *Treatment*, *supra* note 77.

¹⁷⁹ See Sleep Expert Consult, *supra* note 5, at 7-8; see also Cirelli, *supra* note 46.

¹⁸⁰ Sleep Expert Consult, *supra* note 5, at 8; see also Philip, *supra* note 61, at 244-245.

¹⁸¹ Kirsch, *supra* note 48; see also Philip, *supra* note 61, at 244-245.

¹⁸² Sleep Expert Consult, *supra* note 5, at 5; see also Suni, *supra* note 62.

¹⁸³ Sleep Expert Consult, *supra* note 5, at 5.

¹⁸⁴ *Id.* at 6; see also Scammell, *Treatment*, *supra* note 77.

¹⁸⁵ See Sleep Expert Consult, *supra* note 5, at 7.

¹⁸⁶ *Id.* at 7 footnote 45 (“It is self-evident that an arousal occurs upon taking the second dose of Xyrem or Xywav because some degree of consciousness or alertness is needed for the voluntary movements involved in taking medicine”).

¹⁸⁷ Xyrem 2023 Labeling, *supra* note 86, at section 2.3; Xywav 2023 Labeling, *supra* note 93, at section 2.4.

¹⁸⁸ Sleep Expert Consult, *supra* note 5, at 5.

¹⁸⁹ Sleep Expert Consult, *supra* note 5, at 8.

¹⁹⁰ *Id.* at 6; see also Berry *supra* note 64, at 22-33.

after the minimum 5-15 minutes to return to sleep, such sleep does not resume where the patient left off to take their medication.¹⁹¹ If patients do not intentionally awaken to take the second dose (e.g., by setting an alarm), the effect of the drug will wear off, and the patients may awaken anyway and need the second dosing to return to sleep.¹⁹² As explained above, the disruption changes sleep architecture and will increase WASO and is something to be avoided in the narcoleptic patient, if possible.¹⁹³

In contrast to Xyrem and Xywav, Lumryz is an extended-release formulation that is indicated to be administered once daily at bedtime. Importantly, patients on Lumryz do not need to wake mid-sleep to take a second dose. The dosing regimen of Lumryz “provides an opportunity for narcolepsy patients to achieve normal sleep architecture, which is not a possibility for a patient on Xyrem or Xywav who must either wake up to take a second dose (disrupting sleep architecture) or allow the drug to wear off after 2.5-4 hours (reverting patients back to their naturally occurring, disrupted sleep architecture).”¹⁹⁴ This is medically relevant because the purpose of oxybate therapy is to improve sleep consolidation.¹⁹⁵ Additionally, the benefit provided by the dosing regimen of Lumryz is germane to several of the factors that FDA may consider when determining if a drug makes a MCTPC.¹⁹⁶ Lumryz’s extended release properties provide for longer periods between doses, which is significant not only because it reduces the nightly number of doses from two to one but also because it eliminates the need to awaken in the middle of sleep to take a second dose. FDA considers this to be significantly more convenient for patients, an advancement in the ease of drug administration, and a reduction in treatment burden. As explained by FDA’s sleep experts, patients taking Xyrem and Xywav typically prepare both doses before bed, may need to set an alarm to wake up at the proper time to take the second dose, and then may require 5-15 or more minutes to return to sleep. Aside from the medical benefits of not having to awaken to take a second dose already explained above, it is inherently more convenient, easier, and less burdensome for patients to forgo that process on a nightly basis. Importantly, this is in the context of a chronic neurological condition that requires potentially lifelong treatment.

i. MCTPC Finding Consistent with Past Precedent

Our basis for finding a MCTPC for Lumryz is similar to FDA’s MCTPC finding for Procysbi. As introduced above, Procysbi is an enteric-coated cysteamine product that has ODD for the treatment of cystinosis. The ODD was based in part on a plausible hypothesis that enteric-coated cysteamine would be clinically superior to the previously approved cysteamine product, Cystagon, for the same disease based on safety by causing less nausea and vomiting.¹⁹⁷ Procysbi

¹⁹¹ Sleep Expert Consult, *supra* note 5, at 8.

¹⁹² *Id.* at 7.

¹⁹³ *Id.* at 6.

¹⁹⁴ *Id.* at 8.

¹⁹⁵ Scammell, *Treatment*, *supra* note 77.

¹⁹⁶ *See, e.g.*, 2013 Final Rule, 78 Fed. Reg. at 35125 (“The following factors, when applicable to severe or life-threatening diseases, may in appropriate cases be taken into consideration when determining whether a drug makes a major contribution to patient care: convenient treatment location; duration of treatment; patient comfort; reduced treatment burden; advances in ease and comfort of drug administration; longer periods between doses; and potential for self-administration”).

¹⁹⁷ Procysbi Designation Memo, *supra* note 154.

was first approved on April 20, 2013, and to be eligible for ODE, FDA required a demonstration of clinical superiority over Cystagon. Cystagon was labeled to be dosed every six hours, whereas Procysbi was labeled to be dosed every 12 hours (a reduction of 50%).¹⁹⁸ By requiring dosing every six hours, patients taking Cystagon would be required to awaken from sleep to take a dose in order to administer the drug as labeled.¹⁹⁹ FDA concluded that many patients taking Cystagon were unable to follow the strict six-hour-dosing schedule, and that strict six-hour-dosing was required for the drug to be clinically beneficial (by maintaining white blood cell cystine levels below 1.0 nmol/½ cystine/mg protein).²⁰⁰ FDA found that Procysbi made a MCTPC over Cystagon, because Procysbi is effective at 12-hour-dosing, and many patients are unable to follow Cystagon's strict six-hour-dosing, especially due to the need to awaken from sleep to ensure a timely dose.²⁰¹ Similar to Procysbi, Lumryz provides for 50% reduction in dosing frequency that eliminates the need to awaken to take a dose in order to achieve the medication's intended benefit.

ii. Consideration of Sodium Differences

OOPD has also considered whether other relevant factors inform whether Lumryz makes a MCTPC over Xyrem and Xywav.²⁰² Specifically, we considered the sodium differences between Lumryz and Xywav. At the recommended daily dose of 6 g to 9 g, Lumryz contains approximately 1,100 mg to 1,640 mg of sodium whereas Xywav contains 87 mg to 131 mg.

At the recommended daily dose of 6 g to 9 g, Xyrem and Lumryz both have the same sodium content (approximately 1,100 mg to 1,640 mg). The difference in sodium content between Xywav and Xyrem was explained in a DN1 consult for OOPD's Xywav ODE determination:

Given the differences in sodium content between Xywav and Xyrem, Xywav is safer and thus clinically superior to Xyrem in the following: all patients with narcolepsy; the substantial proportion of the narcolepsy population that is salt-sensitive (i.e., individuals who have greater changes in blood pressure with changes in salt intake than those who are not salt sensitive, representing about 50% of the general population); the substantial proportion of the narcolepsy population that is hypertensive (about 30% of the general population is hypertensive); and the substantial proportion of the narcolepsy population (39%) who cannot be prescribed Xyrem due to co-existing medical conditions that can be made worse as a result of the high sodium content of Xyrem.²⁰³

This division consult also states:

¹⁹⁸ Procysbi Exclusivity Memo, *supra* note 161, at 9-10.

¹⁹⁹ *Id.* at 5.

²⁰⁰ *Id.* at 9.

²⁰¹ *Id.* at 10. The reviewer also observed that the safety profile for Procysbi and Cystagon were similar "although a higher incidence of GI AEs were observed in the pivotal trial with delayed-release cysteamine in comparison to Cystagon." *Id.* at 6. The clinical superiority finding for Procysbi reflects multiple MCTPC factors, such as longer period between doses, increased ease of administration, and reduced treatment burden.

²⁰² See OOPD Rebif memo, *supra* note 36, at 3 ("an assessment of the safety or effectiveness of the new form of the subsequent product might be considered in determining whether the drug made a major contribution to patient care").

²⁰³ DN1 2020 Xywav Consult, *supra* note 99, at 6.

The relationship between daily salt intake and cardiovascular morbidity is widely accepted, as is the need for salt intake to be generally restricted and not only in subjects with conditions such as hypertension, cardiac failure, and impaired renal function. The difference in sodium content between Xywav and Xyrem is both substantial and clinically meaningful when daily sodium intake requires restriction in patients who concomitantly have conditions such as cardiac failure, hypertension, and renal impairment. Xywav rather than Xyrem will be the medication of choice in such patients. Such patients, especially those with hypertension, may constitute a significant proportion of those with cataplexy and excessive daytime sleepiness in narcolepsy. The difference in sodium content between Xywav and Xyrem is also very likely to be clinically meaningful in all patients with narcolepsy, including those who are salt sensitive.²⁰⁴

OOPD found Xywav to be clinically superior (within the meaning of the orphan-drug regulations) to Xyrem because the reduction of sodium “will be clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated.”²⁰⁵

OOPD acknowledges that the sodium content of Lumryz raises the same safety concern that was present for Xyrem and that is not present with Xywav. The agency stated in the consult response quoted above that the difference in sodium content between Xywav and Xyrem is “very likely to be clinically meaningful in all patients with narcolepsy”²⁰⁶ and that “[g]iven the differences in sodium content between Xywav and Xyrem, Xywav is safer and thus clinically superior to Xyrem in [. . .] all patients with narcolepsy.”²⁰⁷ The logic of these statements, if extended here, would mean that the difference in sodium content between Xywav and Lumryz is likely to be clinically meaningful in all patients with narcolepsy and that Xywav is safer than Lumryz in all such patients, albeit based solely on one specific measure, i.e., reduced sodium. Nonetheless, FDA has concluded that Lumryz is clinically superior to Xywav as a MCTPC given the benefit of Lumryz’s once-nightly dosing despite Xywav’s greater safety due to reduced sodium. First, as explained above, there is no requirement for comparable safety when making a MCTPC finding, and finding clinical superiority based on one parameter — greater safety, greater efficacy, or a MCTPC — is sufficient to meet the clinical superiority standard.²⁰⁸ Second, for the reasons explained below, we believe that the benefit of Lumryz’s once-nightly dosing outweighs the safety concern raised by its increased sodium content for a substantial number of narcolepsy patients. Neither the statute nor regulations require a MCTPC to benefit the entire patient population for which a drug is intended.

Although it is widely accepted that individuals should limit sodium intake generally, the warning in Lumryz’s labeling regarding sodium is directed only at “patients sensitive to sodium intake”

²⁰⁴ *Id.* at 9-10.

²⁰⁵ FDA, Clinical Superiority Findings, available at <https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings>.

²⁰⁶ DN1 2020 Xywav Consult, *supra* note 99, at 10.

²⁰⁷ *Id.* at 6.

²⁰⁸ As OOPD stated in the Rebif example above, for one drug to be clinically superior in one parameter, it does not also need to be at least equal in all others. See OOPD Rebif memo, *supra* note 36, at 3.

such as “those with heart failure, hypertension, or renal impairment.”²⁰⁹ For narcolepsy patients who are not sensitive to sodium intake, OOPD concludes that a once-nightly dosed oxybate drug will provide a significant therapeutic advantage. It is true that patients who are not sensitive to sodium could also benefit from a reduction in sodium, but we consider the benefit offered by once-nightly dosing to outweigh the risk of increased sodium intake in such patients because having to wake up to take a second dose is antithetical to oxybate’s goal of improving sleep; disrupting sleep contributes to chronic sleep loss, which is well known to cause reduced performance, increased risk for accidents and death, and detrimental effects on both psychological and physical health; and there are other ways such patients may reduce sodium in their diet.²¹⁰ For narcolepsy patients who are sensitive to sodium, healthcare practitioners would need to weigh the benefits of once-nightly dosing against the severity of the patient’s sodium sensitivity and the nature of their comorbidities to determine whether, in the practitioners’ judgment, use of Lumryz or Xywav was appropriate. For certain sodium-sensitive patients with narcolepsy, the benefit offered by once-nightly dosing would outweigh the risk of increased sodium intake for the same reasons (e.g., having to wake up to take a second dose is antithetical to oxybate’s goal of improving sleep; disrupting sleep contributes to chronic sleep loss, which is well known to cause reduced performance, increased risk for accidents and death, and detrimental effects on both psychological and physical health; and there are other ways such patients may reduce sodium in their diet).²¹¹

For a drug to make a MCTPC, the drug should provide adequate safety to meet the approval standard (not necessarily the same or greater safety as a previously approved drug). FDA has weighed the benefits and the risks of Lumryz and determined that the safety profile is adequate to meet the requirements for marketing approval.²¹² Thus, although Lumryz has an increased sodium burden compared to Xywav, the safety risk from such an increase is not significant enough to preclude Lumryz from meeting the requirements for marketing approval. The safety risk associated with sodium for Lumryz is mitigated by labeling with an appropriate warning and precaution for patients sensitive to high sodium intake,²¹³ as has been done for Xyrem.²¹⁴

In summary, OOPD concludes that the benefits of Lumryz’s once-nightly dosing rise to the level of making a MCTPC because Lumryz’s dosing provides for oxybate therapy that does not involve disrupting or fragmenting sleep, whereas Xyrem and Xywav necessitate a nocturnal awakening to take a second dose, which disrupts sleep architecture in patients with known sleep

²⁰⁹ Lumryz labeling, *supra* note 105, at section 5.8.

²¹⁰ Sleep Expert Consult, *supra* note 5, at 2. Jazz argues that approving Lumryz would undermine FDA’s policy regarding the benefits of reducing daily sodium intake. Jazz’s September 2021 Letter, *supra* note 11, at 20. FDA acknowledges the importance of reducing sodium intake generally, and this determination does not erode that stance merely because we have concluded that sodium can be reduced by other means for patients who would benefit from taking this drug.

²¹¹ We note that the DN1 Lumryz Consult explains that “the available safety data for Lumryz do not indicate that the higher sodium content of each dose of that drug is reflected in a greater incidence of adverse events than is observed with equivalent doses of Xywav.” DN1 Lumryz Consult, *supra* note 5, at 3.

²¹² DN1 Lumryz Consult, *supra* note 5, at 3 (“the safety profile of Lumryz meets the Agency’s standards for approval.”). *See also* OOPD Rebif memo, *supra* note 36, at 3 (“A more meaningful standard is a significant therapeutic benefit in terms of increased effectiveness and adequate safety, or increased safety and adequate effectiveness.”).

²¹³ *See* Lumryz Labeling, *supra* note 105, at section 5.8.

²¹⁴ *See* Xyrem 2023 Labeling, *supra* note 86, at section 5.8.

disorder. This decision is based on consultations with DN1 and FDA sleep experts and relies on the scientific understanding about treating narcolepsy by minimizing nocturnal arousals and consolidating sleep. OOPD believes that the science supports a finding that the MCTPC provided by Lumryz over Xyrem and Xywav has been demonstrated.

V. Jazz's Arguments Are Not Persuasive

A. Safety

Jazz argues that Lumryz does not provide greater safety than Xyrem and Xywav and is less safe than Xyrem and Xywav in several ways.²¹⁵ As explained above, OOPD's determination that Lumryz is clinically superior to Xyrem and Xywav is not based on Lumryz providing greater safety than Xyrem and Xywav. Therefore, OOPD has not responded to each safety argument from Jazz.²¹⁶ In addition, OOPD has acknowledged above that Lumryz has a higher sodium content than Xywav and addressed why Lumryz is still clinically superior to Xywav. Finally, as explained below, OOPD is not convinced by Jazz's remaining arguments that there are additional ways that Lumryz is less safe than Xyrem and Xywav.

First, Jazz argues that the risk of falls may be greater with Lumryz than with Xyrem and Xywav.²¹⁷ Jazz characterizes its argument as speculation (“one can equally speculate about alternate scenarios in which nocturnal awakenings and falls increase due to [Lumryz's] extended-release formulation”) and hypothesis (“[Lumryz] introduces its own hypothetical fall risks”).²¹⁸ Jazz speculates that because Lumryz is an extended release formulation, if a patient were to awaken and get out of bed, the patient using Lumryz would have more active drug in their blood compared to Xyrem and Xywav and could be at a higher risk for falls.²¹⁹ Jazz also states that Lumryz has “apparently higher rates of enuresis” (i.e., bedwetting), which may lead to more falls.²²⁰ Jazz's claim is based on a cross-study comparison showing a higher rate of enuresis with Lumryz compared to Xyrem and Xywav. Cross-study comparisons refers to drug studies in which a given drug is independently investigated from a second drug and does not allow direct comparison of results from one study to the other. Inferences cannot be reliably drawn as the two study populations and conditions of each study may not be the same. OOPD consistently has rejected use of such comparisons to conclude one drug has a higher rate of an adverse event than another drug. Nevertheless, even if Lumryz were to have a higher rate of enuresis than Xyrem and Xywav, Jazz's argument is based on speculation that enuresis may lead to falls, because the patient may wake up, get out of bed, and change their sheets.²²¹ DN1 agrees

²¹⁵ Jazz's September 2021 Letter, *supra* note 11, at 6-15.

²¹⁶ See Jazz's September 2021 Letter, *supra* note 11, at 6-15. These arguments include that the pivotal REST-ON study was not designed to detect superiority (at 7-8), that findings of greater safety for other drugs were based on more data than is available for Lumryz (at 8-9), that there is insufficient evidence to support that the risk of falls is reduced with Lumryz compared to Xyrem and Xywav (at 10-13), that there is insufficient evidence to support that Lumryz will have better rates of adherence than Xyrem and Xywav (at 13-15), and that there is insufficient evidence to support that Lumryz will have lower rates of diversion (i.e., illegally transferring the drug to another person) than Xyrem and Xywav (at 15).

²¹⁷ Jazz's September 2021 Letter, *supra* note 11, at 12-13.

²¹⁸ *Id.*

²¹⁹ *Id.* at 12.

²²⁰ *Id.*

²²¹ *Id.*

that Jazz’s arguments are speculative and is not aware of any data to support their arguments.²²² Ultimately, as Jazz admits, its arguments are based on speculation and hypotheses, and there are no scientific data to support a conclusion that there is a higher risk for falls with Lumryz compared to Xyrem and Xywav.

Second, Jazz argues that Lumryz may have worse adherence rates than Xyrem and Xywav.²²³ Jazz states that patients taking Lumryz may decide to skip taking their medication on nights when they do not expect to get 8-10 hours of sleep before they need to awaken the next day, or on nights where they do not limit fluid intake or consume alcohol.²²⁴ Jazz contrasts this with patients taking Xyrem or Xywav who, according to Jazz, in similar situations may choose to forgo the second dose on a given night instead of forgoing oxybate treatment entirely on such a night.²²⁵ These assertions that Lumryz will have lower rates of adherence than Xyrem and Xywav appear to be based upon speculation,²²⁶ and we are unaware of any scientifically valid evidence to suggest that adherence should be different between the two drugs.²²⁷

Third, Jazz speculates that Lumryz may have higher rates of diversion (i.e., illegally transferring the drug to another person) than Xyrem and Xywav.²²⁸ Jazz suggests without evidence that Lumryz has “greater concealability and ease of transport” compared to Xyrem and Xywav, which would make Lumryz easier to divert.²²⁹ Jazz also suggests without evidence that multiple doses of Lumryz can more easily be combined into a single, more powerful dose than Xyrem and Xywav.²³⁰ Jazz presents no evidence that Lumryz would be easier to conceal, transport, and combine into a large dose than Xyrem and Xywav, and FDA is not aware of any such data.²³¹

Fourth and finally, Jazz argues that Lumryz is less safe than Xyrem and Xywav because the dose of Lumryz cannot be adjusted, whereas the dose of Xyrem and Xywav can be adjusted. Specifically, Lumryz comes in four dosage strengths: 4.5 g, 6 g, 7.5 g, and 9 g,²³² and thus the dose of Lumryz can be adjusted to those four strengths. Xyrem and Xywav are oral solutions, in concentrations of 0.5 g per mL,²³³ and administered using a dosing syringe that measures dosing

²²² DN1 Lumryz Consult, *supra* note 5 at 6.

²²³ Jazz’s September 2021 Letter, *supra* note 11, at 14-15.

²²⁴ *Id.* at 14.

²²⁵ *Id.*

²²⁶ We also note that alcohol ingestion is contraindicated for all three medicines.

²²⁷ Jazz also argues: “FT218 patients who do take their medication in these scenarios may also be non-adherent and at greater risk. Patients who take their FT218 with less than 8-10 hours to spend in bed before arising the next morning will be at greater risk of next-day impairment. And patients who do not follow Avadel’s recommendation to limit fluid intake for ‘several hours before dosing,’ or who ingest alcohol, will be at greater risk of enuresis, bed exits, falls, serious respiratory depression, and death.” Jazz’s September 2021 Letter, *supra* note 11, at 14. The DN1 consult states, and OOPD agrees that: “This is again a speculative argument. There should not be a significant difference in the risks cited between Lumryz and Xywav/Xyrem, if those drugs are used as recommended in labeling.” DN1 Lumryz Consult, *supra* note 5, at 6.

²²⁸ Jazz’s September 2021 Letter, *supra* note 11, at 15.

²²⁹ *Id.*

²³⁰ *Id.*

²³¹ DN1 Lumryz Consult, *supra* note 5, at 7.

²³² Lumryz labeling, *supra* note 105, at section 3.

²³³ Xyrem 2023 Labeling, *supra* note 86, at section 3; Xywav 2023 Labeling, *supra* note 93, at section 3.

increments of 0.25 g.²³⁴ Jazz argues that the limited ability to dose adjust Lumryz makes it less safe than Xyrem and Xywav for patients who would need to adjust the dose, including patients taking the anti-epileptic medication divalproex, patients taking other central nervous system (“CNS”) depressants, and patients who are hepatically impaired.²³⁵

Regarding patients taking divalproex sodium, no significant pharmacokinetic interaction between Lumryz and divalproex sodium was observed in a drug-drug interaction study conducted by Avadel, so Lumryz’s labeling does not include a specific dose reduction recommendation when Lumryz is co-administered with divalproex sodium.²³⁶ Therefore, a specific dose reduction recommendation, such as that present in Xyrem and Xywav’s labeling related to Xyrem and Xywav patients taking divalproex sodium, is not necessary for Lumryz patients also taking divalproex sodium. Although FDA concluded that a pharmacodynamic interaction between Lumryz and divalproex sodium cannot be ruled out given that both Lumryz and divalproex sodium are CNS depressants, it has determined that the description of the general risks associated with use of CNS depressants in section 5.1 of Lumryz’s labeling is sufficient to inform healthcare prescribers of the risks associated with using Lumryz with other CNS depressants, including divalproex sodium.²³⁷

Regarding patients taking CNS depressants, the labeling for Xyrem, Xywav, and Lumryz have a contraindication for the use of some CNS depressants (i.e., alcohol and sedative hypnotics) with each of those drugs. The labeling for all three drugs contains the same warning that “Use of other CNS depressants may potentiate the CNS-depressant effects of” Xyrem/Xywav/and Lumryz,²³⁸ and a recommendation that “[i]f use of these CNS depressants in combination with” Xyrem/Xywav/Lumryz “is required, dose reduction or discontinuation of one or more CNS depressants” (including Xyrem/Xywav/Lumryz) “should be considered.”²³⁹ Therefore, a patient taking Xyrem or Xywav and another CNS depressant has the option to reduce the dose of Xyrem/Xywav or the other CNS depressant (along with the option to discontinue Xyrem/Xywav or the other CNS depressant). A patient taking Lumryz and another CNS depressant has the option to reduce the dose of Lumryz to one of the set doses below the maximum of 9 g (4.5 g, 6 g, 7.5 g) or reduce the dose of the other CNS depressant (along with the option to discontinue Lumryz or the other CNS depressant). A patient taking Xyrem or Xywav and another CNS depressant may have more options for dose adjustment than a patient taking Lumryz and another CNS depressant, but this does not mean that Lumryz is less safe than Xywav and Xyrem in patients taking another CNS depressant. Lumryz’s labeling mitigates the risk posed by concurrent use of another CNS depressant by providing the same warning in section 5.1 as provided by Xyrem and Xywav. Lumryz patients have the option to reduce the dose of Lumryz to one of the set doses or reduce the dose of the other CNS depressant. Patients who cannot

²³⁴ Xyrem 2023 Labeling, *supra* note 86, at Instructions for Use; Xywav 2023 Labeling, *supra* note 93, at Instructions for use.

²³⁵ Jazz’s September 2021 Letter, *supra* note 11, at 19-20.

²³⁶ DNI Lumryz Consult, *supra* note 5, at 7.

²³⁷ See Clinical Pharmacology Review, NDA 214755 (October 14, 2021); see Addendum to Clinical Pharmacology Review, NDA 214755 (May 24, 2022).

²³⁸ Xyrem 2023 Labeling, *supra* note 86, at section 7.1; Xywav 2023 Labeling, *supra* note 93, at section 7.1; and Lumryz Labeling, *supra* note 105, at section 7.1.

²³⁹ Xyrem 2023 Labeling, *supra* note 86, at section 5.1; Xywav 2023 Labeling, *supra* note 93, at section 5.1; and Lumryz Labeling, *supra* note 105, at section 5.1.

reduce the dose of the other CNS depressant and need to reduce the dose of oxybate below 4.5 g or at more precise increments than 1.5 g might not be able to use Lumryz but may be able to use Xyrem and Xywav. This in theory could be a disadvantage of Lumryz for this very particular set of patients (i.e., patients taking oxybate and another CNS depressant who cannot reduce the dose of the other CNS depressant and need to reduce the dose of oxybate below 4.5 g or at more precise increments than 1.5 g), but Jazz has provided no evidence to support and FDA is not aware of any such evidence that this population even exists.²⁴⁰

Finally, regarding patients who are hepatically impaired, Jazz's September 2021 Letter states that "1.8% of U.S. adults have been diagnosed with liver disease," and that "it is reported that diseases of the digestive system (including liver disease) are more frequently reported in patients with narcolepsy compared to the general population."²⁴¹ This statistic does not provide an estimate of the number of narcolepsy patients with hepatic impairment, but according to DN1, patients with narcolepsy have not been reported to have coexisting hepatic impairment.²⁴² Nevertheless, for patients with hepatic impairment, the labeling for Xyrem and Xywav recommends that the starting dose should be reduced by half,²⁴³ whereas the labeling for Lumryz states that Lumryz "should not be initiated in patients with hepatic impairment because appropriate dosage adjustments for initiation of LUMRYZ cannot be made with the available dosage strengths."²⁴⁴ However, the labeling also states that "[p]atients with hepatic impairment who have been titrated to a maintenance dosage of another oxybate product can be switched to LUMRYZ if the appropriate dosage strength is available."²⁴⁵ Therefore, Lumryz is labeled for use by some patients with hepatic impairment, but not all such patients. This does not mean that Lumryz is less safe than Xyrem and Xywav in patients with hepatic impairment because when used as labeled, Lumryz should not be used in patients with hepatic impairment who cannot be switched to Lumryz.

In summary, the limited ability to adjust Lumryz's dosage compared to Xyrem and Xywav does not make Lumryz less safe than Xyrem or Xywav. At most, the increased ability to adjust the dose of Xyrem and Xywav compared to Lumryz provides a minor convenience. For the potential limited number of patients who require a lower or more adjustable dose (i.e., (1) patients taking oxybate and another CNS depressant who cannot reduce the dose of the other CNS depressant and need to reduce the dose of oxybate below 4.5 g or at more precise increments than 1.5 g, and (2) patients with hepatic impairment that cannot be switched to Lumryz), Lumryz may not be the right product for them. Nevertheless, given the paucity of evidence supporting the existence of such population, we still conclude that Lumryz makes a MCTPC over Xyrem and Xywav by providing a once-nightly dosing regimen. As discussed above, MCTPC requires a "global assessment" and there "can not [sic] be an infinite number of

²⁴⁰ Jazz's September 2021 Letter, *supra* note 11, at 19 footnote 104 states, "in the latest Xywav and Xyrem REMS Assessment Report, e.g., 6.2% of patients reported use of benzodiazepines, 4.6% reported use of muscle relaxants, and 4.3% reported use of opioid analgesics and subsequently received a shipment of Xyrem or Xywav." This does not reflect a percentage of patients who cannot reduce the dose of the other CNS depressant and need to reduce the dose of oxybate below 4.5 g or at more precise increments than 1.5 g.

²⁴¹ Jazz's September 2021 Letter, *supra* note 11, at 19 footnote 104.

²⁴² DN1 Lumryz Consult, *supra* note 5, at 8.

²⁴³ Xyrem 2023 Labeling, *supra* note 86, at section 8.6; Xywav 2023 Labeling, *supra* note 93, at section 8.6.

²⁴⁴ Lumryz Labeling, *supra* note 105, at section 8.6.

²⁴⁵ *Id.*

comparison criteria.”²⁴⁶ The advantage of Lumryz’s once-nightly dosing is a significant advantage for patients who can take Lumryz and rises to the level of a MCTPC. What is more, Jazz has not demonstrated any safety concerns regarding Lumryz compared to Xyrem and Xywav, aside from the previously discussed lower sodium of Xywav compared to Lumryz. OOPD has already factored in the safety risk associated with the differences in the content of sodium between Lumryz and Xywav, as discussed above, and concluded that Lumryz makes a MCTPC.

B. MCTPC

Jazz also raised several arguments why Avadel has not met the standard to demonstrate that Lumryz makes a MCTPC over Xyrem and Xywav.

First, Jazz suggests that head-to-head comparative trials should be required for FDA to find that Lumryz makes a MCTPC.²⁴⁷ We do not agree; comparative trials are not required for a demonstration of MCTPC. The definition of “clinically superior” in the regulation states that demonstrating greater effectiveness requires direct comparative clinical trials “in most cases,” and that demonstrating greater safety requires direct comparative clinical trials “in some cases,”²⁴⁸ but similar or comparable language for a MCTPC is absent.²⁴⁹ Consistent with the regulation, FDA does not require direct comparative clinical trials to demonstrate that a drug makes a MCTPC.²⁵⁰ Additionally, the types of factors that FDA considers when determining MCTPC (e.g., convenient treatment location; duration of treatment; patient comfort; reduced treatment burden; advances in ease and comfort of drug administration; longer periods between doses; and potential for self-administration)²⁵¹ are not typically studied in a clinical trial for marketing approval.

²⁴⁶ OOPD Rebuttal memo, *supra* note 36, at 3.

²⁴⁷ Jazz’s September 2021 Letter, *supra* note 11, at 15; *see also* Sidley Letter, *supra* note 12, at 9; *see also* Sidley Slides, *supra* note 13, at 31.

²⁴⁸ The clinical superiority findings for BeneFix and Xywav are two examples where FDA found greater safety without direct comparative trials. For BeneFix, FDA concluded that even without direct comparative trials, there was an established epidemiological understanding that certain viruses can be transmitted by plasma-derived coagulation factor IX preparations, and that because those viruses do not exist in the source material for BeneFix, it was reasonable to conclude that the risk of transmitting these viruses is removed for treatment with BeneFix compared to the previously approved drugs. *See* BeneFix memo, *supra* note 163, at 2. Similarly for Xywav, FDA concluded that even without comparative trials, Xywav was clinically superior to Xyrem based on the established scientific knowledge that Xywav’s reduced sodium would be clinically meaningful in reducing cardiovascular morbidity as compared to Xyrem. *See* Xywav Exclusivity Memo, *supra* note 99.

²⁴⁹ 21 CFR § 316.3(b)(3).

²⁵⁰ *See, e.g.*, FDA, *Exclusivity Memorandum DRU-2012-3825, Valtoco (diazepam nasal spray)* (Jan. 10, 2020) (finding an intranasal spray formulation makes a MCTPC over a rectal gel formulation without head-to-head comparative trials, because rectal administration is inherently invasive for the patient and difficult to administer, whereas intranasal administration is inherently more comfortable); Signifor Exclusivity Memo, *supra* note 167 (finding an intramuscular injection dosed once monthly makes a MCTPC over a subcutaneous injection dosed twice daily without head-to-head comparative trials, because of the greatly reduced injections per month); FDA, *Exclusivity Memorandum DRU-2015-5130, Ultomiris (ravulizumab-cwvz)* (Sep. 4, 2020) (finding dosing every eight weeks makes a MCTPC over dosing every two weeks without head-to-head comparative trials, because of the heavy burden associated with each dose); Procybsi Exclusivity Memo, *supra* note 161 (finding dosing every 12 hours makes a MCTPC over dosing every six hours without head-to-head comparative trials, because many patients were unable to follow a strict six-hour-dosing, especially due to the need to awaken from sleep to ensure a timely dose).

²⁵¹ 2013 Final Rule, 78 Fed. Reg. at 35125.

Jazz points to quotations from the regulation preambles to suggest that head-to-head comparative trials should be required for FDA to find that Lumryz makes a MCTPC. Specifically, Jazz cites the 1992 Final Rule, where it states, “While comparative trials are, of course, preferred and will usually be required, it is possible that, in some circumstances, a demonstration of a major contribution to patient care can be made without such trials.”²⁵² Although this comment in the preamble could suggest that findings of MCTPC will usually be supported by comparative trials, the statement makes clear that a demonstration of MCTPC does not require such trials.²⁵³ More importantly, in practice, FDA has not required comparative trials to support findings of MCTPC.²⁵⁴ Jazz also points to the 1992 Final Rule, where it states, “As stated, the kinds of data needed to demonstrate clinical superiority for purposes of the Orphan Drug Act will be the same as the kinds of data required to allow label claims of superiority.”²⁵⁵ In context, this quotation is discussing the final rule, and the words “[a]s stated” mean “as stated in the final rule.”²⁵⁶ As explained above, the final rule requires clinical trials “in most cases” to demonstrate greater efficacy, and “in some cases” to demonstrate greater safety, but does not require clinical trials for a MCTPC.²⁵⁷ Because the quotation is referring to what is stated in the final rule, it cannot be read to superimpose a requirement that there be clinical trials to demonstrate a MCTPC particularly in light of text in the final rule that suggests otherwise.²⁵⁸ Additionally, in context, the quotation is responding to a comment on the proposed rule that suggested FDA require rigorous double-blind, head-to-head comparative clinical trials such as those required to support other comparative safety and efficacy claims.²⁵⁹ The comment only addressed types of studies for safety and efficacy claims. Thus, FDA’s response to the comment only addresses clinical superiority based on greater safety and efficacy. As stated above, in practice, FDA has not required comparative trials to support findings of MCTPC.²⁶⁰ Finally, if comparative trials were required to demonstrate a MCTPC, that would be inconsistent with FDA’s statements that MCTPC is judged on a case-by-case basis and that FDA may take into consideration factors, such as convenient treatment location and patient comfort. Comparative trials are not required to find that Lumryz makes a MCTPC.

Second, Jazz argues that the standard for finding a demonstration of clinical superiority is higher than the standard for finding a plausible hypothesis of clinical superiority and that Avadel has not met that standard for Lumryz. Jazz states that a “mere hypothesis is not enough to support a

²⁵² Jazz’s September 2021 Letter, *supra* note 11, at 15 (quoting 1992 Final Rule, 57 Fed. Reg. at 62079); *see also* Sidley Slides, *supra* note 13, at 31.

²⁵³ To the extent the statement could also be read to be discussing clinical superiority generally, it is simply restating the commonly accepted preference for demonstrating clinical superiority through greater efficacy or greater safety using comparative clinical trials, yet a sponsor can also demonstrate clinical superiority through a MCTPC without such trials.

²⁵⁴ *See supra* note 250.

²⁵⁵ Sidley Letter, *supra* note 12, at 9 (quoting 1992 Final Rule, 57 Fed. Reg. at 62078).

²⁵⁶ *See* 1992 Final Rule, 57 Fed. Reg. at 62078.

²⁵⁷ 21 CFR § 316.3(b)(3).

²⁵⁸ Jazz also cites to 21 CFR § 202.1(e)(6)(ii) regarding the level of evidence required for advertising claims. *See* Sidley Letter, *supra* note 12, at 9. The level of evidence required to make advertising claims comes from a different part of the regulation and is not connected to the level of evidence required to demonstrate clinical superiority for the purposes of the orphan-drug regulations.

²⁵⁹ *See* 1992 Final Rule, 57 Fed. Reg. at 62078.

²⁶⁰ *See supra* note 250.

finding of clinical superiority,”²⁶¹ because the standard for being eligible for ODE is higher than the “plausible hypothesis” standard and the sponsor bears the burden to demonstrate that its drug is in fact clinically superior to the previously approved drug.²⁶²

As a threshold matter, FDA agrees that the standard for clinical superiority for approval and ODE eligibility is higher than the “plausible hypothesis standard” for ODD.²⁶³ Specifically, the condition of clinical superiority for ODE eligibility requires that a sponsor “demonstrate” clinical superiority,²⁶⁴ and “different drug” status for a drug that is otherwise same drug as one with ODE also requires a demonstration of clinical superiority.²⁶⁵ FDA has explained that the difference in standards is meant to meet the intent of the Orphan Drug Act by encouraging “the development of improved versions of existing drugs” by having a lower standard for designation, “while protecting any applicable orphan-drug exclusivity” by requiring an actual demonstration of clinical superiority to overcome such ODE.²⁶⁶

Jazz argues that Avadel’s evidence for clinical superiority is hypothetical and does not meet the demonstration standard.²⁶⁷ Jazz appears to base this argument on an assumption as to what evidence and arguments Avadel has submitted to FDA and what FDA has found compelling in demonstrating clinical superiority. Specifically, Jazz cites public statements from Avadel about market research concerning patient preference for a once-nightly formulation and prescriber surveys that dosing-related challenges are to blame for oxybate-eligible patients not taking oxybate.²⁶⁸ OOPD, however, is not relying on the cited market research and prescriber surveys in its determination that Lumryz makes a MCTPC, and therefore Jazz’s arguments about these sources are moot.

The clinical superiority of Lumryz is not merely hypothetical. As explained above, the science underlying sleep hygiene supports the finding that in the context of oxybate drugs for the treatment of narcolepsy, where the purpose of therapy is to promote sleep consolidation, a drug with once-nightly dosing that avoids disrupting sleep consolidation by avoiding a nocturnal awakening to take a second dose makes a MCTPC over the previously approved drugs for which the patient awakens and disrupts sleep consolidation to take a second dose. Awakening to take a second dose of Xyrem or Xywav fragments sleep and disrupts sleep architecture. If possible, this should be avoided in a narcoleptic patient. Sleep consolidation is the intended purpose of oxybate therapy. Lumryz provides a treatment option that avoids the need to awaken to take a second dose. Thus, based on its scientific expertise and consultation of the literature, FDA has determined that the clinical superiority of Lumryz has been demonstrated.

²⁶¹ Jazz’s September 2021 Letter, *supra* note 11, at 2; *see also* Sidley Slides, *supra* note 13, at 21.

²⁶² Jazz’s September 2021 Letter, *supra* note 11, at 3.

²⁶³ 21 CFR § 316.20(a).

²⁶⁴ Section 527(c)(1) of the FD&C Act.

²⁶⁵ 2013 Final Rule, 78 Fed. Reg. at 35122 (“allowing the subsequent drug to be approved during the pendency of the already approved drug’s exclusivity period (if any) . . . provided that clinical superiority is demonstrated upon approval”).

²⁶⁶ *Id.*

²⁶⁷ Jazz’s September 2021 Letter, *supra* note 11, at 16-18.

²⁶⁸ *Id.* at 16; *see also* Sidley Slides, *supra* note 13, at 31.

The type of evidence on which FDA is basing its finding of Lumryz’s demonstration of clinical superiority over Xywav and Xyrem is quite similar to the type of evidence on which FDA based its finding of Xywav’s demonstration of clinical superiority over Xyrem. FDA found Xywav clinically superior to Xyrem based on greater safety because Xywav provided less sodium than Xyrem, and scientific literature exists that shows reduced dietary sodium generally would be clinically meaningful in reducing cardiovascular morbidity in the general population.²⁶⁹ Jazz did not conduct a head-to-head trial to compare the safety of Xywav and Xyrem.²⁷⁰ Nevertheless, the underlying science supported that “[t]he relationship between daily salt intake and cardiovascular morbidity is widely accepted, as is the need for salt intake to be generally restricted.”²⁷¹ That was sufficient for OOPD to conclude that Xywav was clinically superior to Xyrem, because, as OOPD explained, “although it has never been specifically and adequately investigated whether the sodium content of Xyrem increases cardiovascular risks in patients with narcolepsy, the general base of knowledge about the effects of sodium support that the amount of sodium in Xyrem would increase cardiovascular risks in patients with narcolepsy.”²⁷² By similar logic, for Lumryz, FDA has found that the scientific knowledge of sleep hygiene and the importance of consolidating sleep to treat narcolepsy supports its finding that a drug that avoids a nocturnal awakening to take a second dose provides a significant therapeutic advantage over and above that provided by a drug that necessitates a nocturnal awakening to take a complete nightly dosage.

Third, Jazz argues that Lumryz does not meet the standard for clinical superiority because the change from Xyrem and Xywav’s twice-nightly dosing to Lumryz’s once-nightly dosing does not meet the “high bar” to be considered a MCTPC.²⁷³ Jazz argues that because MCTPC represents a “narrow category”²⁷⁴ of “unusual cases,”²⁷⁵ FDA’s prior MCTPC findings have been based on “much more substantial quantitative and qualitative improvements” than Lumryz’s “50% decrease in dosing frequency relative to Xyrem and Xywav.”²⁷⁶ Jazz cites to two examples where FDA found a MCTPC for a drug going from twice-a-day dosing to once-monthly dosing and a drug going from administration that took one hour to taking one minute.²⁷⁷ FDA does not agree with Jazz’s arguments and finds that Lumryz’s benefit meets the narrow category of MCTPC. All MCTPC determinations are made on a case-by-case basis, and the nature and severity of the disease or condition is a relevant factor.²⁷⁸ More goes into a MCTPC determination than merely a quantitative assessment of the percentage reduction in dosing frequency. For Lumryz, the reduction in the number of doses makes a MCTPC because the dosing eliminates the need to awaken in the middle of sleep to take the second dose. This is relevant in the context of treating narcolepsy with oxybate because the goal of narcolepsy therapy is to enhance sleep consolidation; awakening to take a second dose works directly

²⁶⁹ Xywav Exclusivity Memo, *supra* note 99, at 3.

²⁷⁰ *Id.*

²⁷¹ *Id.* (quoting DN1 2020 Xywav Consult).

²⁷² Xywav Exclusivity Memo, *supra* note 99, at 5.

²⁷³ Jazz’s September 2021 Letter, *supra* note 11, at 15-16.

²⁷⁴ *Id.*, at 15 (quoting 1991 Proposed Rule, 56 Fed. Reg. at 3343).

²⁷⁵ *Id.* (quoting 21 CFR § 316.3(b)(3)).

²⁷⁶ *Id.* at 16.

²⁷⁷ *Id.*

²⁷⁸ 1992 Final Rule, 57 Fed. Reg. at 62078.

against this goal. Furthermore, as noted above, our basis for finding a MCTPC for Lumryz is similar to our basis for FDA’s MCTPC finding for Procysbi.

Fourth, and finally, Jazz argues that FDA should not consider Lumryz to make a MCTPC because FDA did not grant priority review for Lumryz’s marketing application.²⁷⁹ Jazz notes that the standard for priority review is similar to the standard for clinical superiority.²⁸⁰ A review designation type (standard or priority review) for a marketing application is determined on a case-by-case basis at the time that an application is filed based on the information and data available at the time the application is submitted.²⁸¹ As described in the guidance for industry, *Expedited Programs for Serious Conditions – Drug and Biologics* (May 2014), “[a]n application will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness.”²⁸² “Significant improvement” may be illustrated by the following examples: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of a serious or life-threatening condition; (2) elimination or substantial reduction of a treatment-limiting adverse reaction; (3) documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes; or (4) evidence of safety and effectiveness in a new subpopulation.²⁸³

The clinical superiority standard, as described throughout this analysis, includes that “the drug provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, or by providing a major contribution to patient care.”²⁸⁴ FDA makes clinical superiority determinations for the purposes of approval and ODE eligibility *after* the agency has conducted a full and substantive review of the relevant marketing application and determined if the drug meets the safety and efficacy requirements for approval; whereas, the priority review designation is made at the time of submission of the marketing application, based upon a “[p]reliminary review.”²⁸⁵ Although the concepts of “clinical superiority” in the orphan-drug context and “significant improvement” in the priority review context may have some practical overlap, the standard for demonstrating clinical superiority differs from the standard for priority review designation; the analyses are conducted at different times in the review of a marketing application and involve different levels of data scrutiny. Given these differences, there are many reasons why FDA could deny priority review for a marketing application for a drug and find clinical superiority for that drug.²⁸⁶ FDA’s decision not to grant priority review for the Lumryz application is not inconsistent with its determination that Lumryz makes a MCTPC over Xyrem and Xywav.

²⁷⁹ Jazz’s September 2021 Letter, *supra* note 11, at 16; *see also* Sidley Slides, *supra* note 13, at 34.

²⁸⁰ Sidley Slides, *supra* note 13, at 34.

²⁸¹ *See* CDER’s Manual of Policies and Procedures 6020.3 Rev. 2, Review Designation Policy: Priority (P) and Standard (S) at 3-4, June 2013, <https://www.fda.gov/media/72723/download>.

²⁸² *Expedited Programs for Serious Conditions – Drug and Biologics* (May 2014) at 2-3 (accessed at <https://www.fda.gov/media/86377/download>).

²⁸³ *Id.*

²⁸⁴ Section 527(c)(2) of the FD&C Act; *see also* 21 CFR § 316.3(b)(3).

²⁸⁵ MAPP 6020.3 Rev. 2, *supra* note 281, at 6.

²⁸⁶ The drug Valtoco (diazepam nasal spray) is another recent example where FDA granted standard review designation for an application but found clinical superiority over a previously approved otherwise same drug for the same indication or use upon approval.

In sum, FDA finds Jazz's arguments about why Lumryz does not make a MCTPC over Xyrem and Xywav unpersuasive.

VI. Conclusion

For the reasons explained above, we have determined that Lumryz, which is dosed once nightly, is clinically superior to Xyrem and Xywav, which are dosed twice nightly. *See* 21 CFR § 316.3(b)(3). Because Lumryz is clinically superior to Xywav and, therefore, not the "same drug" as Xywav under 21 CFR § 316.3(b)(14) and section 527(a) of the FD&C Act, Xywav's unexpired ODE does not block marketing approval of Lumryz. Additionally, because of its clinical superiority to Xyrem and Xywav, Lumryz has met the condition set forth at section 527(c) of the FD&C Act, and Lumryz is eligible for its own term of ODE for the treatment of cataplexy or EDS in adults with narcolepsy under section 527(a) of the FD&C Act.

Sandra
Retzky -S

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Sandra S. Retzky, D.O., J.D., M.P.H.
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cc:

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Division of Neurology 1 (DN1)
Office of Neuroscience (ON)
Center for Drug Evaluation and Research

Date: May 1, 2023

From: Ranjit Mani, MD
Clinical Reviewer, DN1

Teresa Buracchio, MD
Deputy Director, ON¹

Subject: Office of Orphan Products Development Consult Request #16-5302
NDA 214755
Lumryz (Sodium Oxybate Extended-Release for Oral Suspension [FT218])
Request for Orphan Drug Exclusivity

To: Director
Office of Orphan Products Development

Document Type: Consult

Enclosed is the Division's response to your request

¹ This consult memo was substantially reviewed and prepared by Teresa Buracchio in her former capacity as Director of the Division of Neurology 1. In her current capacity as Deputy Director of the Office of Neuroscience, she continues to be involved in the review and preparation of this consult and is authorized to sign this consult, among other things, for Lumryz.

Review and Evaluation of Clinical Data

NDA (Serial Number)	214755
Sponsor:	Avadel
Product:	Lumryz*
Proposed Indication:	Narcolepsy
Reviewer:	Ranjit B. Mani, M.D.

*Sodium Oxybate Extended-Release for Oral Suspension (FT218)

1. Background

Avadel submitted an original New Drug Application (NDA), #214755, for Sodium Oxybate Extended-Release for Oral Suspension (FT218), which carries the proprietary name “Lumryz,” on December 15, 2020. This NDA seeks approval of Lumryz for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy. The issue currently before the agency is whether Lumryz is clinically superior (as defined in the orphan-drug regulations) to Jazz’s approved oxybate-containing product, Xywav, as well as Jazz’s other oxybate-containing product, Xyrem. The answer to this question will inform whether Lumryz can be approved and whether Lumryz is eligible for its own term of orphan-drug exclusivity (ODE). Jazz, Avadel, and their counsel have made multiple submissions to the agency regarding ODE and Lumryz’s approvability. This memorandum memorializes responses to questions posed by the Office of Orphan Products Development (OOPD) to the Division since NDA 214755 was submitted on December 15, 2020, regarding Lumryz and responses to those questions.

Whether Lumryz is clinically superior to Xywav and Xyrem was previously addressed by this Division in a consultation memorandum completed on August 31, 2021 (appended to this memorandum). This current memorandum updates and supersedes that August 31, 2021 response after further refinement of OOPD and the Division’s thinking based on careful consideration of the legal, regulatory, and scientific issues raised by this question; information submitted by the sponsors of Lumryz and Xywav/Xyrem; and the agency’s own scientific expertise and precedent.

The following provides additional background information:

- Currently, two products are approved for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years and older with narcolepsy. These are Xyrem (sodium oxybate oral solution) and Xywav (a low-sodium oxybate oral solution formulation containing a mixture of calcium, magnesium, potassium, and sodium oxybates); the manufacturer of both formulations is Jazz Pharmaceuticals, Inc. Generic formulations of sodium oxybate oral solution have also been approved for the treatment of cataplexy or excessive daytime sleepiness in narcolepsy.

- Lumryz was granted a tentative approval on July 18, 2022, for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy.
- While the currently-approved formulations of sodium oxybate, Xyrem and Xywav, are liquids, Sodium Oxybate for Extended-Release Oral Suspension (FT218; Lumryz) is a powder for oral suspension. Whereas the approved formulation Xyrem is administered in two separate doses nightly, separated by an interval of 2.5 to 4.0 hours, Sodium Oxybate for Extended-Release Oral Suspension (FT218) is administered once nightly.
- The maximum recommended doses of Xyrem and Xywav are each 9 grams per night, as is the maximum recommended dose of Lumryz. The sodium content of the 9-gram doses of Xyrem, Xywav, and Lumryz is 1640 mg, 131 mg, and 1640 mg, respectively.

2. OOPD Questions and DN1 Responses

- 1. Is there any evidence to suggest that the efficacy of Lumryz may be different from Xyrem or Xywav? If so, please elaborate.**

DN1 Response

There is no evidence suggesting that the efficacy of Lumryz is different from that of Xyrem or Xywav.

- 2. Is there any evidence, including in Avadel's submissions, to support that Lumryz provides greater safety in a substantial portion of the target population when compared to Xyrem or Xywav?**

DN1 Response

The available data do not indicate that Lumryz provides greater safety in a substantial proportion of patients in the target population (i.e., patients who have narcolepsy with cataplexy and/or excessive daytime sleepiness) than Xyrem or Xywav, despite the arguments provided by the applicant. In broad terms, the safety profiles of all 3 products (Lumryz, Xyrem, and Xywav) are not substantially different, but the sodium content of Lumryz is higher than that of an equivalent dose of Xywav and the same as that of an equivalent dose of Xyrem. To address this safety concern, Lumryz's labeling includes a warning (similar to Xyrem's labeling), which states: "LUMRYZ has a high sodium content. In patients sensitive to sodium intake (e.g., those with heart failure, hypertension, or renal impairment), consider the amount of daily sodium intake in each dose of LUMRYZ." We note that available safety data for Lumryz do not indicate that the higher sodium content of each dose of that drug is reflected in a greater incidence of adverse events than is observed with equivalent doses of Xywav, which has a lower sodium content. The safety profile of Lumryz meets the Agency's standards for approval.

3. Does the review division consider Lumryz to be clinically superior based on a major contribution to patient care (MCTPC)?

DN1 Response

In a prior consultation dated August 31, 2021, DN1 stated: “While the once-nightly regimen of Lumryz will be more convenient for patients than a twice-nightly regimen, that attribute cannot be considered a [MCTPC].” Following that consultation, DN1 has reconsidered its conclusion in light of several factors, including scientific, legal, and regulatory considerations raised by OOPD and the expert opinion of FDA’s sleep team, which is also memorialized in a separate consult response.² OOPD has clarified that MCTPC determinations include consideration of factors such as reduced treatment burden, advances in ease of drug administration, and longer periods between doses; that the orphan-drug regulations do not require a drug to be clinically superior for all patients for whom the drug is indicated; and that a drug does not need to have comparable safety to another drug to make a MCTPC over the other drug. OOPD has also made the Division aware of a previous MCTPC determination with delayed release cysteamine (Procysbi) for the treatment of cystinosis. In that case, FDA determined that Procysbi met the MCTPC standard based on dosing every 12 hours compared to dosing every 6 hours for immediate release cysteamine. The need to awaken the patient to maintain an every 6-hour dosing regimen with cysteamine and the chronic nature of the disease were important considerations in that MCTPC determination.

Previously, in its August 31, 2021 response, the Division did not fully consider the issues raised in the paragraph above. The Division has since carefully reconsidered whether Lumryz’s once-nightly dosing may rise to the level of a MCTPC in the setting of a chronic disease such as narcolepsy and now concludes that awakening to take medication on a nightly basis for a long duration of treatment (e.g., every night for the remainder of the patient’s life, because narcolepsy is a chronic condition) would have a significant negative impact on patient care and counteract the purpose of oxybate therapy. In particular, we note that FDA’s sleep team, based on a robust scientific review of the literature and their own scientific expertise, have explained that Lumryz provides an opportunity for narcolepsy patients to achieve normal sleep architecture, which is not a possibility for a patient on Xyrem or Xywav who must either wake up to take a second dose (disrupting sleep architecture) or allow the drug to wear off after 2.5-4 hours (reverting patients back to their naturally occurring, disrupted sleep architecture). We agree with this conclusion. The delayed release cysteamine exclusivity memo also informs our reassessment of MCTPC. For that decision FDA considered that less frequent dosing eliminated the need to awaken to take a dose in a situation where the timing of the dose was critical to achieving the drug’s intended benefit.

² See *generally* Mahadevappa Hunasikatti MD FCCP and Nargues Weir MD FCCP FAASM ATSF, *Consult request on Lumryz* (Apr. 29, 2023) (“Sleep Expert Consult”).

The Division also acknowledges the sodium content of Lumryz raises the same safety concern that was present for Xyrem and that is not present for Xywav. However, it is our opinion that the benefit of Lumryz's once-nightly dosing outweighs the safety concern raised by its increased sodium content for a substantial number of narcolepsy patients. Although it is widely accepted that individuals generally should limit sodium intake, the warning in Lumryz's labeling regarding sodium is directed only at patients sensitive to sodium intake such as those with heart failure, hypertension, or renal impairment. For narcolepsy patients who are not sensitive to sodium intake, it is our opinion that a once-nightly dosed oxybate drug will provide a significant therapeutic advantage. It is true that patients who are not sensitive to sodium could also benefit from a reduction in sodium, but it is our opinion that the benefit offered by once-nightly dosing outweighs the risk of increased sodium intake in such patients because, for example, having to wake up to take a second dose is antithetical to oxybate's goal of improving sleep, and there are other ways such patients may reduce sodium in their diet.³ For narcolepsy patients who are sensitive to sodium, healthcare practitioners would need to weigh the benefits of once-nightly dosing against the severity of the patient's sodium sensitivity and the nature of their comorbidities to determine whether, in the practitioners' judgment, use of Lumryz or Xywav was appropriate. For certain sodium-sensitive patients with narcolepsy, the benefit offered by once-nightly dosing would outweigh the risk of increased sodium intake for the same reasons (e.g., having to wake up to take a second dose is antithetical to oxybate's goal of improving sleep, and there are other ways such patients may reduce sodium in their diet).

Taking all of these factors into consideration and for the reasons explained above, DN1 has reconsidered its prior assessment dated August 31, 2021, and now concludes that Lumryz provides a MCTPC over Xywav and Xyrem.

- 4. Risk of Falls. Can you address the arguments Jazz raised in its letter dated September 16, 2021 ("Jazz's September 2021 Letter") on pages 12-13 that Lumryz may increase the risk of falls over Xywav? Specifically, is there any basis for thinking, as Jazz speculates, that "nocturnal awakenings and falls increase due to FT218's extended-release formulation"? Is there any basis for thinking that "FT218 patients who get out of bed will have sustained therapeutic blood levels of oxybate throughout the night, potentially putting them at higher risk of falls than with...Xywav's immediate release formulations" or that "FT218's apparently higher rates of enuresis may lead to more falls"?**

³ We note that the sleep expert consult explains that disrupting sleep contributes to chronic sleep loss, which is well known to cause reduced performance, increased risk for accidents and death, and detrimental effects on both psychological and physical health.

DN1 Response

This is entirely speculative. We are unaware of data to support these statements. We note that our clinical superiority recommendation is not based on a claim of superior safety for Lumryz.

5. Adherence. Can you address the arguments on pages 13-15 of Jazz's September 2021 Letter that "one can equally speculate that FT218's extended-release formulation will result in reduced adherence compared to...Xywav"?

- a. Is there any basis for thinking that Lumryz will result in reduced adherence compared to Xywav? Is there any basis for thinking that patients will be more likely to forgo taking Lumryz compared to Xywav in situations where they do not expect to be able to sleep for 8-10 hours, or if they had not been limiting fluid intake or had been ingesting alcohol?**

DN1 Response

This is also a speculative argument. We have no scientifically valid evidence to suggest that adherence should be different between the two drugs. Additionally, use of alcohol with oxybate is contraindicated in the PI.

We also note that adherence did not factor into the Division's clinical superiority determination described above.

- b. Is there any basis for thinking that "[p]atients who take their FT218 with less than 8-10 hours to spend in bed before arising the next morning will be at greater risk of next-day impairment [over Xywav]"? And is there any basis for thinking that "patients who do not follow Avadel's recommendation to limit fluid intake for 'several hours before dosing,' or who ingest alcohol, will be at greater risk of enuresis, bed exits, falls, serious respiratory depression, and death"?**

DN1 Response

This is again a speculative argument. There should not be a significant difference in the risks cited between Lumryz and Xywav/Xyrem, if those drugs are used as recommended in labeling.

6. Diversion. Can you address the arguments on page 15 of Jazz's September 2021 Letter that there is an increased risk of diversion and abuse with Lumryz compared to Xywav? Is there any basis for thinking that it is easier to conceal and transport Lumryz sachets and that it would lead to more diversion compared to Xywav? Is there any basis for thinking that combining multiple Lumryz

sachets is easier than creating an equivalent dose of Xywav and that will lead to a greater risk of diversion and abuse?

DN1 Response

This is also a speculative argument. The Division is not making a clinical superiority recommendation for Lumryz based on superiority with regard to diversion. There is no evidence to suggest that Lumryz would be any different from Xywav in that regard. There is no reason to think that a sachet would be any easier to divert than a solution. Vials can be as easily transported as sachets, and a powder poured into a drink may dissolve less rapidly and be more noticeable than a solution.

7. Dose Adjustment. Can you address the arguments on pages 19-20 of Jazz's September 2021 Letter that Lumryz is less safe than Xyrem and Xywav because patients cannot dose adjust Lumryz?

DN1 Response

Lumryz comes in four dosage strengths: 4.5 g, 6 g, 7.5 g, and 9 g, and thus the dose of Lumryz can be adjusted to those four strengths. Xyrem and Xywav are oral solutions, in concentrations of 0.5 g per mL, and administered using a dosing syringe that measures dosing increments of 0.25 g. Jazz argues that the limited ability to dose adjust Lumryz makes it less safe than Xyrem and Xywav for patients who would need to adjust the dose, including patients taking the anti-epileptic medication divalproex, patients taking other central nervous system ("CNS") depressants, and patients who are hepatically impaired. We do not agree with these arguments.

Regarding patients taking divalproex sodium, no significant pharmacokinetic interaction between Lumryz and divalproex sodium was observed in a drug-drug interaction study conducted by Avadel, so Lumryz's labeling does not include a specific dose reduction recommendation when Lumryz is co-administered with divalproex sodium. Therefore, a specific dose reduction recommendation, such as that present in Xyrem and Xywav's labeling related to Xyrem and Xywav patients taking divalproex sodium, is not necessary for Lumryz patients also taking divalproex sodium. Although FDA concluded that a pharmacodynamic interaction between Lumryz and divalproex sodium cannot be ruled out given that both Lumryz and divalproex sodium are CNS depressants, it has determined that the description of the general risks associated with use of CNS depressants in section 5.1 of Lumryz's labeling is sufficient to inform healthcare prescribers of the risks associated with using Lumryz with other CNS depressants, including divalproex sodium.⁴

We note that the labeling for Xyrem, Xywav, and Lumryz have a contraindication for the use of some central nervous system (CNS) depressants (i.e., alcohol and

⁴ See Clinical Pharmacology Review, NDA 214755 (October 14, 2021); see Addendum to Clinical Pharmacology Review, NDA 214755 (May 24, 2022).

sedative hypnotics) with each of those drugs. Aside from those CNS depressants contraindicated, Section 7.1 describes a potential pharmacodynamic effect where other CNS depressants may potentiate the CNS-depressant effects of Xyrem, Xywav, or Lumryz. Section 5.1 in the labeling for Xyrem, Xywav, and Lumryz state that “[i]f use of these CNS depressants in combination with” Xyrem, Xywav, or Lumryz “is required, dose reduction or discontinuation of one or more CNS depressants” including Xyrem, Xywav, or Lumryz “should be considered.” Therefore, a patient taking Xyrem or Xywav and another CNS depressant has the option to reduce the dose of Xyrem/Xywav or the other CNS depressant (along with the option to discontinue Xyrem/Xywav or the other CNS depressant). A patient taking Lumryz and another CNS depressant has the option to reduce the dose of Lumryz to one of the set doses below the maximum of 9 g (4.5 g, 6 g, 7.5 g) or reduce the dose of the other CNS depressant (along with the option to discontinue Lumryz or the other CNS depressant). A patient taking Xyrem or Xywav and another CNS depressant may have more options for dose adjustment than a patient taking Lumryz and another CNS depressant, but this does not mean that Lumryz is less safe than Xywav and Xyrem in patients taking another CNS depressant. Lumryz’s labeling mitigates the risk posed by concurrent use of another CNS depressant by providing the same warning in section 5.1 as provided by Xyrem and Xywav. Lumryz patients have the option to reduce the dose of Lumryz to one of the set doses or reduce the dose of the other CNS depressant. Patients who cannot reduce the dose of the other CNS depressant and need to reduce the dose of oxybate below 4.5 g or at more precise increments than 1.5 g might not be able to use Lumryz but may be able to use Xyrem and Xywav. This in theory could be a disadvantage of Lumryz for this very particular set of patients (i.e., patients taking oxybate and another CNS depressant who cannot reduce the dose of the other CNS depressant and need to reduce the dose of oxybate below 4.5 g or at more precise increments than 1.5 g), but Jazz has provided no evidence to support and FDA is not aware of any such evidence that this population even exists.

The safety of these oxybate products in patients with hepatic impairment is addressed in Section 8.6 of their respective labeling. The labeling for Xyrem and Xywav recommends that the starting dose should be reduced by half, whereas the labeling for Lumryz states that Lumryz should not be initiated in patients with hepatic impairment because appropriate dosage adjustments for initiation of Lumryz cannot be made with the available dosage strengths. The labeling for Lumryz also states that patients with hepatic impairment who have been titrated to a maintenance dosage of another oxybate product can be switched to Lumryz if the appropriate dosage strength is available. Therefore, Lumryz is labeled for use by some patients with hepatic impairment but not all such patients. Patients with narcolepsy have not been reported to have coexisting hepatic impairment, and Lumryz should not be less safe than Xyrem or Xywav in patients with hepatic impairment because when used as labeled, Lumryz should not be used in patients with hepatic impairment who cannot be switched to Lumryz.

For the reasons described above, Lumryz is not less safe than Xywav for reasons related to dose adjustment.

3. Summary Comments

Our conclusion is that Lumryz provides a major contribution to patient care over Xywav. The basis for that opinion is explained above.

Ranjit B. Mani - S  Digitally signed by Ranjit B. Mani -S
Date: 2023.05.01 09:35:48 -04'00'

Ranjit B. Mani, M.D.
Medical Reviewer, DN1

Teresa Buracchio -S  Digitally signed by Teresa Buracchio -S
Date: 2023.05.01 09:48:41 -04'00'

Teresa Buracchio, M.D.
Deputy Director, ON

rbm
cc:
HFD-120
NDA 214755

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

Date: August 30, 2021

From: Eric Bastings, MD
Division Director (Acting)

Subject: Office of Orphan Products Development Consult Request #16-5302
NDA 214755:
Lumryz (Sodium Oxybate Extended-Release for Oral Suspension [FT218])
Request for Orphan Drug Exclusivity

To: Director
Office of Orphan Products Development

Document Type: Consult

Enclosed is the Division's response to your request

Review and Evaluation of Clinical Data

NDA:	214755
Sponsor:	Avadel
Product:	Lumryz*
Proposed Indication:	Narcolepsy
Material Submitted:	Consultation Request
Date Of Request:	7/6/21
Date Request Received By Reviewer:	7/6/21
Date Review Completed:	8/30/21
Reviewer:	Ranjit B. Mani, M.D.

*Sodium Oxybate Extended-Release for Oral Suspension (FT218)

1. Background

This consultation request has been received from the Office of Orphan Products Development (OOPD), and pertains to a request from the sponsor for orphan drug exclusivity for Sodium Oxybate Extended-Release for Oral Suspension (FT218), which carries the proprietary name “Lumryz™.” This request for orphan drug exclusivity for Lumryz™ was submitted on December 15, 2020.

An original New Drug Application (NDA), #214755, seeking the approval of Lumryz™ for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy is currently under review by the Agency. That application was also submitted on December 15, 2020, and included a copy of the request for orphan drug exclusivity that was submitted on the same date.

A supplement to the main request (dated December 15, 2020) for orphan drug exclusivity for Lumryz™ was submitted on July 14, 2021, and is also currently under review by OOPD. That supplement was also submitted to NDA 214755 and its contents will also be addressed in this consultative review. That supplement is entitled “*Exclusivity Claim – Supplemental Information in Demonstration of Clinical Superiority of FT218.*”

Currently, two products are approved for the treatment of cataplexy or excessive daytime sleepiness, (both products) in patients 7 years and older with narcolepsy. These are Xyrem® (sodium oxybate oral solution) and Xywav™ (a low-sodium oxybate oral solution formulation containing a mixture of calcium, magnesium, potassium, and sodium oxybates); the manufacturer of both formulations is Jazz Pharmaceuticals, Inc. Generic formulations of sodium oxybate oral solution have also been approved for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy.

While the currently-approved formulations of sodium oxybate, Xyrem® and Xywav™, are liquids, Sodium Oxybate for Extended-Release Oral Suspension (FT218) is a powder for oral suspension. Whereas the

approved formulation Xyrem® is administered in two separate doses nightly, separated by an interval of 2.5 to 4.0 hours, the sponsor anticipates that Sodium Oxybate for Extended-Release Oral Suspension (FT218) will be administered once nightly.

In this review, the names “Lumryz™,” “Sodium Oxybate Extended-Release for Oral Suspension,” and “FT218,” will be used interchangeably. The term “applicant” has also been interchangeably with sponsor.

2. Text Of Main Consultation Request

The full text of this consultation request, dated July 6, 2021, is copied verbatim below in purple font. That text is both comprehensive and self-explanatory.

Background:

The Office of Orphan Products Development (OOPD) granted orphan drug designation to sodium oxybate extended-release oral suspension on 1/08/2018 for the treatment of narcolepsy. With input from the review division (consult dated 11/24/17), this designation was granted based on a plausible hypothesis that the drug may be clinically superior to the same drug that was already approved for the same indication because it “may be more safe due to the ramifications associated with the dosing regimen for the previously approved sodium oxybate in treating patients with narcolepsy.” On 12/15/2020, the sponsor, Avadel, submitted a marketing application for sodium oxybate extended-release oral suspension, with the proposed trade name Lumryz, for the treatment of cataplexy and excessive daytime sleepiness in adults with narcolepsy (NDA 214755).

Another sponsor, Jazz, has received marketing approval for the same active moiety, oxybate, for use in the treatment of narcolepsy. Specifically, Xywav (calcium, magnesium, potassium, and sodium oxybates) was approved on 7/21/2020 and has orphan-drug exclusivity (ODE) until 7/21/2027 for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. In addition, Xyrem (sodium oxybate) was previously approved for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. Xyrem has ODE only for the portion of the indication pertaining to pediatric patients until 10/26/2025.

In order for Lumryz to receive marketing approval for the treatment of cataplexy and EDS in adults with narcolepsy, it must be clinically superior, as defined in the orphan drug regulations, to the previously approved same drugs, Xywav and Xyrem, for the same indication. If Lumryz is clinically superior to Xywav and Xyrem, it may also be eligible for its own 7-year period of ODE. For the purpose of orphan drug exclusivity, clinical superiority can be based on greater effectiveness, greater safety in a substantial portion of the target population, or a major contribution to patient care (MCTPC), with

all else being equal (see definition below). Please note that for orphan drug exclusivity purposes we apply the definition of clinical superiority from the regulations below and do not apply the substantial evidence standard as is required for a labeling claim.

Avadel submitted a request to the OOPD on 12/15/20 for orphan drug exclusivity for Lumryz based on clinical superiority over Xyrem and Xywav. The same request was also submitted to the NDA on the same date (see NDA 214755 eCTD Sequence Number 0001). In this document, the sponsor contends that Lumryz is clinically superior to Xyrem and Xywav with respect to safety and it also provides a major contribution to patient care (MCTPC). Appendix 2 of Avadel's submission contains several letters from Key Opinion Leaders in the field of narcolepsy and patient advocacy groups which support Avadel's arguments.

Safety:

Avadel notes that both Xyrem and Xywav require a twice-nightly dosing regimen, once at bedtime and once again 2.5-4 hours later. In contrast, Lumryz is an extended-release formulation of sodium oxybate that is given once nightly and therefore obviates the need for awakening to take a second dose. Avadel argues that this provides a safety advantage for Lumryz because it reduces the risk of nighttime falls. This is due to the fact that patients that forcibly wake after receiving one dose of Xyrem may get out of bed, ambulate, and fall because of a drug-induced groggy or stuporous state. Also, because of the rapid onset of effects, patients are at risk of falls or other accidental injuries if the second dose of Xyrem is not consumed while they are in bed. To support their argument, Avadel has provided an analysis of cases of falls in patients receiving Xyrem that were reported to the FDA Adverse Event Reporting System (FAERS) database. Avadel indicates that for the time period from 1/01/03 to 6/30/20, there were 2,056 cases that reported a reaction of fall in patients receiving Xyrem, and they have reviewed 120 of these cases. Of these, there were 14 (11.67%) in which a patient experienced a fall after the second dose of Xyrem. Injuries reported include lacerations and various broken bones. In some cases following these injuries, Xyrem was discontinued or the dose was reduced.

In addition, Avadel indicates that PK differences between these drugs result in Lumryz having lower rates of well-known adverse events compared to Xyrem. They have provided a summary of reported rates of nausea, vomiting, dizziness, somnolence, and tremor for Lumryz and Xyrem. Although it does not appear that these two drugs were compared in a head-to-head manner, and the orphan drug regulations do not necessarily require head-to-head studies to support clinical superiority based on safety, generally, the rates of nausea, vomiting, and dizziness provided appear to be lower with Lumryz versus Xyrem.

Avadel also indicates that there is a risk of misuse associated with the second dose of Xyrem because patients are supposed to measure out both nightly doses prior to

bedtime and place the second dose near the bed. They note that a child could consume the second dose if the child-resistant container is not used, the second dose could be stolen, or patients could accidentally consume both doses.

Another argument presented by Avadel related to safety concerns, illicit use and diversion. They note that Lumryz will be formulated as white granules while Xyrem is a clear to slightly opalescent oral solution. Avadel states that Lumryz will be cloudy in solution and both its appearance and gritty consistency should alert individuals if it has been added to their drink. They also note that Lumryz tastes salty and bitter; however, they do not describe the taste of Xyrem or Xywav, and they do not describe the appearance of Xywav.

Avadel's last argument regarding safety concerns sodium content in Lumryz, Xyrem, and Xywav. Lumryz contains a similar amount of sodium as Xyrem. Avadel argues that the reduced sodium in Xywav does not render Xywav clinically superior to Xyrem. These arguments have already been evaluated in DN1 consult responses to OOPD dated 11/27/20 and 3/08/21 regarding Xywav. Avadel concludes that overall, the safety, efficacy, and quality of life issues related to the second dose of twice-nightly sodium oxybate present a greater risk to patients than sodium content, and each of these greater risks is significantly improved and addressed with the once-nightly formulation of Lumryz.

Major Contribution to Patient Care:

Avadel provides other arguments that appear to be aimed at making a case for Lumryz providing a MCTPC. The OOPD notes that a MCTPC can only be considered in cases where greater effectiveness or greater safety have not been demonstrated. To support their argument, Avadel references a survey of 1,350 individuals impacted by narcolepsy, the results of which were distributed at the September 24, 2013 FDA Meeting on Drug Development for Narcolepsy. This survey found that patients' ideal therapy was "a drug that would provide consistent and adequate control of the daytime sleepiness without the hard crash and one that would require one dose taken at bedtime resulting in 8 hours of restorative sleep." Avadel also conducted a study using publicly available digital Xyrem and narcoleptic-related data from 9/01/17 to 10/15/19. Sources included things such as blogs, forums, message boards, social media outlets, and OpenFDA. Data are provided from this study regarding the volume and type of quality of life issues that are associated with the need for a second nightly dose of Xyrem, such as trouble waking up to take the second dose.

Avadel also indicates that there is a food effect which appears to be more pronounced with Xyrem and Xywav compared to Lumryz. They note that both the Xyrem and Xywav labels instruct patients to take the first nightly dose at least two hours after eating. Examples are mentioned of patients reporting reduced effectiveness after taking Xyrem too close to a meal. Avadel states that Lumryz's reduced food effect and subsequent impact on blood levels, could result in greater efficacy and improved quality of life.

In addition, Avadel conducted a Discrete Choice Experiment (DCE) to quantitatively characterize the preferred treatment attributes of narcolepsy patients. This consisted of a 30-minute web-based survey of 75 narcolepsy patients that were past or current Xyrem users. This survey found that dosing frequency (once nightly vs. twice nightly) was the single most important attribute when selecting a narcolepsy treatment, and the most common reasons for overall product preference were lack of need to wake up in the middle of the night to take a second dose (48%), fewer side effects (46%), and ease of taking/handling (32%).

The OOPD notes that most of the arguments provided regarding a MCTPC, suggest that Lumryz would provide greater convenience than Xyrem and Xywav, and that patients may prefer it over these other oxybate products. Improved convenience and patient preference alone may not rise to the level to support a claim of clinical superiority for the purpose of orphan drug exclusivity. However, given that narcolepsy is a chronic sleep disorder and requires long-term therapy, the impact that Lumryz's once-nightly dosing may have on patient quality of life may be substantial enough to constitute a MCTPC. In addition, the fact that there is no second nightly dose for patients to potentially miss and effect the efficacy of the drug may also render Lumryz as a MCTPC compared to Xyrem and Xywav.

In summary, one of the definitions of clinical superiority that is stated in the orphan drug regulations is greater safety in a substantial portion of the target populations. "Substantial" is not defined in the regulations. Thus, it is not necessary for a drug to provide greater safety in all of the indicated population in order for it to be considered clinically superior. This definition also recently served as the basis for finding Xywav clinically superior to Xyrem since the differences in the sodium content of these two products at the recommended doses will be clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated. Among the arguments provided by Avadel, the OOPD finds most persuasive the argument for greater safety due to reduced fall potential with Lumryz compared to Xyrem and Xywav. It appears that there may be a substantial portion of the indicated population of adult patients with narcolepsy that may achieve greater safety with Lumryz due to its once nightly dosing compared to the twice nightly dosing required for Xyrem and Xywav.

Consult Questions:

1. Is there any evidence to suggest that the efficacy of Lumryz may be substantially different from Xyrem or Xywav? If so, please elaborate.
2. Does the review division agree that Lumryz provides greater safety in a substantial portion of the target population when compared to Xyrem and Xywav? If so, what safety advantage does Lumryz provide? Please elaborate. (As a reminder, the orphan drug regulations do not require head-to-head studies for safety.)

3. Does the review division agree with the sponsor that Lumryz has less potential for illicit use and diversion compared to Xyrem and Xywav? Please explain.
4. Does the review division consider Lumryz to provide a major contribution to patient care (MCTPC) compared to Xyrem and Xywav? If so, on what basis?
5. Are there any other issues not addressed above that the review division would like the OOPD to consider in its determination of eligibility for orphan-drug exclusivity for Lumryz?

Regulations:

21 CFR 316.3(b)(3) defines clinical superiority as follows:

- (3) Clinically superior means that a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in one or more of the following ways:
- (i) Greater effectiveness than an approved drug (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative effectiveness claim for two different drugs; in most cases, direct comparative clinical trials would be necessary; or
 - (ii) Greater safety in a substantial portion of the target populations, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. In some cases, direct comparative clinical trials will be necessary; or
 - (iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.

3. Contents Of Review

The contents of this consultative review will be in the same consecutive order as below.

- Request for priority review designation for Lumryz™.
- Response to questions in original OOPD consultation request of July 6, 2021.
- Supplement to request for orphan exclusivity: July 14, 2021.
- Summary comments.

4. Request For Priority Review Designation For Lumryz™

A request for priority review designation accompanied the original submission of NDA 214755. That request was denied by the Agency after full review of its contents. As many components of that request are pertinent to the current consultation, the Agency's criteria for priority review designation, the contents of that request, and the Agency's action in response to that request are further summarized below.

The full text of the applicant's priority review request is available at the following link

<\\CDSESUB1\evsprod\nda214755\0001\m1\us\12-cov-let\priority-review-request.pdf>

4.1 Criteria For Granting Priority Review Designation

The core criteria for granting priority review designation to a marketing application for a drug or biologic are as follows:

1. The product is intended to treat a serious condition.
2. The product if approved would provide a significant improvement in safety or effectiveness

These criteria are discussed in more detail in an Agency Guidance for Industry publication entitled "*Expedited Programs for Serious Conditions – Drugs and Biologics*" (May 2014) available at:

<https://www.fda.gov/media/86377/download>

4.2 Summary Basis For Applicant's Request For Priority Review Designation

The applicant's request for priority review designation for Lumryz™ was based on the following overall conclusion: the once-nightly dosing regimen for that product would provide a significant improvement in safety and effectiveness in the treatment of cataplexy and excessive daytime sleepiness in narcolepsy compared to currently available therapies, including Xyrem® and Xywav™.

The above overall conclusion was based in turn on the following summary assertions (for which additional data was provided in the request).

- A once-nightly dosing regimen, as with Lumryz™ would remove the anxiety and sleep disruption resulting from the need to awaken to take a second dose (as is the case with Xyrem® and Xywav™).

- A once-nightly dosing regimen would be less likely to result in missed doses, and would thus improve effectiveness and quality of life, as compared with a twice-nightly regimen.
- The need to awaken at night to take a second dose (as with Xyrem® and Xywav™) increases the risk of adverse events, such as falls. Since the C_{max} of oxybate products may correlate with other adverse events such as nausea and vomiting, a second C_{max} as occurs the twice-nightly formulations make increase the risk of those adverse events, too.
- Data from the key efficacy study of Lumryz™ (Study CLFT218-1501; REST-ON) indicate that the better known adverse events associated with sodium oxybate are less frequent with Lumryz™ than with Xyrem®.
- Data from a patient survey indicate a preference for a once-nightly dosing regimen (i.e., with Lumryz™) than for the twice-nightly regimen used for Xyrem® and Xywav™.

It is readily apparent that the arguments used by the applicant in support of the priority review designation request for Lumryz™ were very similar to those used in support of the current request for orphan exclusivity currently under review.

4.3 Agency Action In Response To Request For Priority Review Designation

The Agency was not persuaded by the arguments used in support of the applicant's request for priority review designation and in a letter dated February 26, 2021, assigned this application a standard review.

5. Response To Questions In Original OOPD Consultation Request Of July 6, 2021

Please note that our responses to the question are based in part on our preliminary review of data submitted with NDA 214755, the review of which is ongoing, and of the available data for Xyrem® and Xywav™.

Question 1. Is there any evidence to suggest that the efficacy of Lumryz may be substantially different from Xyrem or Xywav? If so, please elaborate.

Division of Neurology 1 Response to Question 1

There is no evidence suggesting that the efficacy of Lumryz™ is substantially different from that of Xyrem® or Xywav™.

Question 2. Does the review division agree that Lumryz provides greater safety in a substantial portion of the target population when compared to Xyrem and Xywav? If so, what safety advantage does Lumryz provide? Please elaborate. (As a reminder, the orphan drug regulations do not require head-to-head studies for safety.)

Division of Neurology 1 Response to Question 2.

The available data do not indicate that Lumryz™ provides greater safety in a substantial proportion of patients in the target population (i.e., patients who have narcolepsy with cataplexy and/or excessive daytime sleepiness) than Xyrem® or Xywav™, despite the arguments provided by the applicant. Very limited conclusions, if any, can be drawn from the comparison of the frequency of specific individual adverse events seen with Lumryz™ with those seen with Xyrem® that has been presented by the sponsor. That comparison is flawed for a number of readily-evident reasons. In broad terms, the safety profiles of all 3 products (Lumryz™, Xyrem®, and Xywav™) are not substantially different.

Question 3. Does the review division agree with the sponsor that Lumryz has less potential for illicit use and diversion compared to Xyrem and Xywav? Please explain.

Division of Neurology 1 Response to Question 3

We are not persuaded by the applicant's arguments that Lumryz™ has meaningfully less potential for illicit use and diversion compared with Xyrem® and Xywav™, based either on the appearance and taste of each these products, or on the administration of a once-nightly dose of Lumryz™ versus two nightly doses of Xyrem® and Xywav™.

Question 4. Does the review division consider Lumryz to provide a major contribution to patient care (MCTPC) compared to Xyrem and Xywav? If so, on what basis?

Division of Neurology 1 Response to Question 4

While the once-nightly regimen of Lumryz™ will be more convenient for patients than a twice-nightly regimen, that attribute cannot be considered a major contribution to patient care.

Question 5. Are there any other issues not addressed above that the review division would like the OOPD to consider in its determination of eligibility for orphan-drug exclusivity for Lumryz?

Division of Neurology 1 Response to Question 5

From the perspective of this Division, there are no other issues that appear to warrant further consideration by OOPD when determining the eligibility of Lumryz™ for the grant of orphan drug exclusivity,

6. Supplement To Request For Orphan Exclusivity: July 14, 2021

As noted earlier, this supplement to the original request for orphan exclusivity for Lumryz™ is being primarily reviewed by OOPD. However, this Division has been asked to review and comment on this supplement in conjunction with the response to the original consultation request of July 6, 2021.

6.1 Summary Of Supplement To Original Request For Orphan Exclusivity

As already noted, this supplement is entitled “*Exclusivity Claim – Supplemental Information in Demonstration of Clinical Superiority of FT218.*”

A full link to the contents of this supplement is available at the link below:

<\\CDSESUB1\evsprod\nda214755\0022\m1\us\13-admin-info\exclusivity-ode.pdf>

The key observations and assertions made by the applicant in this supplement are as follows.

- A proportion of the 67 patients who transitioned from twice-nightly Xyrem® or Xywav™ to once-nightly Lumryz™ in an interim analysis of an ongoing open-label uncontrolled study CLFT218-1901 reported the following while receiving the twice-nightly regimen: falls while taking the second nightly dose (6%), nausea and/or vomiting after taking the second nightly dose (23%), missing the second nightly dose at least once over a 3-month (85%), and “anxiety related to the second nightly dose” (21%). 28 out of 30 patients who had completed 3 months of stable dosing with FT218 preferred the once-nightly regimen of Lumryz™ to the twice nightly regimen of either Xyrem® or Xywav™.
- A market analysis of physicians experienced in prescribing Xyrem® and Xywav™ may have suggested that a once-nightly regimen may be preferred to a twice-nightly regimen by patients.
- Poor sleep quality, sleep interruption, short sleep duration, and other sleep disturbances may all be associated in themselves with an increased cardiovascular risk based on a review of the medical literature (further details are provided in this submission). A once-nightly dosing regimen, as with Lumryz™, is less likely to interrupt sleep than a twice-nightly regimen, as with Xyrem® and Xywav™, which cannot result a normal sleep pattern. Data from the efficacy study CLFT218-1501 included in NDA 214755 indicate that patients receiving Lumryz™ have an improvement in several

parameters that measure nocturnal sleep. Thus Lumryz™ has the potential to provide a cardiovascular safety benefit, unlike Xyrem® and Xywav™ which may be associated with an increased cardiovascular risk on account of the interruption in nighttime sleep associated with the need to taking a second dose.

6.2 Division Of Neurology 1 Comments

The contents of this supplement suggest, not unexpectedly, that patients may prefer a once-nightly dosing regimen (as with Lumryz™) to a twice-nightly dosing regimen (as with Xyrem® and Xywav™).

Any conclusions that Lumryz™ may have the potential for being associated with a lower cardiovascular risk than Xyrem® or Xywav™ on account of being administered only once-nightly are at best highly speculative.

7. Summary Comments

In this Division's opinion, no evidence has been provided by the applicant that Lumryz™ is clinically superior to Xyrem® or Xywav™ as defined in the orphan drug regulations [21 CFR 316.3(b)(3)].

Ranjit B. Mani -S

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Ranjit B. Mani, M.D.
Medical Reviewer

Eric P.
Bastings -S

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Date: 2021.08.31 14:01:43 -04'00'

Eric Bastings, M.D.
Division Director (Acting)

cc:
HFD-120
IND

Date: April 29, 2023

From: Mahadevappa Hunasikatti, MD FCCP

Mahadevappa Hunasikatti -S
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Date: 2023.04.29 08:46:03 -04'00'

Nargues Weir, MD FCCP FAASM ATSF

Nargues A. Weir -S
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Date: 2023.04.29 06:53:17 -04'00'

Sleep Team/DSRA/OHT1/CDRH

Through: Rachana Visaria Ph.D.
Assistant Director/Sleep Team/DSRA/OHT1/CDRH

Rachana Visaria -S
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Date: 2023.04.29 10:44:41 -04'00'

To: Sandra Retzky DO, JD, MPH
Director, Office of Orphan Product Development

OPCR: DRU 16-5302

Subject: Consult request on Lumryz (extended-release sodium oxybate) administered as an oral solution once at bedtime for treatment of cataplexy or excessive daytime sleepiness associated with narcolepsy.

OOPD (“you”) have consulted the Sleep Team/DSRA/OHT1/CDRH for input on whether Lumryz (extended-release sodium oxybate), with once nightly administration, is “clinically superior” to Xywav and Xyrem based on being a “major contribution to patient care” or MCTPC. Specifically, you seek our opinion, as board certified sleep specialists, on whether Lumryz, with once nightly dosing, makes a MCTPC over Xywav and Xyrem, both with twice nightly dosing, and if so, why. We understand that other factors may also inform the agency’s MCTPC determination, and this memo considers solely Lumryz’s once nightly dosing.

Summary Response

It is our opinion that Lumryz is clinically superior because it provides a significant therapeutic advantage over and above that of Xywav and Xyrem. The underpinning of our rationale is that patients with narcolepsy, a sleep disorder, will not need to awaken from sleep to take a second dose of Lumryz—which is dosed only once at bedtime—unlike Xywav and Xyrem, which are both labeled for twice nightly dosing.¹ From a therapeutic perspective, it is highly desirable to eliminate, or at least minimize, nocturnal arousals from sleep—especially for patients who have

¹ See Section 2.1, *Adult Dosing Information*, Xyrem labeling, (accessed at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=926eb076-a4a8-45e4-91ef-411f0aa4f3ca>); See Section 2.1 *Dosing Information in Adult Patients with Narcolepsy*, Xywav labeling (accessed at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1e0ae43a-037f-42af-8e23-a0e51d75abe8>).

a sleep disorder and seek treatment.² A nocturnal arousal from sleep to take a second dose of sleep medication will fragment sleep and disrupt sleep architecture.^{3, 4, 5}

The goal of treatment for all sleep disorders—including narcolepsy—is to restore a normal sleep pattern. To that end, not awakening the patient to take a second dose of sleep medication is highly preferable from a clinical standpoint. Therefore, a once nightly dose of oxybate, makes a MCTPC because Lumryz, as compared to Xywav and Xyrem, avoids an arousal from sleep and will help to minimize sleep disruption.

Normal sleep

Adequate sleep is essential for humans as it physically and psychologically restores bodily functions.⁶ Without adequate sleep, humans function poorly and may die prematurely.⁷ Chronic sleep loss, sometimes called sleep debt, is well known to cause reduced performance, increased risk for accidents and death, and detrimental effects on both psychological and physical health.⁸

² The American Academy of Sleep Medicine (AASM) defines “arousal” as a finding on a sleep study using an electroencephalogram (EEG) to view brain wave patterns. An arousal leads to wakefulness and is a type of sleep disturbance in which the person awakens, or shifts to lighter sleep, preventing progression to deeper more restorative sleep. Richard Berry, et. al, *The AASM Manual for the Scoring of Sleep and Associated Events (ver 2.6)* American Academy of Sleep Medicine (Jan 2020) at 46 (describing rules in adults that define arousals by certain EEG wave patterns and behavioral cues, e.g., eyes open, chin movement, etc. Arousals shift sleep stages, N2, N3, and R, back to stage N1 or stage Wake, and this fragments and disrupts sleep.). Awakening to take a second dose of oxybate, and having to set an alarm to do so (*see* fn 5 on AASM terminology defining arousal by Berry; *see* fn 27 on Xyrem and Xywav labeling) will cause sleep disruption and negatively impact sleep consolidation which is important for restorative sleep.

³ Douglas Kirsch, *Stages and architecture of normal sleep*, UpToDate (Sep 12, 2022) (explaining that “[s]coring of sleep stages occurs in 30-second epochs based on current American Academy of Sleep Medicine (AASM) scoring rules.”). *See* Richard Berry, et. al, *Arousal rule, The AASM Manual for the Scoring of Sleep and Associated Events, Rules, Terminology and Technical Specifications*, American Academy of Sleep Medicine (2020), version 2.6 at 46.

⁴ Richard Berry, et. al, *Arousal rule, The AASM Manual for the Scoring of Sleep and Associated Events, Rules, Terminology and Technical Specifications*, American Academy of Sleep Medicine (AASM) (2020), version 2.6 at 46 (explaining that arousals are defined with EEG criteria during stages N1, N2, N3, or R and are based on “an abrupt shift of EEG frequency . . . that lasts at least 3 seconds, with at least 10 seconds of stable sleep preceding this stage.”). When an individual awakens to take a second dose of medicine an “arousal” occurs because “behavioral cues, including open eyes [and] movement . . . demonstrates alertness”—a change in consciousness. *See* Douglas Kirsch, *Stages and architecture of normal sleep*, UpToDate (Sep 12, 2022). These behavioral cues inevitably occur in order to take a second dose of medicine, and even if the awakening is not remembered, nonetheless, it will fragment or disrupt sleep and is counterproductive to the treatment of narcolepsy.

⁵ Douglas Kirsch, *Stages and architecture of normal sleep*, UpToDate (Sep 12, 2022) (stating that: “[s]leep is a rapidly reversible state of reduced responsiveness, motor activity, and metabolism. It is a phenomenon observed in all animals in some form; this universality suggests that the act of sleeping likely has some evolutionary relevance. Humans spend approximately one-third of their life, or about eight hours per night, sleeping. The purpose of sleeping is poorly understood, however, and multiple theories exist. These theories include restoration, energy conservation, and memory consolidation.”) (internal citation omitted).

⁶ Kiran Maski, *Insufficient sleep: evaluation and management*, UpToDate (May 23, 2022) at https://www.uptodate.com/contents/insufficient-sleep-evaluation-and-management?search=sleep&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.

⁷ Chiara Cirelli, *Insufficient sleep: Definition, epidemiology, and adverse outcomes*, UpToDate (Oct 10, 2022) at <https://www.uptodate.com/contents/insufficient-sleep-definition-epidemiology-and-adverse-outcomes>. (explaining that “individuals may experience reduced performance, increased risk for accidents and death, and detrimental effects on both psychological and physical health.”).

⁸ *Id.*

Normal sleep architecture is characterized in adults as a progression of 90 to 120 minute sleep cycles starting with non-REM Stage 1 sleep (NREM or N1 sleep), then non-REM Stage 2 (NREM or N2) sleep, then non-REM Stage 3 (NREM or N3) sleep, and ending in Rapid Eye Movement (REM or stage R) sleep.⁹ “Stage R is characterized by the presence of rapid eye movements and . . . is a unique time of the night in that dreaming occurs during Stage R sleep.”¹⁰ After Stage R, the normal adult has a very brief return to stage Wake (stage W), in the transition of going from cycle to cycle, though this awakening is not typically remembered, is normal and does not contribute to sleep fragmentation, sleep loss, or daytime sleepiness.^{11, 12} It is part of the normal structure of sleep.¹³ The normal sleep cyclical pattern repeats 4-5 times per night allowing sufficient time for all the purposes of sleep to be met.¹⁴ Cycling progression through these stages is the basic structural organization of normal sleep and is called “sleep architecture.”¹⁵

Each sleep stage has unique features. Stage N1 sleep is light sleep (easily arousable), Stage N2 sleep is intermediate in depth (less light sleep), and Stage N3 is deep sleep, otherwise known as restorative sleep, slow-wave sleep (SWS), or delta sleep.¹⁶ Brain activity is low during Stage N3 sleep, and importantly, many recovery functions in the body occur only in this stage of sleep.¹⁷ “For an average individual in their second decade, Stage N1 is 2–5% of the total sleep

⁹ Douglas Kirsch, *Stages and architecture of normal sleep*, UpToDate (Sep 12, 2022) (accessed at https://www.uptodate.com/contents/stages-and-architecture-of-normal-sleep?source=history_widget) (stating that “[s]coring of sleep stages occurs in 30-second epochs based on current American Academy of Sleep Medicine (AASM) scoring rules.” Figure 10 portrays a hypnogram [sleep study] of a 36-year-old man in a sleep laboratory and it “represents the movement of a patient through various sleep cycles over the course of a single night . . .”).

¹⁰ James A. Rowley & M. Safwan Badr, *Normal Sleep at 3-5* in Chapter 1, *Essentials of Sleep Medicine a Practical Approach to Patients with Sleep Complaints*, (Meir Kryger et al. eds., 6th ed. 2017)

¹¹ See Figure 1.2, James A. Rowley & M. Safwan Badr, *Normal Sleep at 5* in Chapter 1, *Essentials of Sleep Medicine a Practical Approach to Patients with Sleep Complaints*, (Meir Kryger et al. eds., 6th ed. 2017) (depicting normal sleep architecture which includes 4-5 sleep cycles per night with five progressive stages, beginning at stage W and ending in stage R before the cycle begins anew).

¹² Douglas Kirsch, *Stages and architecture of normal sleep*, UpToDate (Sep 12, 2022) (explaining that: “[t]he polysomnogram is the primary tool for assessing sleep in the laboratory for both clinical and research purposes. During a polysomnogram, electroencephalography (EEG) and other sensors are used to categorize sleep in discrete stages.”).

¹³ M. A. Carskadon & W. C. Dement. *Monitoring and staging human sleep*, Chapter 2, in *Principles and practice of sleep medicine*, (Meir Kryger, et. al eds., 5th ed. 2011) at 12 (accessed at

<http://apsychoserver.psych.arizona.edu/jbareprints/psyc501a/readings/Carskadon%20Dement%202011.pdf>) (explaining that “[b]rief episodes of wakefulness tend to intrude later in the night, usually near REM sleep transitions, and they usually do not last long enough to be remembered in the morning”).

¹⁴ C. S. Nayak, et. al, *EEG Normal Sleep*. (accessed at <https://www.ncbi.nlm.nih.gov/books/NBK537023/>) (explaining that “[i]n normal adults, each cycle lasts for about 90 to 120 minutes, and there are about 4 to 5 such cycles that occur during a normal 8 hour night sleep.”).

¹⁵ James A. Rowley and M. Safwan Badr, *Normal Sleep*, Chapter 1 at 3-5 in *Essentials of Sleep Medicine A Practical Approach to Patients with Sleep Complaints*, 2e (M. Safwan Badr ed., 2022) (describing sleep architecture as “the organization of the sleep stages over the course of the night.”).

¹⁶ M. A. Carskadon & W. C. Dement. *Monitoring and staging human sleep*, Chapter 2, in *Principles and practice of sleep medicine*, (Meir Kryger, et. al eds., 5th ed. 2011) (accessed at <http://apsychoserver.psych.arizona.edu/jbareprints/psyc501a/readings/Carskadon%20Dement%202011.pdf>) at 11 (explaining that “[i]nvestigators often refer to the combined stages 3 and 4 sleep as slow-wave sleep [SWS], delta sleep, or deep sleep.”). In the most current sleep terminology, Stage 4 is now part of Stage 3 and is no longer considered an independent sleep stage.

¹⁷ D-J Dijk, et. al, *Regulation and functional correlates of slow wave sleep*, *Journal of Clinical Sleep Medicine* (2009) (accessed at <https://pubmed.ncbi.nlm.nih.gov/19998869/>) at 1 (stating that “[d]eep nonrapid eye movement

time, Stage N2 is 45–55%, Stage N3 13–23%, and Stage R is 20–25%.”¹⁸ Normally, the sleep cycles progress through the night with increasing time in Stage N3 during initial sleep cycles and increasing REM sleep in each later sleep cycle during the night.¹⁹

Stage N3 sleep has a unique and important role in restoring the mind and body.²⁰ With sleep loss or deprivation or interruption, one enters Stage N3 sleep earlier and with increased quantity during the night.²¹ Thus, the body attempts to achieve sleep equilibrium by rapidly restoring this critical stage of sleep. On polysomnography (PSG)—a diagnostic full sleep study with an electroencephalogram (EEG)—REM sleep is a time of active brain EEG waves and physiological instability characterized by somewhat irregular heart rate and breathing patterns.²² REM is associated with paralysis of all muscles except the essential respiratory muscles (the diaphragm).²⁴

(NREM) sleep, also known as slow wave sleep (SWS), is considered to be the most restorative sleep stage and to be associated with sleep quality and maintenance of sleep.”)

¹⁸ James A. Rowley and M. Safwan Badr, *Normal Sleep*, Chapter 1 at 3-5 in *Essentials of Sleep Medicine A Practical Approach to Patients with Sleep Complaints* (M. Safwan Badr, ed., 2nd ed. 2022). The second decade of life is often used as a standard or heuristic in sleep medicine literature. The percent of time spent in each sleep stage declines with age when adulthood is reached. *See, also, Kirsch* (explaining how “[s]leep architecture also varies across the lifespan.”); Figure 11: graphic representation of the changes of sleep as humans age. The graph portrays “age-related trends for stage 1 sleep, stage 2 sleep, slow wave sleep, rapid eye movement sleep, wake after sleep onset, and sleep latency (in minutes).”

¹⁹ *See* fn 13, Figure 2-7 at 11 (picturing a sleep histogram with the progression of sleep stages across a single night in a normal young adult). The text describes the ideal or average pattern of time spent per stage.

²⁰ Lixia Chen, *et. al*, *The association between sleep architecture, quality of life, and hypertension in patients with obstructive sleep apnea*, *Sleep and Breathing* (2023) (accessed at <https://doi.org/10.1007/s11325-022-02589-z> at 192 (explaining that “N3 or SWS sleep is considered the most ‘restorative’ type of sleep . . .”).

²¹ Douglas Kirsch, *Stages and architecture of normal sleep* UpToDate (Sep 12, 2022) (accessed at https://www.uptodate.com/contents/stages-and-architecture-of-normal-sleep?search=stage%20N3%20sleep%20and%20sleep%20loss&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1 (explaining “[p]rior acute or chronic sleep deprivation may cause increases in stage N3 sleep and REM sleep.”). *See also* M.A Carskadon and W. C. Dement *Monitoring and staging human sleep*, Chapter 2, in *Principles and Practice of Sleep Medicine*, (Meir Kryger, et. al eds., 5th ed. 2011) accessed at <http://apsychoserver.psych.arizona.edu/jbareprints/psyc501a/readings/Carskadon%20Dement%202011.pdf>) at 12, 15 (stating that “[t]he SWS pattern reflects the homeostatic sleep system, highest at sleep onset and diminishing across the night as sleep pressure wanes. . . . Therefore, with total sleep loss, SWS tends to be preferentially recovered compared with REM sleep, which tends to recover only after the recuperation of SWS”).

²² Ye Zhang, *Polysomnographic nighttime features of narcolepsy: A systematic review and meta-analysis*, *Sleep Medicine Reviews* (Aug 2021) at 1 (stating that: [p]olysomnography . . . is the gold standard for objectively assessing sleep quantity and sleep quality.”). *See also* Carley, et. al *Physiology of Sleep* at 6 (explaining that: “[p]hysiologically, the gold standard for assessment of sleep and wake states is the laboratory polysomnogram (PSG)” and further describing the numerous noninvasive sensors are attached to a subject).

²³ Douglas Kirsch, *Stages and architecture of normal sleep*, UpToDate UpToDate (Sep 12, 2022) (accessed at https://www.uptodate.com/contents/stages-and-architecture-of-normal-sleep?search=stage%20N3%20sleep%20and%20sleep%20loss&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=10; M. A. Carskadon & W. C. Dement. *Monitoring and staging human sleep*, Chapter 2, in *Principles and practice of sleep medicine*, (Meir Kryger, et. al eds., 5e. 2011) (accessed at <http://apsychoserver.psych.arizona.edu/jbareprints/psyc501a/readings/Carskadon%20Dement%202011.pdf>) at 3-4 (explaining that REM sleep is characterized by bursts of rapid eye movements, muscle twitches and cardiorespiratory irregularities. “The mental activity of human REM sleep is associated with dreaming, based on vivid dream recall reported after approximately 80% of arousals from this state of sleep. . . . A shorthand definition of REM sleep, therefore, is an activated brain in a paralyzed body.”).

²⁴ *See* James A. Rowley & M. Safwan Badr, *Normal Sleep*, Chapter 1 in *Essentials of Sleep Medicine A Practical Approach to Patients with Sleep Complaints*, (ed. M. Safwan Badr, 2nd ed. 2022) at 5.

Arousals

When an arousal occurs, e.g., to take medication during the night after falling asleep, there is a shift in an EEG pattern—one that leads to a longer stage W with alertness or consciousness, even if not remembered.²⁵ Both Xyrem and Xywav labeling explain that after a dose, it usually takes at least 5 to 15 minutes to fall asleep, which means it usually takes at least 5 to 15 minutes to fall back asleep after taking the second dose.²⁶ Awakening to take a second dose necessarily disrupts sleep and causes fragmented sleep.^{27, 28} That duration of time in stage W is prolonged and will adversely impact a clinical measure called Wake After Sleep Onset (WASO)—a metric of how much wakefulness happens in a night of sleep.²⁹ In treating sleep disorders, including

²⁵ Douglas Kirsch, *Stages and architecture of normal sleep*, UpToDate UpToDate (Sep 12, 2022) (accessed at https://www.uptodate.com/contents/stages-and-architecture-of-normal-sleep?search=stage%20N3%20sleep%20and%20sleep%20loss&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=10) (explaining that arousals “bring[] the individual from deeper to lighter sleep or to wakefulness.” See also Pierre Philip, et. al, *Sleep Fragmentation in Normals: A Model for Sleepiness Associated with Upper Airway Resistance Syndrome*. *Sleep* (Apr 1994) at 244-245 (explaining that in an experiment simulating arousals in healthy young volunteers, “the mean duration of an EEG arousal was 11 seconds. Sleep architecture was significantly modified after sleep fragmentation [using the external stimulation]. There was a significant increase in stage 1 NREM sleep from a mean of 10.4 ± 8% to 23 ± 6%. . . . [D]espite prolongation of sleep to avoid sleep deprivation and a protocol set up to obtain sleep fragmentation with transient arousals only, the sleep architecture was significantly altered compared to the baseline night.”). This study demonstrates that even short arousals will significantly increase wakefulness and disrupt sleep leading to sleep fragmentation resulting with new daytime complaints of sleepiness. The authors state: “[t]his investigation thus indicates a progressive increase in daytime sleepiness from morning to evening after 1 night of sleep fragmentation.”

²⁶ Section 2.3 *Important Administration Instructions for All Patients*, Xyrem, (accessed at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=926eb076-a4a8-45e4-91ef-411f0aa4f3ca>) (the product labeling stating that “[p]atients will often fall asleep within 5 minutes of taking Xyrem, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night. Patients may need to set an alarm to awaken for the second dose. Rarely, patients may take up to 2 hours to fall asleep.”) (emphasis added); Section 2.4 *Important Administration Instructions for All Patients*, Xywav, (accessed at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1e0ae43a-037f-42af-8e23-a0e51d75abe8>) (explaining that “[p]atients will often fall asleep within 5 minutes of taking XYWAV, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night.”) (emphasis added).

²⁷ The term “arousal” is based on PSG—a test used to diagnose sleep disorders—which is performed at night and “nocturnal arousals” are those arousals that occur at night. The definition of “arousal” is derived from the AASM Scoring Manual v 2.6, page 19 and fn 3 *supra*, defines wakefulness as Stage Wake. Arousals will lead to wakefulness or lighter stage sleep. Wakefulness also refers to a clinical term of the state of not being asleep with varying degrees of consciousness. See Jonathan R.L. Schwartz & Thomas Roth, *Neurophysiology of Sleep and Wakefulness: Basic Science and Clinical Implications*, *Current Neuropharmacology* (2008) at 367, 370 (accessed at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2701283>) (describing the states of sleep and wake as an “on-off switch” between these behaviors, called a “sleep-wake switch.” Per Schwartz and Roth: “[t]hese findings suggest that when the self-reinforcing properties of the circuitry are weakened, individuals shift back and forth between sleep and wakefulness more frequently as well.” See, also Figure 3 at 370—a schematic diagram of the “flip-flop switch model.” This scientific explanation means that sleep and wake are two distinct states, when one is “on” the other must be “off.” Arousals, like that for taking a second dose of oxybate, flips the switch from “off” to “on” and this undoubtedly will disrupt sleep, cause fragmented sleep, and sleep loss.

²⁸ See fn 2 for the American Academy of Sleep Medicine’s definition of “arousal.”

²⁹ *What Is Wakefulness After Sleep Onset (WASO)?* Sleep Foundation (accessed at <https://www.sleepfoundation.org/sleep-studies/wakefulness-after-sleep-onset#:~:text=Wakefulness%20after%20sleep%20onset%20is,their%20WASO%20is%2025%20minutes>) (explaining that “[w]akefulness after sleep onset [WASO] is a measurement used to assess a person's sleep. It is the total number of minutes that a person is awake after having initially fallen asleep. For example, if someone wakes up once during the night and is awake for 25 minutes, their WASO is 25 minutes.”).

narcolepsy, the goal is to maximize the time in sleep and minimize wake time. i.e., minimize WASO.

Disruption of sleep leads to the inability to enter Stage N3, or disruption of N3, and such individuals will revert back to Stage W and subsequently progress to Stage N1 sleep and so forth.³⁰ The disruption changes sleep architecture and will increase WASO. This disruption is something to be avoided in the narcoleptic patient, if possible.

Narcolepsy

Narcolepsy is a disorder of REM intrusion into wakefulness.³¹ Sudden REM sleep onset during wakefulness causes loss of motor tone (sleep paralysis) along with a dream like state called cataplexy.³² REM intrusion can also occur during sleep, disrupting the normal sleep architecture described above.³³ Individuals with narcolepsy “generally fall asleep rapidly but can spontaneously awaken several times during the night and have difficulty returning to sleep. This sleep maintenance insomnia seems paradoxical in a disorder characterized by daytime sleepiness, and it may reflect a low threshold to transition from sleep to wakefulness.”³⁴ REM intrusion shifts sleep stages and prevents sleep continuity (also called sleep consolidation), fragments normal sleep architecture, and prevents sufficient deep sleep (prevents N3 restorative sleep from occurring because the sleep stages keep shifting to lighter sleep).³⁵ Often Stage N1 increases at the debt of Stage N3 sleep given the increased number of shifts between sleep stages.³⁶ This is seen in many sleep disorders, including narcolepsy.³⁷ This results in daytime sleepiness with the

³⁰ Richard Berry, et. al, *Arousal rule*, The AASM Manual for the Scoring of Sleep and Associated Events, Rules, Terminology and Technical Specifications, American Academy of Sleep Medicine (AASM) (2020), version 2.6 at 22-32.

³¹ Thomas E. Scammell, *Clinical features and diagnosis of narcolepsy in adults*, UpToDate (Jul 12, 2022) (accessed at https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-narcolepsy-in-adults?search=narcolepsy%20&source=search_result&selectedTitle=1~120&usage_type=default&display_rank=1).

³² Thomas E. Scammell, *Clinical features and diagnosis of narcolepsy in adults*, UpToDate (Jul 12, 2022).

³³ Imran Ahmed & Michael Thorpy, *Narcolepsy and Idiopathic Hypersomnia*, at 328 in Chapter 15 in *Essentials of Sleep Medicine* (M. Safwan Badr et. al, eds., 2nd ed. 2022) (explaining that “[t]he effects of narcolepsy can be considered a manifestation of REM sleep dissociation, with features of REM sleep that intrude into [the NREM stages of] sleep and wakefulness” , instead of progressing normally).

³⁴ Thomas E. Scammell, *Clinical features and diagnosis of narcolepsy in adults*, UpToDate (Jul 12, 2022).

³⁵ Michelle T. Cao, et. al, *Narcolepsy: Diagnosis and Management* (explaining that “[n]arcolepsy disrupts the maintenance and orderly occurrence of wake and sleep stages.”); Ye Zhang, *Polysomnographic nighttime features of narcolepsy: A systematic review and meta-analysis*, Sleep Medicine Reviews (Aug 2021) (accessed at <https://pubmed.ncbi.nlm.nih.gov/33934047/>) at 11 (stating that: “nighttime PSG changes . . . demonstrate[] poor sleep continuity and altered sleep architecture in narcolepsy. It has been suggested that some PSG changes in narcolepsy such as frequent SS [stage shifts] and short bouts of wakefulness occur primarily in the second NREM sleep episode which hinders slow wave activity and provides inadequate NREM intensity.”). Slow wave sleep only occurs in N3 and when SWS does not occur with enough intensity, an individual does not get restorative sleep. See fn 18 (explaining that: “[d]eep nonrapid eye movement (NREM) sleep, also known as slow wave sleep (SWS), is considered to be the most restorative sleep stage and to be associated with sleep quality and maintenance of sleep.”).

³⁶ Ye Zhang, *Polysomnographic nighttime features of narcolepsy: A systematic review and meta-analysis*. Sleep Med Reviews. (Aug 2021) (accessed at <https://pubmed.ncbi.nlm.nih.gov/33934047/>) at 1 (stating “[m]eta-analyses revealed significant reductions in sleep latency, sleep efficiency, *slow wave sleep percentage*, rapid eye movement sleep (REM) latency, cyclic alternating pattern rate, and increases in total sleep time, *wake time after sleep onset (WASO)*, *awakening numbers (AWN) per hour*, *stage shift (SS) per hour*, *N1 percentage*, apnea hypopnea index, and periodic limb movement index in narcolepsy patients compared with [healthy controls]”) (emphasis added).

³⁷ Zhang at 4 (explaining that a “meta-analysis revealed significantly decreased . . . SWS% . . . and increased . . . N1 percentage” in narcolepsy compared with healthy controls.”).

consequences of sleep fragmentation or sleep deprivation, i.e., altered sleep architecture which may affect daytime performance.³⁸

EDS is the most common and chronic symptom of narcolepsy.³⁹ Per Scammell: “[t]he sleepiness may be so severe that patients with narcolepsy can rapidly doze off with little warning; these episodes are commonly referred to as ‘sleep attacks.’”⁴⁰ Another symptom of narcolepsy, cataplexy, is an “emotionally-triggered transient muscle weakness” that can cause a patient to collapse.⁴¹

Xyrem, Xywav, and Lumryz

The FDA-approved labeling for Xyrem and Xywav instructs patients to awaken to take a second dose approximately 2.5 to 4 hours after initial administration and falling asleep.⁴² If patients do not intentionally awaken to take the second dose (e.g., by setting an alarm), the effects of the drug will wear off, and the patients may awaken anyway and need the second dosing to return to sleep. It is our opinion that awakening to take a second dose of sleep medication, such as Xywav or Xyrem, is not optimally supportive of the continual sleep necessary to restore sleep architecture and daytime alertness with more normal functioning.

Lumryz combines both short-acting and long-acting salts of sodium oxybate allowing once nightly dosing.⁴³ Lumryz provides “a proprietary drug delivery technology . . . [and this] technology provides an early single peak, following a gradual decline in [oxybate] concentration . . . The premeasured dosing packets contain a mix of immediate-release and controlled-release microparticles of [oxybate].”⁴⁴ This formulation of oxybate provides a novel dosing characteristic of once nightly dosing, which in our expert opinion provides a MCTPC over the immediate-release formulations alone, i.e., Xyrem and Xywav.

As stated above, Xyrem and Xywav are both dosed twice nightly, which means patients experience a nocturnal arousal to take the medication.⁴⁵ Such arousals lead to awakening, i.e., consciousness, and this awakening disrupts sleep with the detrimental and harmful consequences that are known to occur with sleep loss.⁴⁶ Even with a single nocturnal arousal, there can be

³⁸ *Id.* at 1 (stating “[n]arcolepsy . . . is one of the most common causes of excessive daytime sleepiness (EDS) and is associated with an increased risk of car accidents, occupational problems, and injuries.”).

³⁹ Thomas E. Scammell, *Clinical features and diagnosis of narcolepsy in adults*, UpToDate (Jul 12, 2022).

⁴⁰ *Id.*

⁴¹ *Id.*

⁴² Section 2.1, *Dosage and administration*, Xyrem labeling, (accessed at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=926eb076-a4a8-45e4-91ef-411f0aa4f3ca>); Section 2.1, *Dosage and administration*, Xywav labeling (accessed at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1e0ae43a-037f-42af-8e23-a0e51d75abe8>).

⁴³ Clete A. Kushida, et. al, *Once-nightly sodium oxybate (FT218) demonstrated improvement of symptoms in a phase 3 randomized clinical trial in patients with narcolepsy*, Sleep (Jun 2022) at 2 (accessed at <https://pubmed.ncbi.nlm.nih.gov/34358324/>).

⁴⁴ Clete A. Kushida, et. al, *Once-nightly sodium oxybate (FT218) demonstrated improvement of symptoms in a phase 3 randomized clinical trial in patients with narcolepsy*. Sleep (Jun 2022) at 2 (accessed at <https://pubmed.ncbi.nlm.nih.gov/34358324/>).

⁴⁵ It is self-evident that an arousal occurs upon taking the second dose of Xyrem or Xywav because some degree of consciousness or alertness is needed for the voluntary movements involved in taking medicine.

⁴⁶ See fn 3, 5 *supra*.

impairment of alertness and decline in cognitive performance the following day.⁴⁷ It is known that disrupting sleep, even briefly, changes sleep architecture—the normal pattern of NREM and REM cycles requisite for daily restoration.⁴⁸ Nocturnal arousals should be avoided—especially in those with sleep disorders—as the goal of treatment is to restore normal sleep architecture.⁴⁹

It is incorrect to assume that a person with disrupted sleep can simply return to sleep and resume their normal sleep cycle. Rather, upon taking a second dose of Xyrem or Xywav, it may take at least 5-15 minutes to return to sleep—and such sleep does not resume where the patient left off to take their medication. Rather a new cycle of sleep must begin anew.⁵⁰ Thus, this disruption to take a second dose of Xyrem or Xywav should be avoided, if possible. An oxybate product that is dosed once nightly provides an opportunity for narcolepsy patients to achieve normal sleep architecture, which is not a possibility for a patient on Xyrem or Xywav who must either wake up to take a second dose (disrupting sleep architecture) or allow the drug to wear off after 2.5-4 hours (reverting patients back to their naturally occurring, disrupted sleep architecture).⁵¹

Conclusion

In summary, in our opinion, Lumryz provides a MCTPC over Xyrem and Xywav due to its once nightly dosing because, in treating a sleep disorder, it is best to eliminate or minimize nocturnal arousals to improve sleep quality and sleep architecture. This is a significant therapeutic advantage over the short-acting oxybate products. We defer to OOPD and the DNI to determine

⁴⁷ Chiara Cirelli, *Insufficient sleep: Definition, epidemiology, and adverse outcomes*, UpToDate (Oct 10, 2022) at <https://www.uptodate.com/contents/insufficient-sleep-definition-epidemiology-and-adverse-outcomes> (stating that: “[s]leep has two dimensions: duration (quantity) and depth (quality). When individuals fail to obtain adequate duration or quality of sleep, daytime alertness and function suffer. In response to sleep deprivation, sleep is often both longer and deeper. In many cases, however, sleep intensity can change without major changes in sleep duration. Sleep duration alone is therefore not a good indicator of how much sleep is needed to feel refreshed in the morning and function properly. . . . Sleep insufficiency exists when sleep is insufficient to support adequate alertness, performance, and health, either because of reduced total sleep time (decreased quantity) or *fragmentation of sleep by brief arousals (decreased quality)*”) (emphasis added).

⁴⁸ See fn 26 *supra*. Once an arousal occurs, falling back to sleep begins at N1, not where the person left off in their sleep cycle prior to the arousal, and therefore, arousals will change sleep architecture.

⁴⁹ Thomas E. Scammell, *Treatment of narcolepsy in adults*, UpToDate (Nov 14, 2022) accessed at https://www.uptodate.com/contents/treatment-of-narcolepsy-in-adults?source=history_widget (explaining that “[m]anagement of narcolepsy is symptomatic, and there are no disease-modifying therapies yet available. . . . Sleep deprivation [including nocturnal arousals] may worsen narcolepsy symptoms, and therefore patients should be counseled to maintain a regular and adequate sleep schedule.”).

⁵⁰ This is because once arousal occurs, falling back to sleep begins at N1, not where the person left off in their sleep cycle prior to the arousal—a missed opportunity to get into deep sleep (N3) which is restorative sleep.

⁵¹ See Figure 1, Emmanuel Mignot, et. al, *Sleep problems in narcolepsy and the role of hypocretin/orexin deficiency* in Steiner MA, (eds): *The Orexin System. Basic Science and Role in Sleep Pathology*, Frontiers in Neurol Neuroscience (2021) at 105 (depicting a 24-hour hypnogram (a sleep study which is read from left to right). Panels 1(a) and 1(b) are hypnograms from the same patient suffering from narcolepsy. In Figure (a), the patient is close to onset of disease; Figure (b) is the same patient 6 months after diagnosis. Figure c is a control (person with no sleep disease). Figures 1(a) and 1(b) represent the natural state of narcolepsy. During the day, the patient is falling asleep and has periods of daytime REM sleep (blue bars). The fine needle like projections during nighttime sleep (after 8pm) shows cycling between N1 and wake representing fragmented sleep. This is not restorative sleep because rapid cycling to wake and N1 prevent stable progression to deeper stages of restorative sleep. The patient will be impacted the following day because their sleep has been disrupted—even if they do not awaken during the night—and this is what occurs when oxybate wears off.)

whether and how considerations other than those considered in this consult may factor into the agency's MCTPC analysis.



**U.S. FOOD & DRUG
ADMINISTRATION**

Office of Orphan Products Development
Food and Drug Administration
WO32- 5295
10903 New Hampshire Avenue
Silver Spring, MD 20993

JAN 08 2018

The Weinberg Group Inc.
1129 Twentieth St., NW, Suite 600
Washington, DC 20036

Attention: Marla Scarola, MS
Senior Consultant
marla.scarola@weinberggroup.com

Re: Designation request # DRU-2016-5302
Amendment dated: October 13, 2017
Amendment received: October 13, 2017

Dear Ms. Scarola:

This letter responds to your amended request submitted on behalf of Flamel Ireland Limited for orphan-drug designation of sodium oxybate for extended-release oral suspension for “treatment of cataplexy and excessive daytime sleepiness in narcolepsy.”

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your orphan-drug designation request of sodium oxybate extended-release oral suspension is granted for *treatment of narcolepsy*. Please note that the designation granted is broader than the indication proposed in your designation request

Our decision to grant designation is based on the *plausible hypothesis* that your drug may be clinically superior to the same drug(s) already approved for the same indication because your drug may be more safe due to the ramifications associated with the dosing regimen for the previously approved sodium oxybate in treating patients with narcolepsy. See section 527 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360cc) and 21 CFR 316.3(b)(3) (defining “clinically superior”); and see 21 CFR 316.3(b)(14) (defining “same drug” in this context). Our determination that this hypothesis is plausible does not suggest that this is the only plausible hypothesis for your drug to be clinically superior to any same drug(s) already approved for the same indication.

In order to obtain orphan-drug exclusivity upon approval, you will need to demonstrate that your drug is clinically superior to any already approved version of the same drug for the same indication. Failure to demonstrate clinical superiority over the already approved same drug(s) will result in your drug not receiving orphan-drug exclusivity. *See* 21 CFR 316.34(c). The demonstration of clinical superiority does not need to substantiate the precise hypothesis upon which we based this designation, but instead may demonstrate clinical superiority any way that meets the statutory definition.

If your drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to submission of your marketing application, we request that you compare the drug's orphan designation with the proposed marketing indication and submit additional information to amend the orphan-drug designation if warranted. 21 CFR 316.26.

You must submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval. 21 CFR 316.30.

Please notify this Office within 30 days of submitting a marketing application for the drug's designated use. Once your marketing application is approved, please contact Jeffrey Fritsch, RPh at 301-796-8682 or alternatively at 301-796-8660 to assess eligibility for orphan-drug exclusivity.

If you have questions regarding the development of your designated product, please feel free to contact Gumei Liu, MD, PhD, at 301-796-0495 or alternatively at 301-796-8660. Congratulations on obtaining your orphan-drug designation.

Sincerely,

A handwritten signature in blue ink, appearing to read "Debra Y. Lewis" with a stylized flourish at the end.

Debra Y. Lewis, OD, MBA

Acting Director

Office of Orphan Products Development



Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32-5295
Silver Spring, MD 20993

AUG 23 2016

The Weinberg Group, Inc.
1129 Twentieth Street, NW
Suite 600
Washington, DC 20036

Attention: Marla Scarola, MS
Senior Consultant

Re: Designation request # 16-5302
Dated: April 20, 2016
Received: April 20, 2016

Dear Ms. Scarola:

This letter responds to your request on behalf of Flamel Ireland Limited for orphan-drug designation submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), of sodium oxybate for extended-release oral suspension (FT218) for “treatment of cataplexy and excessive daytime sleepiness in narcolepsy.”

The Office of Orphan Products Development (OOPD) has reviewed your request for orphan-drug designation and we are unable to grant your request at this time. While your population estimate and scientific rationale are adequate for the purposes of orphan drug designation, the concern with your request is described below.

The sponsor of a drug that is otherwise the same drug as an already approved drug may seek orphan-drug designation for the subsequent drug for the same rare disease or condition if they can provide a plausible hypothesis for the possible clinical superiority of the subsequent drug. The OOPD acknowledges that the proposed dosing regimen of FT218 is more convenient to the patient and/or caregivers than that of Xyrem[®]. However, based on your current submission, this reduction in dosing frequency is not considered as providing a major contribution to patient care. You have also not submitted a plausible hypothesis for superior efficacy or safety for your product over the approved product used per marketing label.

Further review of this application will be held in abeyance pending receipt of the above requested information. **Within 1 year of the date of this letter, please submit this additional information to OOPD or else submit a written request for an extension of time to respond.** Any extension request must include the reason(s) for the requested extension and the length of time of the requested extension. 21 CFR 316.24(a). Please

send such information or extension request to the following address and include reference to your designation request # 16-5302:

Office of Orphan Products Development
Food and Drug Administration
WO32-5295
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

This will be your only notice of the 1-year deadline to respond to the identified deficiencies or request an extension of time to respond. Failure to meet this deadline may result in OOPD considering your designation request voluntarily withdrawn. 21 CFR 316.24(a).

OOPD believes that you may benefit from a meeting with us to discuss your application. Please refer to the FDA's guidance document titled "Draft Guidance for Industry, Researchers, Patient Groups, and Food and Drug Administration Staff – Meetings with the Office of Orphan Products Development." This draft guidance is available at the following webpage:

<http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/OOPDNewsArchive/ucm350716.htm>"]

21 C.F.R. 316.20(b)(7) requires the sponsor of an orphan-drug designation request to submit a "summary of the regulatory status and marketing history of the drug." To complete this summary, please certify whether or not you ever submitted a marketing application for the same active moiety for the same rare disease or condition prior to the time you submitted this designation request. This information is relevant to confirm your drug meets the statutory and regulatory requirements for orphan drug designation. See Section 526(a)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb(a)(1)) ("A request for [orphan-drug] designation...shall be made before the submission of an application under section 505(b) for the drug.") *See also* 21 CFR 316.23(a) ("A sponsor may request orphan-drug designation at any time in its drug development process prior to the time that sponsor submits a marketing application for the drug for the same rare disease or condition.") Therefore, please self-certify that "Flamel Ireland Limited has not previously submitted a marketing application to the FDA for the same active moiety for the same rare disease or condition prior to the submission of this request for orphan drug designation #16-5302." This certification should be included in the amendment addressing the deficiencies noted above if you intend on continuing to pursue orphan drug designation.

Should you have any questions, please contact Jeff Fritsch, RPh in this Office at 301-796-8682 or alternatively at 301-796-8660.

Sincerely,

A handwritten signature in black ink that reads "Gayatri R. Rao" with a stylized flourish at the end.

Gayatri R. Rao, MD, JD

Director

Office of Orphan Products Development

cc:

OOPD/File # 16-5302
OOPD/Chron

History:
J. Fritsch 8/18/16
G. Liu
G. Rao

DEFICIENCY

REVIEW OF REQUEST FOR ORPHAN DRUG DESIGNATION

Date Submitted by Sponsor: 04/20/2016
Date Received by FDA: 04/20/2016
Date Review Completed: 07/28/2016
Designation Number: DRU-2016-5302
Trade name: N/A
Generic name (active ingredient): FT218 (sodium oxybate for extended-release oral suspension)
Sponsor: Flamel Ireland Limited
Block 10-1 Blanchardstown Corporate Park
Ballycoolin
Dublin 15
Ireland
Primary Contact: U.S. Agent for Flamel
Marla Scarola
Phone: 202.730.4129
E-mail: marla.scarola@weinberggroup.com
Manufacturer: The drug substance, sodium oxybate is manufactured in accordance with Good Manufacturing Practice at the following facilities:
(b) (4)
Manufacture of FT218 drug product is conducted in accordance with Good Manufacturing Practice at the following facility:
(b) (4)
Regulatory Status: FT218 is currently being tested under IND (b) (4) for the treatment of cataplexy (b) (4). It is not approved or marketed in any country including the US for any indication. No adverse regulatory actions have been taken against FT218 in any country.
Proposed Orphan Designation: For the treatment of (b) (4) narcolepsy

Orphan Drug Designation History: Six drugs currently hold orphan drug designation for the treatment of narcolepsy: DRU-2016-5268, DRU-2012-3751, DRU-2010-3072, DRU-1994-858, DRU-1993-737 and DRU-1987-263. Two have been approved: DRU-1994-858 (oxybate) and DRU-1993-737 (modafinil).

1. Disease Background^{i,ii}

Narcolepsy is a neurological disorder characterized by excessive daytime sleepiness, cataplexy, hypnagogic hallucination and sleep paralysis. The prevalence of narcolepsy in the US is 0.02-0.18%. Narcolepsy preferentially affects males with a male to female ratio of 2 to 1. Narcolepsy is thought to have genetic predispositions. Certain human leukocyte antigen (HLA) subtypes and abnormal hypocretin (orexin) neurotransmission have been associated with narcolepsy. An autoimmune etiology is also suggested.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines narcolepsy as recurrent episodes of irrepressible need to sleep, lapsing into sleep, or napping occurring within the same day. These sudden sleep attacks may occur during any type of activity at any time of the day. Although narcolepsy has traditionally been considered to be a disease of adulthood, most cases have their onset in childhood or adolescence. Sleep attacks must have been occurring at least three times per week over the past 3 months for the diagnosis of narcolepsy. There also must be the presence of at least one of the following:

- Episodes of cataplexy occurring at least a few times per month
- Hypocretin deficiency
- REM sleep latency ≤ 15 minutes, or a mean sleep latency ≤ 8 minutes and two or more sleep-onset REM periods (SOREMPs)

Two tests that are considered essential in confirming a diagnosis of narcolepsy are the polysomnogram (PSG) and the Multiple Sleep Latency Test (MSLT). Three forms of narcolepsy are recognized: narcolepsy with cataplexy, narcolepsy without cataplexy, and narcolepsy due to a medical condition.

Treatments of narcolepsy include both pharmacologic and nonpharmacologic approachesⁱⁱⁱ. Pharmacologic treatment of narcolepsy involves the use of central nervous system (CNS) stimulants such as methylphenidate, modafinil, dextroamphetamine sulfate, methamphetamine, and amphetamine. Modafinil (Provigil, Modasomil, Modiodal, Vigil) is the first-line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep in association with behavioral measures. Sodium Oxybate (XYREM®) is currently the first-line treatment for cataplexy in patients with narcolepsy. Antidepressants, either tricyclics or newer

ⁱ Scammell Thomas E. Narcolepsy. *N Engl J Med* 2015; 373: 2654–2662. doi:10.1056/NEJMra1500587.

ⁱⁱ Maret S, Tafti M; Tafti. Genetics of narcolepsy and other major sleep disorders. *Swiss Medical Weekly (EMH Swiss Medical Publishers Ltd.)* 2005;135 (45–46): 662–5. PMID 16453205.

ⁱⁱⁱ Thorpy M, Dauvilliers Y. Clinical and practical considerations in the pharmacologic management of narcolepsy. *Sleep Medicine*. 2015;16:9-18

antidepressants, are used treatments. (b) (4)

2. Population Estimate

The sponsor cited prevalence data from three sources, the National Organization for Rare Diseases, Longstreth et al. study in Washington state^{iv} and Silber et al. study in Minnesota^v. The cited prevalence are 1 per 2,000, 30.6 per 100,000 and 36 per 1,000 in the general population respectively. The sponsor states that all three indicate a prevalence of less than 200,000 in the US.

Reviewer's Comments: The sponsor stated that the Silber et al. reported a 36 per 1,000 prevalence. However, it appears that the sponsor misrepresented the data. The Silber et al. study actually reported a 56.3 per 100,000 prevalence in 1985. Also the sponsor did not provide an estimated number of the population but only a statement that it is under 200,000 in the US.

Using the prevalence of 56.3 per 100,000 and US population of 324 million, this reviewer estimate the population of narcolepsy to be approximately 180,000 (182,412) in the US. This prevalence estimate is consistent with other orphan drug designation for narcolepsy. The estimated prevalence meets the statutory requirement for orphan drug designation.

3. Scientific Rationale

FT218 is a one-dose sustained release formulation of sodium oxybate which is the same active moiety as the FDA approved Xyrem® for the same indication. Efficacy of sodium oxybate for treatment cataplexy and excessive daytime sleepiness in narcolepsy is well-demonstrated although the mechanism of action is not well understood.

Xyrem® has a half-life of 0.5 to 1 hour which necessitates a twice-nightly dosing in order to achieve 6 to 8 hours of nighttime sleep. Current labeling for Xyrem® states that patients may need to set an alarm to awaken for the second dose. If the window for the second dose (2.5 to 4 hours after the first dose) is missed, patients are instructed to skip the second dose because of the potential negative effects on functioning/alertness the following day. Comparison of blood levels from sodium oxybate achieved with a single 4.5 g dose of FT218 and split 2.25 g doses of Xyrem® (Figure 1) demonstrate the ability of the FT218 formulation to maintain therapeutic blood levels of the drug longer than a single dose of Xyrem®. Further, FT218 shows elimination of plasma levels at the end of the night similar to that achieved with Xyrem® taken twice, indicating that carryover sedation is unlikely to exceed that of the currently marketed product.

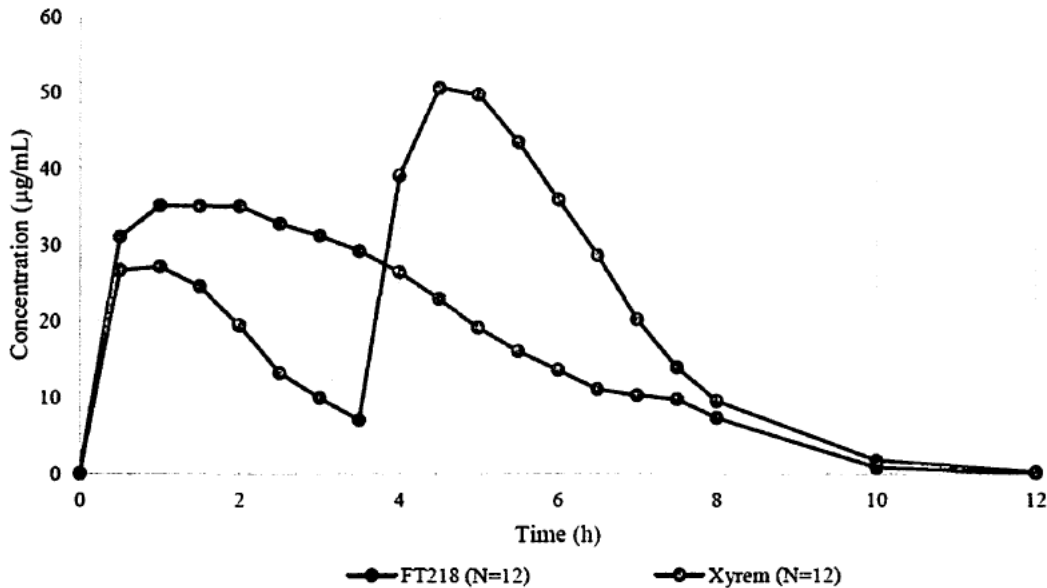
Reviewer's Comments: Scientific rationale for FT218 for the treatment is sufficient. It has been demonstrated that a single dose of 4.5g of FT218 is able to achieve a similar therapeutic level of

^{iv} Longstreth WT, Ton TGN, Koepsell T, Gersuk VH, Hendrickson A, Velde S. 2009. Prevalence of narcolepsy in King County, Washington, USA. *Sleep Med.* 10:422-426.

^v Silber MH, Krahn LE, Olson EJ, Pankratz VS. 2002. The epidemiology of narcolepsy in Olmsted County, Minnesota: A population-based study. *SLEEP* 25:197-202.

the approved Xyrem and a similar level of clearance at in 10-12 hours to eliminate carryover sedation.

Figure 1: Mean Plasma Sodium Oxybate Concentrations ($\mu\text{g/mL}$) – Time Profiles after a Single Oral Administration of 4.5 g of FT218 or Two 2.25 g Administrations of Xyrem[®]



Superiority over a similar already-approved product

The sponsor claims that FT218 provides a major contribution to patient care (MC to PC) over the approved marketed product Xyrem[®] (NDA 021196) by reducing the twice nightly dosing to once before bedtime. The sponsor did not make claims on superior clinical safety and efficacy.

To support the MC to PC claim, the sponsor cited a statement distributed at the September 24, 2013 FDA meeting on Drug Development for Narcolepsy: " ...an ideal therapy included, a drug that would provide consistent and adequate control of the daytime sleepiness without the hard crash and one that would require dose taken at bedtime resulting in 8 hours of restorative sleep". The statement is the result of a survey of 1,350 narcolepsy patients which suggested that patients suffering from fragmented sleep and overall sleep deficit consider the elimination of the need for a second nighttime dose to be a substantial advancement in therapy^{vi}.

The sponsor also provided several other probable benefits to support the MC to PC claim:

- Eliminate the obvious disadvantage of needing to disrupt sleep in order to take a drug that promotes sleep.
- Reduce the potential for decreased efficacy if the second of dose of Xyrem[®] is missed.

^{vi} Unite Narcolepsy. 2013. Patient-Focused Narcolepsy Survey: Interim Analysis as of September 16, 2013. Available at: <http://www.unitenarcolepsy.org/>

- Eliminate the need to disrupt the sleep of roommates and partners or parents/caregivers of affected children.
- Reduce safety risks of a second nightly dose of Xyrem® which include:
 - potential for consumption of the product left on a bedside table by a child
 - risk of falls or other accidental injuries if the second dose is not consumed in bed because of the rapid onset of effects
 - the risk of accidental measurement errors in nightly dose preparations

(b) (4)

Reviewer's Comments: I have discussed this MC to PC claim with Dr. Startzman. OOPD acknowledges that the elimination of the second nightly dose provides convenience in patient's care. However, OOPD does not consider this reduction in dosing frequency has risen to the level of major contribution to patient care.

Although not provided with this submission, I have downloaded a copy of the interim analysis report of the Patient-Focused Narcolepsy Survey (a hard copy is attached with this review). In this report, dosing schedule, though not specified, was identified as one of the main drawbacks of current available treatments. The first answer to the question of what specific things you look for in an ideal therapy for your condition was "A drug that would provide consistent and adequate control of the daytime sleepiness without the hard crash and one that would require one dose taken at bedtime resulting in 8 hours of restorative sleep" (as cited by the sponsor). It is not clear on what percentage of surveyed patients and/or caregivers identified the dosing schedule as a major issue and made the above cited statement. In my opinion, additional discussion may be beneficial to determine whether a patient survey or other forms of patient input can be accepted to support a MC to PC claim.

4. Recommendation

This submission contains an orphan drug designation request for FT218 for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy. Estimated population of narcolepsy in the US is less than 200,000. The active moiety of FT218, sodium oxybate, has been shown to be effective in narcolepsy. However, sodium oxybate is also the active moiety of the approved drug Xyrem for the treatment of narcolepsy. The sponsor claims that FT218 is superior to Xyrem® by providing major contribution to patient care. While OOPD acknowledges that the reduction in nighttime dosing frequency is convenient, it has not risen to the level which OOPD considers as major contribution to patient care.

Therefore, I recommend this designation request not be granted and the following deficiency be conveyed to the sponsor.

Deficiency: OOPD acknowledges that the proposed dosing regimen of FT218 is more convenient to the patients and/or caregivers than that of Xyrem[®]. However, based on your current submission, this reduction in dosing frequency is not considered as providing major contribution to patient care.

Note: Please also include the standard languages on meetings with OOPD.

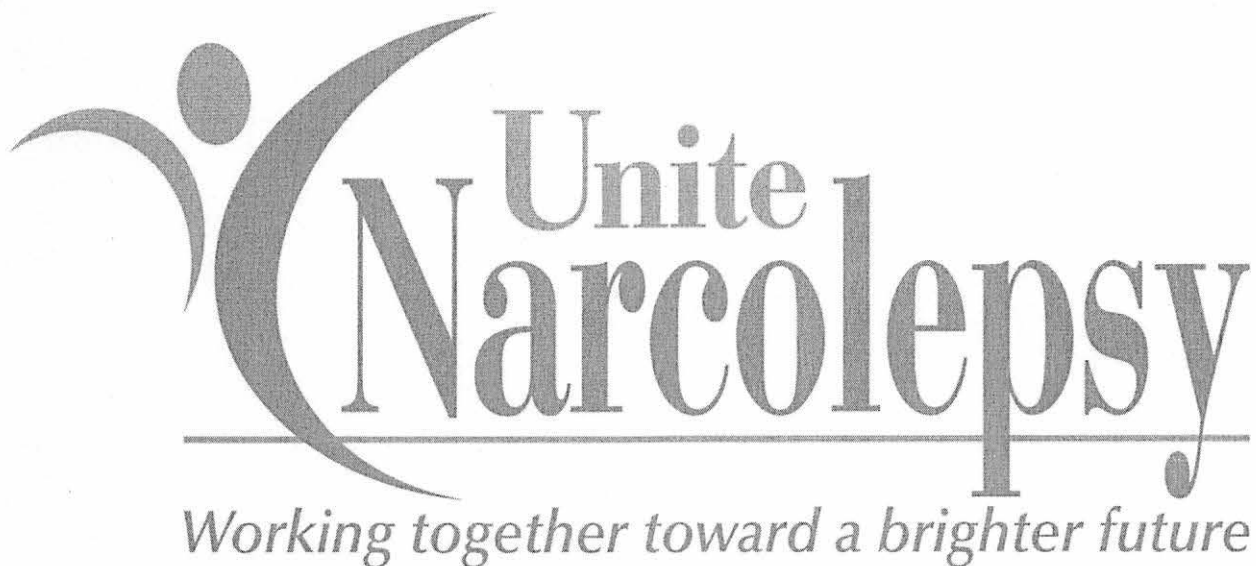


Gumei Liu, MD, PhD
Staff Fellow

Concur:  Date: 8/8/2016

Henry H. Startzman III, M.D.
Director, Orphan Drug Designation Program
Office of Orphan Products Development

Cc:
HF-35 / Designation File # 16-5302
HF-35 / Chron File
HF-35 / Gumei Liu



**PATIENT-FOCUSED NARCOLEPSY SURVEY
Interim Analysis as of September 16, 2013**

For Distribution at September 24, 2013 FDA Meeting on Drug Development for Narcolepsy

On September 24, 2013, patients with narcolepsy, family members and caregivers will gather at the Silver Spring, Maryland, campus of the U.S. Food & Drug Administration (FDA) to provide direct input on drug development issues affecting nearly 200,000 Americans with narcolepsy. The meeting, the fourth in the FDA’s Patient-Focused Drug Development Initiative series mandated under a 2012 law, will be the first session dedicated to a rare disease.

To prepare the patient community for this opportunity to speak directly with FDA regulators, Wake Up Narcolepsy, Inc., a nonprofit working to speed diagnosis of narcolepsy and help in the search for a cure, launched a special patient education and engagement initiative, Unite Narcolepsy. A comprehensive survey based on questions about narcolepsy posed by FDA was initiated on August 26, 2013 and has since generated response from more than 1,350 individuals, including more than 1,000 people diagnosed with narcolepsy by a physician. This is the largest survey ever conducted by a narcolepsy patient organization.

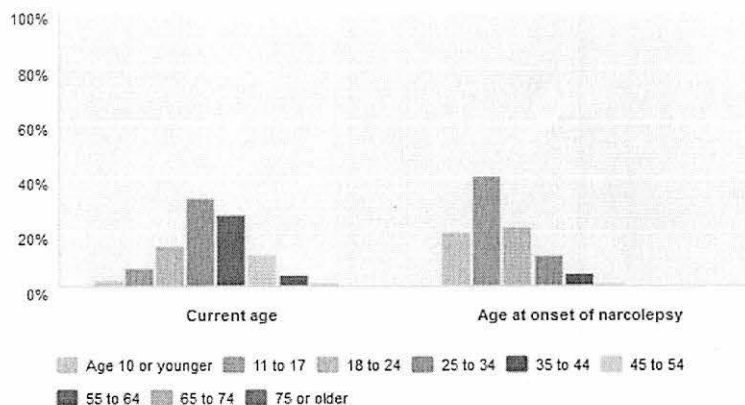
The survey will remain open until November 15, 2013 and a final analysis will be presented to the FDA through a public docket established for the purpose of hearing from the narcolepsy patient community. A summary of interim survey results is presented here:

Participant Profile:

- Of the 1,350 total respondents, 74% were individuals diagnosed with narcolepsy by a physician. 17% were the parent, spouse or other family caregiver for a person diagnosed with narcolepsy. 6% had been diagnosed with idiopathic hypersomnia or had a condition resembling narcolepsy but had not received a diagnosis from a physician.

What is your age (or the age of the person with narcolepsy with whom you are close)?

Answered: 1,128 Skipped: 222

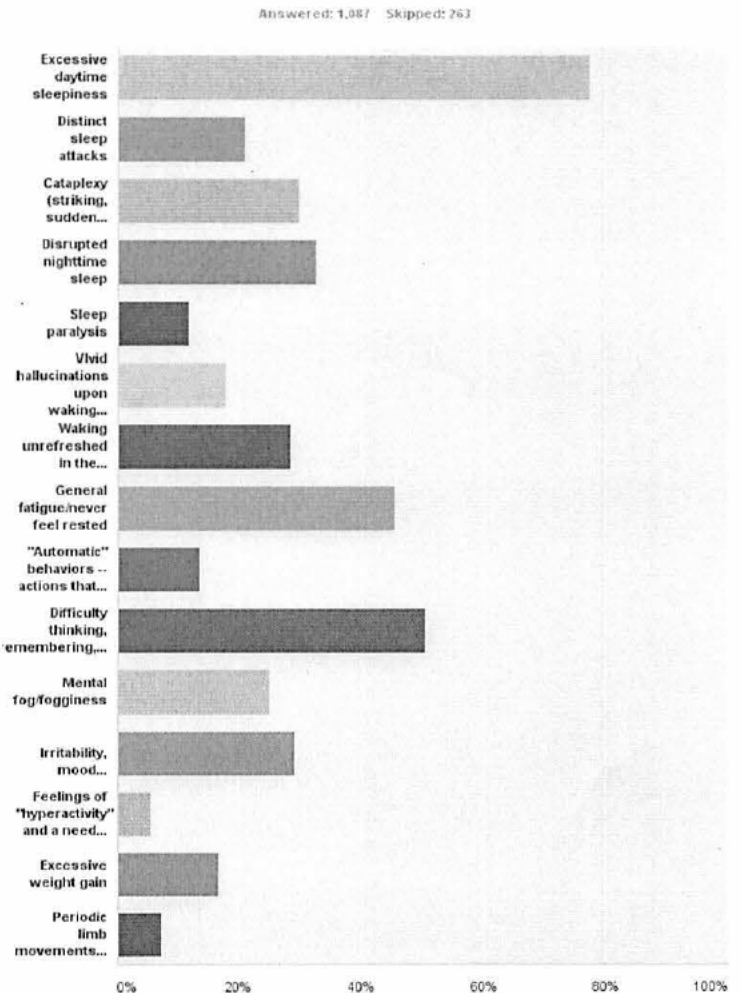


- More than half of respondents, 55%, have been affected by narcolepsy for more than 10 years.
- Nearly 51% of survey respondents reported that it took 6 years or longer to get properly diagnosed.
- 40% reported being between the ages of 11 and 17 when symptoms first appeared. There are currently no medications approved for use by children or teens with narcolepsy, adding challenges to management of the condition for younger patients.
- There is a high rate of other comorbid conditions reported through the survey. Two-thirds of respondents had one or more other medical conditions and one-fifth had three or more conditions in addition to narcolepsy. Anxiety, sleep apnea, migraines, fibromyalgia and other chronic pain conditions were among the most frequent diagnoses reported by respondents.
- Here are representative excerpts from comments about diagnosis submitted by respondents:
 - “It took me many years to realize that something was wrong – this was my ‘normal’ but I didn’t consider that it wasn’t normal at all. Once I decided to see a doctor when I was lucky enough to have insurance, things moved quickly although I’ve had an assortment of diagnoses over the years.”
 - “I have spent thousands of dollars on tests, prescription medicines, and doctors that did not help me. I have been made to feel crazy, like a hypochondriac, that I am really just lazy and have no self-control. I had severe onset at age 17, and since then have been on scores of antidepressants and mood stabilizers. I went from being a high achieving student to a college dropout with multiple suicide attempts and a dead-end blue collar job. I don’t see a future for myself.”
 - “As doctors and even a university hospital weren’t able to diagnose anything, I searched the Internet and found a possible diagnosis which was confirmed in the sleep laboratory soon afterwards.”
 - “My daughter has seen more than 15 specialists over the past 5 years and they couldn’t find anything wrong. It took the right doctor asking the right questions to pick up on something that prompted a sleep study.”

Symptoms:

- Cataplexy, a striking and sudden episode of muscle weakness often triggered by strong emotion, was reported by 64% of

Q11 Of all the symptoms that you experience because of your condition, which one to three symptoms have the MOST SIGNIFICANT impact on your life?



respondents. For those who experience cataplexy, it was most often triggered by laughing excitedly (43%), being angry (42%) and/or being startled (39%).

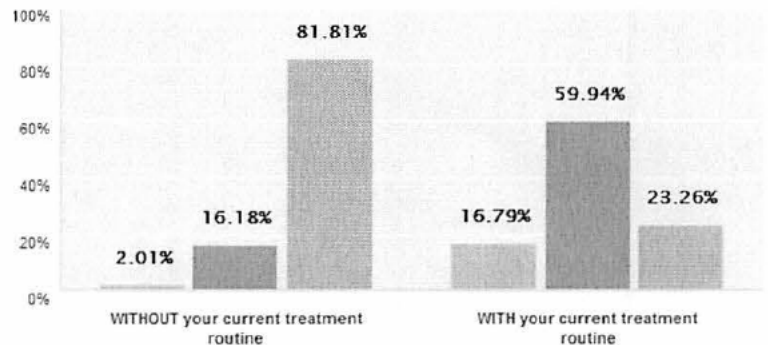
- The three symptoms rated as having the most significant impact on patients' lives were excessive daytime sleepiness (77%), difficulty thinking, remembering, concentrating or paying attention (50%) and general fatigue/never feeling rested (45%). For those with narcolepsy plus cataplexy, cataplexy was also rated as having a significant life impact.
- When describing their symptom patterns, 74% indicated that symptoms are present on a daily basis, with 29% reporting that they can vary from day-to-day and week-to-week. More than one-third (35%) noted that the level of symptoms varies according to other factors in their lives.
- Here are representative excerpts from comments about symptoms submitted by respondents:
 - "It is very hard to limit to only three symptoms, as the severity of the 11 of the symptoms contribute to destroying my quality of life."
 - "I have a condition that forces me to sleep and yet I am absolutely terrified of what sleep brings. Imagine being so sleepy you can't keep talking to your fiancé on the phone and nod off mid-sentence. I have hallucinations consisting of strange men at my door or thousands of bees coming of my fan, dreams so vivid it takes 10 minutes to recite them."
 - "Sleep paralysis is very scary and I have almost every one of the symptoms listed. Periodic limb movements affect my sleep too."
 - "So unfair to limit us to three! They are all connected. You sleep badly and it makes you feel more fatigued. More fatigue = more irritability and worse concentration. In 16 years I would answer this question differently depending on immediate circumstances. Today, memory loss is #1."
 - "Hallucinating with sleep attacks in the classroom is really disturbing."
 - "In all honesty, I can't quite pinpoint which symptom has 'the MOST SIGNIFICANT IMPACT' because they all do. It is a symptomatic concoction of misery."

Daily Life Impacts:

- 84% report not being able to perform as they wish at work or in school. 77% indicate that they have difficulty interacting with family or friends and 71% can't get through the day without falling asleep.
- In describing how their condition has changed over time, 37% responded that they are better informed and prepared to manage their conditions, but the symptoms and severity are about the same as when narcolepsy first started. A quarter of respondents indicated that the condition is more stable and manageable now; another quarter stated that it is worse and more unpredictable than when it first started.
- Here are representative excerpts from comments about daily life impacts submitted by respondents:
 - "I am afraid to hold my infant daughter for fear of losing muscle control at any moment."
 - "I don't cook alone anymore because I almost started a fire when cataplexy hit while I was at the stove one night."

How would you describe the severity of your condition?

Answered: 1,120 Skipped: 230

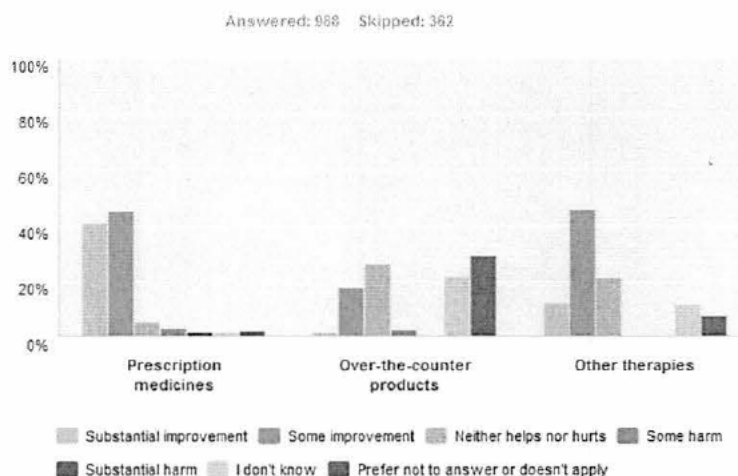


- "My daughter hardly goes out and when she does, she is so exhausted during the activity and the following day. She is afraid to drive. She is unable to work and gets tired just taking a walk. I do her laundry, shopping and cleaning."
- "I am trapped and can't contribute to society anymore. Even my own home is filled with perils because I am so prone to many cataplexy attacks. I miss going out with friends and loved ones, but I have no energy anymore."
- "We held off on a family and it's caused major issues in our relationship over the years."
- "I no longer recognize my own life because everything has changed."
- "I want to be/feel part of the family again."
- "I want to have full trust of my body again, not feel like I'm going to fall over and hurt myself or damage something."

Current Treatment:

- Overall, 82% of respondents describe their untreated condition as "severe" – significantly impacts daily activities. With treatment, only 22% report the same severe impact on function, with 61% describing their treated condition as "moderate" – causing some limitation on daily activities.
- Nearly 95% of survey respondents reported having been prescribed one or more of the four medications approved by FDA for treatment of narcolepsy or its key symptoms (Adderall, Nuvigil, Provigil and Xyrem). 79% use one or more of those medications currently. Other prescriptions medications (including stimulants, antiepileptics and hypnotics/sedatives) have been used by 70% of respondents; 90% use other therapies (including lifestyle modification, vitamins, nutritional supplements, diet and/or yoga) to help manage their condition. Over-the-counter products were currently used by just 23% of respondents. Fewer than 7% reported that they currently pursue no form of treatment for the condition.
- Without treatment, 77% of patients report experiencing 6 or more episodes of excessive daytime sleepiness each day. With treatment, the frequency of such symptoms falls dramatically to 1-2 times each day for 38% and 3-5 times each day for 41%. Episodes of cataplexy can be reduced as well; 41% report 3 or more daily cataplexy events without treatment, but just 13% experience as many episodes with currently available treatments.
- 41% of respondents credit prescription medicines with providing "substantial improvement" in their ability to do important activities of daily living and another 45% indicated that prescription medications provide some improvement in their function. By contrast, just 2% rated over-the-counter (OTC) products as providing "substantial improvement" and 18% rated OTC products as providing "some improvement." Other therapies (lifestyle modification, vitamins, etc.) were also an important factor in managing the condition, with 12% reporting "substantial improvement" with use of these approaches and 46% reporting "some improvement."
- The main drawbacks of currently available therapies reported by respondents include bothersome side effects (such as headaches, dry mouth, racing heart, nausea), dosing schedule, concerns about long-term use, cost and insurance reimbursement issues. To ensure safe and effective use of the four

How well do these therapies improve your ability to do specific activities that are important in your daily life?

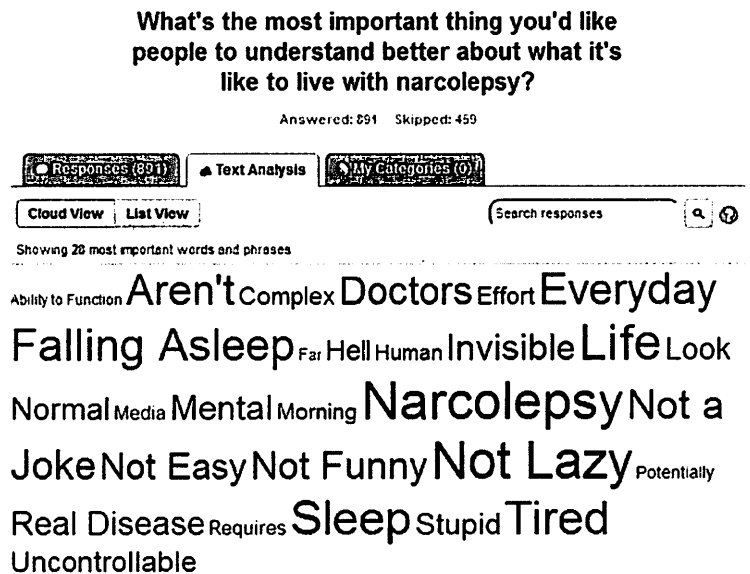


medications approved by FDA to be marketed for narcolepsy, FDA requires them to be distributed as controlled substances.

- Here are representative excerpts from comments about treatment submitted by respondents:
 - “Nothing is fool-proof. It is trial and error with every technique and/or medicine that is used.”
 - “Medications are not widely available. They’re too costly. Docs prefer not to prescribe them and pharmacies cannot or will not order them due to scheduled nature.”
 - “Caffeine and naps are my lifestyle changes.”
 - “Trying to find the right dosing schedule is a definite challenge so that I am effective but minimize my intake as much as possible and so I don’t hit the brick wall of meds not working.”
 - “All medications I take are not safe while pregnant and I would like to start a family soon. The medications are not safe for my heart and I worry about the side effects years down the road.”
 - “I am constantly afraid of taking my medication in public. Almost all narcolepsy drugs are heavily stigmatized.”
 - “The most significant downside to my medication is cost. I am concerned that I will lose coverage or no longer be approved for patient assistance. If I lose my medication, I will not be able to function and I’ll lose my job.”
 - “Inconvenient dosing and eating schedules make it hard to eat and sleep when my family does. I’m willing to do it because I don’t ever want to go back to how my life was before treatment.”
 - “Side effects can be annoying but the alternative is not functioning at all. I don’t like the fact that my heart has to work extra hard and I don’t know the damage it’s doing.”
 - “I tried dietary changes and lifestyle modifications while I was waiting for specialist referral. They helped even more than I thought they would, but my condition improved even more substantially after the addition of a prescription medication.”

Hopes For the Future:

- FDA asked, “Assuming there is no complete cure for your condition, what specific things would you look for in an ideal therapy for your condition?” Here are representative excerpts from comments submitted by survey respondents:
 - “A drug that would provide consistent and adequate control of the daytime sleepiness without the hard crash and one that would require one dose taken at bedtime resulting in 8 hours of restorative sleep.”
 - “Better sleep without acting out dreams and injuring myself. Being able to say awake for several hours without feeling like I need to sleep.”
 - “My ideal therapy would be education of others. Having an invisible illness that is misunderstood takes a huge emotional toll. I am neither lazy, incompetent or unfocused. I am living impaired in an unforgiving world.”
 - “Ability to start a family while on medication. Ability to drive a long distance.”
 - “Something that would let me be awake without having my life ruled by pills.”



- “Longer-acting medications. Fewer side effects.”
- “Something that ‘directly’ addresses the hypocretin/orexin deficiency that causes narcolepsy and corrects that deficiency.”
- “Having more than two hours a day with my mind and body functioning at the same time.”
- Unite Narcolepsy asked, “What’s the most important thing you’d like people to understand better about what it’s like to live with narcolepsy?” Here are representative excerpts from comments submitted:
 - “We’re not lazy. It’s not a joke. These conditions are real. Most of us would give anything to be like an average person again.”
 - “Narcolepsy robs you of your life’s goals and dreams and is also humiliating.”
 - “That even if she looks ‘normal’ on the outside, she is struggling with symptoms all the time which makes everyday things a battle.”
 - “I don’t want to sleep all the time. I want to be awake and doing things with my family and children.”
 - “We are still humans with emotions.”
 - “It’s a life-changing disease that has slowly taken everything away I used to love doing.”
 - “It’s uncomfortable and we hate it. Please be patient with us. We need support from our family and friends. We need you to understand, even if you don’t.”
 - “For people to understand there is no ‘magic pill’ that completely controls narcolepsy. Even with the proper dose of my medications and lifestyle modifications, I still have to work hard to function anywhere close to normal.”
 - “One more cup of coffee will not make me more alert. When my body wants to sleep, I am at its mercy, no matter what plans I thought I had for the day.”
 - “That we have a disability like Parkinson’s or MS or lupus. We have a form of brain damage. We cannot be expected to do everything a healthy person can do and yet we are ignored, denied help and treatment, and medically mistreated because health care professionals don’t know about our condition.”
 - “MY tired is not YOUR tired.”
 - “You don’t LIVE with narcolepsy. You EXIST with it. Not DEAD but not really ALIVE either.”

Wake Up Narcolepsy co-founder and executive director Monica Gow is gratified by the community’s candor in sharing their experiences and perspectives. “Our family has seen first-hand through my son’s experience all the ways in which narcolepsy robs a person of his or her life, but the survey results underscore the breadth and depth of losses patients and their loved ones bear. The thousands of comments submitted tell a heart-breaking story of dreams deferred, career and educational plans put on hold, independence lost, and families torn apart. Simple things we take for granted are lost to people combatting narcolepsy,” said Gow.

Life with a rare disease that’s often the butt of jokes can be very isolating. Unite Narcolepsy organizers took care to reach far and wide across the community to educate patients about this unique invitation from the FDA. They created a new website and hosted a series of webinars to provide ample resources explaining the FDA program and a growing role for patients in drug development. A popular narcolepsy blogger, author and spokesperson, Julie Flygare, J.D., helped launch and sustain the effort via social media. Other organizations including Global Genes Project and the Patient Advocate Foundation helped spread the word through rare disease and disability communities.

Narcolepsy is a neurological sleep disorder that affects some 200,000 Americans and 3 million adults and children worldwide. To learn more about narcolepsy, the Unite Narcolepsy initiative and the upcoming FDA meeting, please visit www.UniteNarcolepsy.org or www.WakeUpNarcolepsy.org. To complete the survey, please visit <https://www.surveymonkey.com/s/unitenarcolepsy>.



July 21, 2021

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Re: Approval and Orphan Drug Exclusivity for FT218 (sodium oxybate for extended-release oral suspension)

Dear Dr. Wolanski and Mr. Raza:

Avadel CNS Pharmaceuticals, LLC (“Avadel”) submits this correspondence to the Food and Drug Administration (“FDA”) Office of Orphan Products Development (“OOPD”) and Office of the Chief Counsel regarding approval and orphan drug exclusivity for Avadel’s proprietary drug product, FT218 (sodium oxybate for extended-release oral suspension). Specifically, this correspondence provides the legal and regulatory basis for FDA approval of FT218 notwithstanding the recent grant of orphan drug exclusivity to Jazz Pharmaceuticals, Inc.’s (“Jazz’s”) Xywav[®] (calcium, magnesium, potassium, and sodium oxybates oral solution) for the treatment of cataplexy and excessive daytime sleepiness (“EDS”) in narcolepsy.

On December 8, 2020, Avadel submitted correspondence to OOPD requesting that OOPD refrain from granting orphan drug exclusivity to Xywav. As discussed in this correspondence, by way of background, Jazz obtained approval and orphan drug exclusivity for Xyrem[®] (sodium oxybate oral solution) for the treatment of cataplexy and EDS in adult patients with narcolepsy in 2002 and 2005, respectively. These exclusivities expired in 2009 and 2012. In 2018, Jazz obtained approval and orphan drug exclusivity for Xyrem for the same indications in pediatric patients 7-18 years of age, and these exclusivities are set to expire in 2025. On July 21, 2020, Jazz received approval for Xywav, a mixed salts oxybate product, for treatment of cataplexy and EDS in patients 7 years of age and older with narcolepsy. However, Xywav did not receive orphan drug exclusivity at the time of approval. In our prior correspondence, we stated that although Xywav may serve as an alternative for the relatively small portion of sodium oxybate-eligible patients with heart failure, hypertension, or impaired renal function, significant research indicates that there is no clinically supported benefit to the vast majority of narcolepsy patients associated with reducing the sodium content of sodium oxybate treatment. Accordingly, we requested an FDA finding that Xywav did

not meet the clinical superiority standard of providing greater effectiveness, greater safety, or a major contribution to patient care.

On June 24, 2021, OOPD nonetheless issued a determination that Jazz had demonstrated clinical superiority of Xywav over Xyrem and awarded Xywav its own period of orphan drug exclusivity expiring seven years from the Xywav approval on July 21, 2027. On the same day, OOPD issued a response to Avadel's December 8, 2020 letter stating that the Agency determined Xywav is clinically superior to Xyrem "by means of greater safety, because Xywav provides a greatly reduced chronic sodium burden compared to Xyrem," and "[t]he differences in the sodium content of the two products at the recommended doses will be clinically meaningful in reducing cardiovascular morbidity in a substantial portion of patients for whom the drug is indicated." OOPD made clear, however, that "FDA has not yet evaluated the impact of Xywav's orphan-drug exclusivity on the new drug application (NDA) [Avadel] submitted for [its] sodium oxybate product."

Avadel's FT218 is a novel sodium oxybate product formulated in a proprietary, extended-release powder for oral suspension that enables once-nightly dosing. With just a single dose before bedtime, FT218 provides comparable systemic drug exposure to Xyrem and Xywav oral solution products, which are both twice-nightly products—both Xyrem and Xywav require patients to take the first dose at bedtime and then set an alarm to wake up 2.5 to 4 hours later to take the required second dose. Avadel received orphan drug designation for FT218 in January 2018 based on a plausible hypothesis of clinical superiority over twice-nightly sodium oxybate, and Avadel submitted its demonstration of clinical superiority in its NDA for FT218, which has a PDUFA date of October 15, 2021. As discussed in Avadel's demonstration of clinical superiority (which was provided to OOPD in a courtesy copy at the time of NDA submission), FT218 provides both greater safety and a major contribution to patient care over the existing sodium oxybate formulations due to its once-nightly dosing, which has been shown to significantly mitigate safety risks, compliance issues, potential misuse, and other challenges associated with middle-of-the-night dosing.

Whether Avadel has satisfactorily demonstrated clinical superiority will determine FT218's eligibility for its own seven-year orphan exclusivity period. However, even if OOPD determines that Avadel has not demonstrated clinical superiority for FT218, FDA may still approve the NDA. Stated another way, OOPD's recent finding of clinical superiority for Xywav should not block FT218 from approval. In particular, as acknowledged in FDA's June 24, 2021 response letter to Avadel, "[u]nder this exclusivity, with limited exceptions, FDA may not approve an application from another sponsor for the *same drug* for the same use or indication for seven years from the date of approval of Xywav" (emphasis added). Pursuant to the Orphan Drug Act and FDA's implementing regulations, as a result of FDA's determination that Xywav is clinically superior to Xyrem, FT218 is not the "same drug" as Xywav and is therefore not blocked from approval by the Xywav orphan drug exclusivity.

FDA May Approve FT218 Notwithstanding the Xywav Orphan Drug Exclusivity

Under the Orphan Drug Act, as amended, the effect of orphan drug exclusivity is that FDA may not approve another marketing application "for the *same drug* for the same disease or condition" for seven years from the date of approval of the orphan drug, except in limited

circumstances.¹ In addition, if a sponsor seeks approval of a designated orphan drug that is “otherwise the same, as determined by the Secretary, as an already approved or licensed drug,” then “the Secretary shall require such sponsor, as a condition of such exclusive approval or licensure, to demonstrate that such drug is clinically superior to any already approved or licensed drug that is the *same drug*.”²

Use of the term “same drug” in the statute was codified in 2017, when Congress sought to better align the text of the Orphan Drug Act with FDA’s orphan drug regulations at part 316 of title 21 in the Code of Federal Regulations.³ Under these regulations, again, the effect of orphan-drug exclusive approval is that “FDA will not approve another sponsor’s marketing application for the *same drug* for the same use or indication before the expiration of 7 years from the date of such approval as stated in the approval letter from FDA,” except in certain limited circumstances.⁴ In the case of a drug that is “otherwise the *same drug* as a previously approved drug for the same use or indication, FDA will not recognize orphan-drug exclusive approval if the sponsor fails to demonstrate upon approval that the drug is clinically superior to the previously approved drug.”⁵ Within this framework, for small-molecule drugs, “same drug” is defined as “a drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug..., *except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.*”⁶ Thus, as FDA explained in its rulemaking proceeding, “even a drug considered the ‘same’ drug structurally could become a ‘different’ drug by showing clinical superiority.”⁷

FDA has advanced this “same drug” interpretation in employing its regulations over the years. For example, in litigation where the government sought to explain its clinical superiority framework, attorneys for FDA made clear that “[a] clinically superior drug, under this framework, is therefore considered to be different from the previously approved drug, even if they share the same chemical structure.”⁸ Thus, “[u]nder FDA’s regulations, ... [in] a situation in which a subsequently approved sponsor obtained exclusivity by demonstrating clinical superiority, ... it

¹ 21 U.S.C. § 360cc(a) (emphasis added).

² *Id.* § 360cc(c)(1) (emphasis added).

³ FDA Reauthorization Act of 2017, Pub. L. 115–52 § 607, 131 Stat. 1005, 1049 (Aug. 18, 2017).

⁴ 21 C.F.R. § 316.31(a) (emphasis added).

⁵ *Id.* § 316.34(c) (emphasis added).

⁶ *Id.* § 316.3(b)(14)(i) (emphasis added).

⁷ Orphan Drug Regulations, Proposed Rule, 76 Fed. Reg. 64868, 64870 (Oct. 19, 2011) (quoting Orphan Drug Regulations, Proposed Rule, 56 Fed. Reg. 3338, 3342 (Jan. 29, 1991)) (internal punctuation omitted).

⁸ Defendants’ Response to Plaintiff’s Motion for Summary Judgment and Cross-Motion, *Eagle Pharms., Inc. v. Burwell*, No. 16-0790 (D.D.C. Aug. 19, 2016), at 6.

would no longer be the same drug as the previously approved drug”; rather, the subsequently approved drug would be a “clinically superior (and different) drug.”⁹

In applying this framework, then, FDA is free to approve the pending FT218 NDA without regard to any outstanding orphan drug exclusivity for Xywav. When Avadel submitted the FT218 NDA on December 15, 2020, Xyrem, Xywav, and FT218 could all be considered the “same drug” for orphan drug purposes—all contained the sodium oxybate active moiety, all were intended to treat cataplexy and EDS in narcolepsy, and none had yet been subject to a finding of clinical superiority by FDA. Since then, FDA has determined that Xywav is clinically superior to Xyrem. As a result, pursuant to the statute, regulations, and applicable precedent, Xywav is no longer the “same drug” as Xyrem. Rather, Xywav is now a “different drug” that must be defined by the product characteristics that resulted in its clinical superiority—low sodium. Although FT218 contains the same sodium oxybate active moiety as both Xyrem and Xywav and is intended for the same narcolepsy indications, FT218 is not the “same drug” as Xywav because it is not and does not purport to be a low-sodium product. Indeed, FT218 provides the same amount of sodium as Xyrem. FT218 is, therefore, the “same drug” as Xyrem, not Xywav. It could not be any other way—given that Xyrem and Xywav are themselves “different drugs” under this framework, FT218 cannot simultaneously be the “same drug” as both of them. In sum, because Xywav is now a “different drug,” FDA is not precluded from approving the FT218 NDA during the seven-year Xywav orphan drug exclusivity, regardless of whether Avadel makes its own demonstration of clinical superiority.¹⁰

FDA Should Grant Orphan Drug Exclusivity to FT218 Upon Approval

As noted above, at the time Avadel requested and received orphan drug designation for FT218, and at the time Avadel submitted its NDA, FT218 would have been considered the “same drug” as both Xyrem and Xywav for orphan drug purposes. Accordingly, in the FT218 NDA, Avadel provided a demonstration of clinical superiority over both previously approved drugs. Namely, regardless of the fact that Xywav provides lower sodium than Xyrem, both products must still be dosed on a twice-nightly basis, making FT218’s once-nightly formulation clinically superior. Now that Xywav is a “different drug” than Xyrem, Avadel need only demonstrate clinical superiority over Xyrem in order for FT218 to obtain its own seven-year orphan drug exclusivity. Regardless, Avadel has still demonstrated clinical superiority over both Xyrem and Xywav in its NDA. Indeed, Avadel just recently submitted a supplement to its already compelling

⁹ FDA Response Regarding Certain Products Containing Bendamustine, Docket No. FDA-2018-N-3773 (Feb. 20, 2019), at 8.

¹⁰ We note that, if FDA were to require Avadel to demonstrate clinical superiority in order for FT218 to receive effective approval, Avadel could satisfy that requirement by demonstrating superiority over Xyrem. Namely, in seeking approval of a designated orphan drug that is otherwise the “same drug” as an already approved drug, FDA must require the sponsor, as a condition of orphan-drug exclusive approval, “to demonstrate that such drug is clinically superior to *any* already approved or licensed drug that is the same drug.” 21 U.S.C. § 360cc(c)(1) (emphasis added). Thus, under the statute’s plain terms, the requirement of demonstrating clinical superiority is met when clinical superiority is shown as to any one of multiple previously approved “same drugs”—Avadel could therefore show clinical superiority of FT218 over Xyrem, rather than Xywav.

demonstration of clinical superiority with additional literature and data showing that disrupted sleep and disordered sleep architecture (as required for effective dosing of Xywav and Xyrem) is associated with an increased risk of cardiovascular disease; by eliminating the necessity of a forced awakening for patients to take a second dose in the middle of the night, FT218 offers greater sleep consolidation and improved sleep architecture for narcolepsy patients, providing both greater safety and a major contribution to patient care. In short, Avadel has provided FDA more than enough data and clinical support not only to approve FT218, but also to find it clinically superior in order to recognize orphan drug exclusivity for FT218 upon approval.

* * * *

We thank you for your attention to this issue of great importance to Avadel. We respectfully request that OOPD and OCC ensure that the Agency may approve the FT218 NDA notwithstanding the recent grant of orphan drug exclusivity to Xywav and facilitate availability of a superior once-nightly dosing option to the orphan narcolepsy patient population.

Please do not hesitate to contact me at 636-730-1420 or jseurer@avadel.com with any questions.

Sincerely,



Jerad G. Seurer
Vice President, Legal Affairs

Cc: Henry Startzman, M.D.
Director, Orphan Drug Designation Program
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Food and Drug Administration
10903 New Hampshire Avenue
Building 32, Room 2346
Silver Spring, MD 20993

Dear FDA,

My name is Maria Picone, and I am the Chief Executive Officer of TREND Community, a digital health analytics company that works to give a voice to underserved rare and chronic disease communities. We have been engaging with the narcolepsy community in this capacity since 2017.

TREND Community learns through listening, and we spark progress through insight. This community-centric approach fills an important gap between patient-reported outcomes in a clinical setting and the real-world experiences that are often underreported because of stigma, fear of losing access to treatments, and other communication barriers.

Following the FDA's decision to grant tentative approval to LUMRYZ, also known as FT218, earlier this year, we began documenting patient experiences with sodium oxybate by surveying and interviewing community members and analyzing shared stories and experiences on social media. Through this work, ***we have realized the urgent need for a once-at-bedtime sodium oxybate therapy***. This work was funded by Avadel Pharmaceuticals as part of their ongoing effort to quantify the need for a once-nightly sodium oxybate therapy; however, Avadel Pharmaceuticals did not influence the analysis or output in any way. We thank PWN4PWN, a patient-led narcolepsy advocacy organization, for supporting this initiative. The perspectives shared within this letter are those of TREND Community and the narcolepsy community members who participated.

Our first step was to listen to the community. What were people saying—unprompted—on social media on the topic of sodium oxybate? We analyzed more than 25,000 posts and comments contributed by more than 15,000 participants over a span of approximately 11 years. The results show that the need to take a second dose of sodium oxybate creates disruptions and various other issues for the patients and their caregivers. These issues range from challenges with waking up to take the second dose to struggling with getting back to sleep in some cases or dealing with daytime sleepiness in other instances. The community also spoke of the physical side effects and their impact on their mental health. The full report, [*Data Exploration: Social Listening and Sodium Oxybate*](#), is provided as an appendix.

Next, we fielded a survey prompting the community for input, and 87 qualified patients and caregivers responded. Fifty of 85 survey respondents (59%) reported taking the second dose of oxybate therapy more than 4 hours after the first dose, with 74% reporting that this occurs once per month or more often. Eighteen respondents reported taking the second dose less than 2.5 hours after the first dose once a month or more often. When asked about accidentally missing a second dose of oxybate therapy, three-quarters (75%) reported this type of experience. The full report, [*Understanding Patient Experience With Oxybate Therapy*](#), is provided as an appendix. Notable impacts reported include the following:

- 32% have experienced injuries after waking to take the second dose
- Other impacts and issues reported with missing the second dose include poor sleep quality, brain fog, increased daytime sleepiness, decreased awareness, migraines, and worsening symptoms
- For some, taking the second dose more than 4 hours after the first dose has resulted in missing/being late to school or work, including disciplinary action or termination

Finally, keeping in mind that these data represent real people navigating life with a narcolepsy diagnosis, we interviewed 4 community members and asked them to share their experiences (in their own words) with sodium oxybate therapy and the challenges they face while taking the medication. I close this letter with their messages to the FDA. You can read more about (b) (6), and (b) (6) at the end of this report.

(b) (6) is a 53-year-old husband and father who was diagnosed with narcolepsy at age 22, following a 12-year journey to diagnosis:

“I passionately urge the FDA to consider an immediate approval of Avadel Pharmaceuticals’ investigational formulation of sodium oxybate, LUMRYZ™. Greater predictability and consistency in [a] medication regimen is vital to the successful management of this lifelong chronic condition, especially during the night when people with narcolepsy need restful sleep the most.”

(b) (6) is a 36-year-old woman who was diagnosed with narcolepsy at age 33, following a 7-year journey to diagnosis:

“Sodium oxybate is invaluable to the quality of lives of people with narcolepsy. Providing more options can help with compliance and help people have a better structured nighttime sleep. The decision to delay treatment is unfair to the patient community.”

(b) (6) is a 24-year-old man who was diagnosed with narcolepsy at age 15, following a 2-year journey to diagnosis:

“The benefits of sodium oxybate are so profound and have made my life possible. While I’m incredibly grateful to have this support and access to the medication, I think more formulations and options are needed.”

(b) (6) is a 33-year-old woman who was diagnosed with narcolepsy at age 23, following a 10-year journey to diagnosis:

“Inaction is not harmless! Why is it taking so long to bring this medication to market? Not approving this medication is causing real-world consequences. The safety and effectiveness of the medication are established. With the current twice-nightly option, many people can’t maximize the benefits of oxybate therapy. These delays are resulting in familial and employment consequences. We deserve to have options.”

The narcolepsy community is asking for your leadership in addressing their unmet medical needs and approving LUMRYZ™ without further delay. With the promise of a once-nightly sodium oxybate therapy

on the horizon, we expect a reduction in the number of injuries that result from missing the second dose and improved quality of life for many living with narcolepsy. I appreciate you taking the time to read the letter.

Best,

Maria Picone

Digitally signed
by Maria Picone
Date: 2022.11.29
15:12:23 -05'00'

Maria Picone, CEO
TREND Community

Community Letters to the FDA

(b) (6) is a 53-year-old husband and father who was diagnosed with narcolepsy at age 22, following a 12-year journey to diagnosis:

“I don’t remember much beforehand, but excessive daytime sleepiness was a ‘normal’ part of my life in middle school. It was a daily struggle for me to stay awake on the school bus and in my classes. Even though I wasn’t very good in athletics, I looked forward to Phys Ed because it was the one class I was not sitting and falling asleep.”

Sodium oxybate has been a part of (b) (6) treatment protocol for narcolepsy; however, it is not easy to manage taking it:

“It’s been difficult for me to maintain routine usage with Xyrem. It is not uncommon for me to believe I woke to take my second dosage only to realize in the morning that this, too, was just part of my dream and it’s still sitting on the nightstand.”

For (b) (6), the challenge of taking Xyrem goes beyond missed second doses; he also battles increased sleep inertia and brain fog from doses after 4 hours:

“I was unable to take the second dose of Xyrem the same time every night, and sometimes not at all. While staying awake during the day is difficult, waking up is the hardest thing I do all day. Sometimes, the brain fog during oxybate therapy lasted longer than anticipated, and a few times, this resulted in my driving impaired and damaging my vehicle.”

(b) (6) has experienced more losses than just an automobile accident. His inability to work through the grogginess from late doses impacted his employment and family relationships:

“After initially being understanding, (b) (6) because I could not consistently arrive on time for early morning meetings. (b) (6) the stigmas associated with a person with narcolepsy (lazy, rude, etc.) makes it even harder. This left me (b) (6).”

Narcolepsy has had a profound effect on (b) (6) daily life. The related impact on his family weighs heavy on him as a husband and father:

“After more than 25 years of living with narcolepsy, it has broken and continues to ravage what remains of my marriage, my family, my jobs, my body, my mind, and my life.”

(b) (6) message to the FDA:

“I passionately urge the FDA to consider an immediate approval of Avadel Pharmaceuticals’ investigational formulation of sodium oxybate, LUMRYZ™. Greater predictability and consistency in [a] medication regimen is vital to the successful management of this lifelong chronic condition, especially during the night when people with narcolepsy need restful sleep the most.”

(b) (6) is a 36-year-old woman who was diagnosed with narcolepsy at age 33, following a 7-year journey to diagnosis:

“I believe that my narcolepsy gene was triggered in (b) (6) when I had a long hospital stay with (b) (6).”

Narcolepsy has had a profound impact on (b) (6) and her family’s life:

“Narcolepsy affects my life daily and is always on my mind. I need to remember my daytime meds, monitor my water intake, [and] watch for mood shifts, which are often the first indicator that I need a nap or an afternoon medication to get through the day. I rely heavily on my mom/family to help me remember appointments and get there, as many are too far for me to safely drive.”

Confusion and even injuries have occurred as a result of (b) (6) awakening for the second dose of Xyrem:

“I have gotten confused while preparing my nighttime meds because I am tired, and that automatic behavior kicks in for all of us when we are doing our routine, but especially for a person with narcolepsy, as we might actually be microsleeping.”

“On multiple occasions, I have fallen asleep while on the toilet in between doses. I already touched on how brain fog can hinder and be dangerous when mixing and preparing nighttime doses of medication, but I have also experienced injuries and extreme confusion. A few examples are stumbling through doorways and hallways while trying to get up to take my second dose. I have also been so completely sure that I heard my alarm (an auditory hallucination) and gotten up to take my second dose when I already had. On a few occasions, I awoke the next day to see the full bottle was on the floor—realizing I had missed my dose.”

(b) (6) also shared the impact of missing or mis-timing doses:

“Missing doses makes people feel sick. Mis-timing doses leaves you ‘seasick’... My world seems wobbly, and my head is cloudy afterwards.”

For (b) (6), the benefit of a once-nightly formulation is apparent:

“Avoiding a midnight alarm clock will allow my sleep cycle to be less disruptive. People with narcolepsy experience disrupted sleep already, and adding another nighttime awakening is unnecessary and more disruptive.”

(b) (6) message to the FDA:

“Sodium oxybate is invaluable to the quality of lives of people with narcolepsy. Providing more options can help with compliance and help people have a better structured nighttime sleep. The decision to delay treatment is unfair to the patient community.”

(b) (6) is a 24-year-old man who was diagnosed with narcolepsy at age 15, following a 2-year journey to diagnosis:

“I consider myself fortunate to have been diagnosed after only 2 years. Most of my friends living with narcolepsy had to look for answers for 5 to 10 years before getting a diagnosis.”

Narcolepsy has had a profound impact on (b) (6) daily life:

“One of my greatest passions is the overseas mission work I did in (b) (6) between graduating high school and returning to college. While it was a joy and an honor to help others as an English tutor, I couldn’t fully engage because of being undermedicated. I’m currently pursuing a (b) (6) to help others find answers.”

(b) (6) has struggled with awakening for the second dose and spilling doses in the process:

“There are times when I don’t wake up to take the second [dose], and there are other times when I spill the vial or only take part of a dose.”

(b) (6) also shared the impact of missing or mis-timing doses:

“When I miss doses or miss the timing, I must weigh the benefit of taking the full amount or only part of it. If I don’t take the second, then I might not be able to make it to school or work. If I do take the second dose later than 4 hours, then I might be late or have really bad brain fog.”

The impact of brain fog resulting from missed or mis-timed doses is overwhelming for (b) (6)

“I don’t drink anymore, but from what I remember, the impact of late doses is worse than a hangover. A cloud of confusion sets in, and I feel disoriented, dehydrated, and nauseous. Normally my sleep schedule is fairly consistent; however, when sleep time is variable, the missed doses are increased. This makes enjoying time off even more of a challenge.”

For (b) (6) the benefit of a once-nightly formulation is about compliance and convenience:

“The convenience of taking a once-nightly sodium oxybate formulation means it will be easier to stay compliant on my doses. Measuring out 1 prepackaged dose takes the guesswork out of dosing and possibly missing a dose. Another advantage of prepackaged packets is not having to carry liquids around during travel. During a trip to (b) (6), I had the bottle top become slightly loose and ended up having some of the liquid medication leak out into my luggage.”

(b) (6) s message to the FDA:

“The benefits of sodium oxybate are so profound and have made my life possible. While I’m incredibly grateful to have this support and access to the medication, I think more formulations and options are needed.”

[(b) (6)] is a 33-year-old woman, who was diagnosed with narcolepsy at age 23, following a 10-year journey to diagnosis:

“I’ve been labeled ‘sleepy’ for as long as I can remember. My symptoms began to become overwhelming during my teen years and into early college. In addition to being diagnosed with narcolepsy, I have also been diagnosed with [(b) (6)]. It’s hard to separate the impacts of the conditions, but at the foundation is sleepiness and narcolepsy.”

Narcolepsy has had a profound impact on [(b) (6)]’s daily life:

“Prior to getting the diagnosis, I was sleeping through exams, and keeping up seemed nearly impossible.”

Medication provided [(b) (6)] with a new look on life:

“I often compare receiving my diagnosis and being medicated to putting on glasses for the first time. Medication opened my eyes to a world I didn’t realize was possible; however, even with current treatments, the outlook is foggy.”

[(b) (6)] has difficulties making sure she takes both doses of oxybate:

“Making sure I get the second dose has been a huge hurdle for me. When I don’t get in both doses, it disrupts my schedule. This leads to waking up late or in a cloud of brain fog. This creates a cycle of missed doses causing more missed doses. Trying to measure out both doses at night and figure out timing is made more difficult because of the sleepiness.”

For [(b) (6)] taking Xyrem is often like balancing a mathematical equation:

“The process of figuring out the ‘Xyrem Math’ is a big part of my routine. My work and school schedules require flexibility. I need to have the medication out of my system to drive safely and function. Calculating how much medication to take and when to take the second dose is critical. Solving the ‘Xyrem Math’ problem when I have sluggish thinking complicates the decision.”

[(b) (6)] also shared the impact dosing on her family:

“In order to wake up for my second dose, I have a ‘sonic boom’ alarm clock. Even though the noise is very disruptive to my partner, oftentimes I don’t wake up without his help.”

For [(b) (6)] the benefits of a once-nightly formulation are apparent:

“My physician and I came up with workarounds due to frequently missing my second dose. I take a higher amount during my first dose (6 g) in case I miss my second. Creating a once-nightly, premeasured dose would allow me to get the full benefit of the medication. Equally as important, this once-nightly dose would not disrupt my partner’s sleep as well, reducing these unnecessary awakenings.”

(b) (6) s message and question to the FDA:

“Inaction is not harmless! Why is it taking so long to bring this medication to market? Not approving this medication is causing real-world consequences. The safety and effectiveness of the medication are established. With the current twice-nightly option, many people can’t maximize the benefits of oxybate therapy. These delays are resulting in familial and employment consequences. We deserve to have options.”



TREND Community™
Turning Anecdotes Into Evidence™

Data Exploration

Social listening and sodium
oxybate

November 16, 2022



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Purpose

The purpose of this report is to understand the treatment impact of sodium oxybate (SO) in the narcolepsy community via social listening. The data sources being used in this report are two online support groups: **Facebook and a subreddit, r/Narcolepsy**.

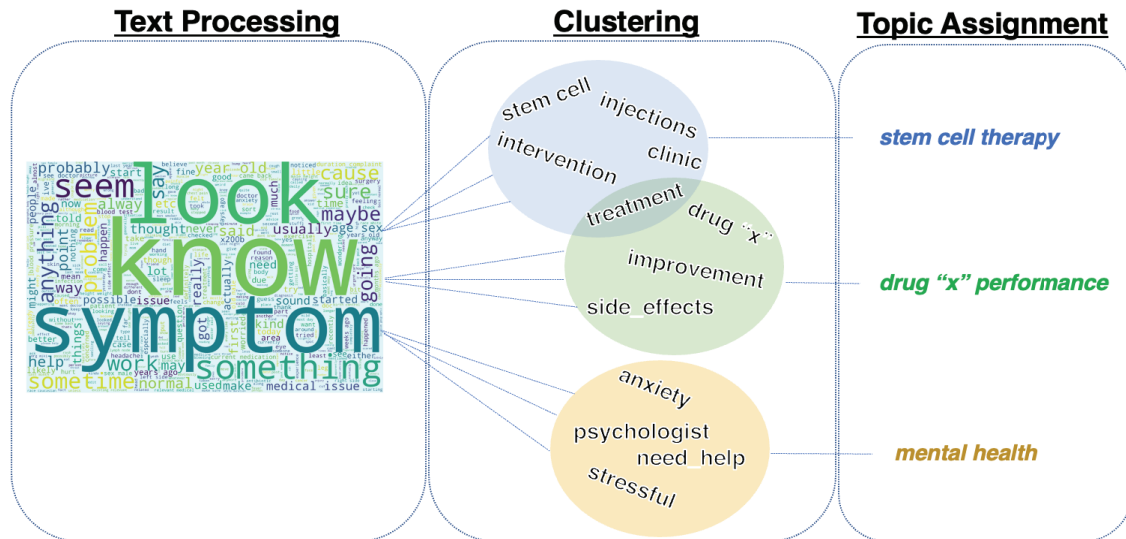
TREND Community Technology

TREND Community harnesses machine learning and natural language processing techniques with Krystie™, our proprietary analytics engine to capture the perspective and experiences shared online by people living with rare and chronic diseases. Krystie was the daughter of one of our community members and the inspiration driving everything we work towards. Krystie—and the millions of others facing rare, chronic, and emerging diseases—is always at the heart of TREND Community.

Our Methodology

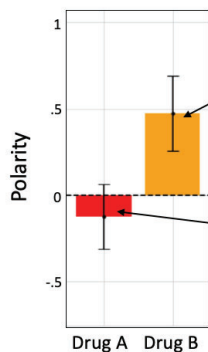
Krystie™ enables TREND to identify conversations in domains that tend to be prevalent in social media-based discussions regarding chronic and rare diseases (e.g., disease burden, management, mental health). After isolating conversations within domains of interest, we leverage a variety of analytical techniques to characterize the language and emotions associated with patient experiences and perspectives. These techniques are implemented both independently and in conjunction with one another to offer converging support for discoveries. We offer a summary of the key methodologies:

TOPIC MODELING



TREND implements various topic modeling approaches to determine language that tends to cluster together. These machine learning techniques rely on statistical probabilities and pre-trained knowledge of words, phrases, and their meanings to identify significant groupings.

POLARITY ANALYSIS



Drug B has an overall positive average sentiment (above 0).

Example comments:

- "drug b improved my symptoms"
- "I would recommend drug b".

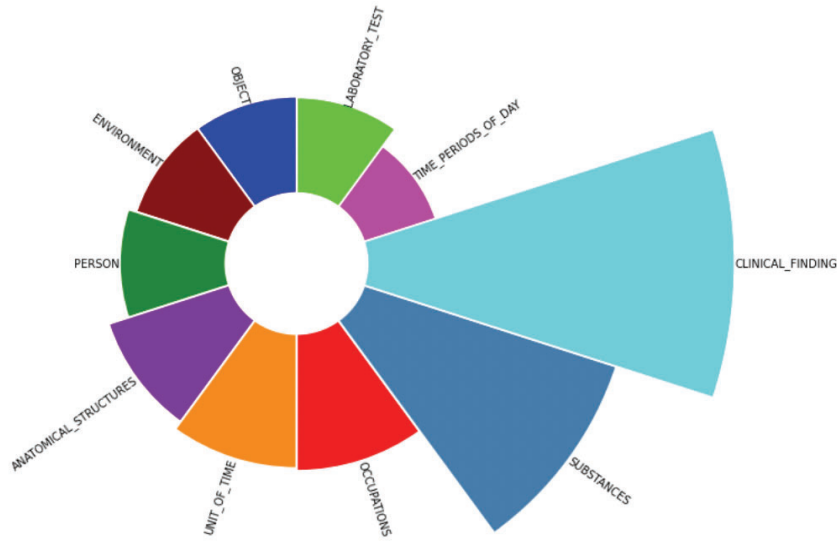
Drug A has a negative average sentiment (below 0).

Example comments:

- "drug a does not help me much"
- "my symptoms were worse with drug a".

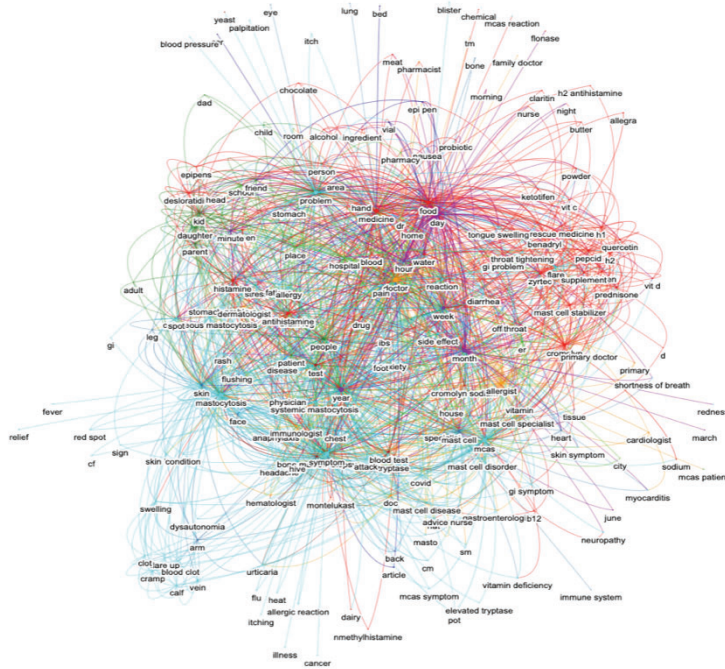
We use a variety of polarity and sentiment analysis techniques to broadly understand user emotions and feelings on given topics. These include both word and conversation level analyses.

CLINICAL ENTITY RECOGNITION



We use a custom clinical entity recognition (CER) tagger to mark language based on its membership to 10 clinical domains: clinical findings, substances, occupations, units of time, anatomical parts, persons, environments, objects,

NETWORK ANALYSIS



Using our CER tagger, we use network analysis to evaluate relationships between entities. We can begin to understand trends in conversations when we know what entities occur often (e.g., count of a specific substance) and what entities occur together (e.g., a substance and clinical finding co-occurrence).

Data Set

Data Sources:

**Facebook
r/Narcolepsy**

15,280

People
Participating

25,018

Posts
Shared

229,626

Comments
Elicited

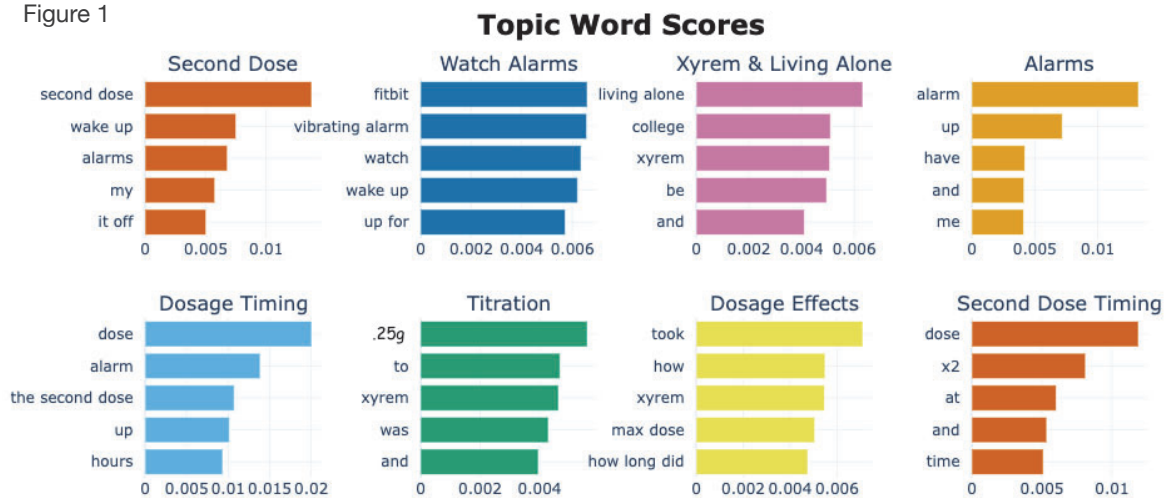
August 2011 - October 2022

Date Range

Topic Modeling

First, we extracted the conversations that mention sodium oxybate from the entire data set. To be more inclusive, we used multiple names and synonyms to perform the extraction, including sodium oxybate, Xyrem, and Xywav, etc. The complete list can be found in Appendix A. The total number of conversations that mentioned sodium oxybate is 26,088 and the total number of reddit users who mentioned sodium oxybate is 4,275. We applied topic modeling on this filtered data set to get a general understanding of the topics being discussed and the results are meant to be taken in aggregate. The model identified several topics related to the sodium oxybate doses. The takeaway is that these topics are all highly related and represent "sodium oxybate and second doses" overall and are used for further analysis as a composite. Figure 1 below shows eight topics and their word representation (top five words).

Figure 1



From the topic model, we identified the following issues related to taking sodium oxybate in the community.

- Having difficulties taking second dose, including:
 - Hard to wake up for second dose
 - Sleeping through the alarm(s) for second dose
 - Dreaming that had taken the second dose
 - Need help from parents/partners to wake up for second dose
 - Worry the second dose alarm will wake up other people
- Issues on scheduling the doses

- Insomnia after doses
- Skipped doses because of drinking
- Binge eating or craving foods after taking a dose
- Timing meals with the medication

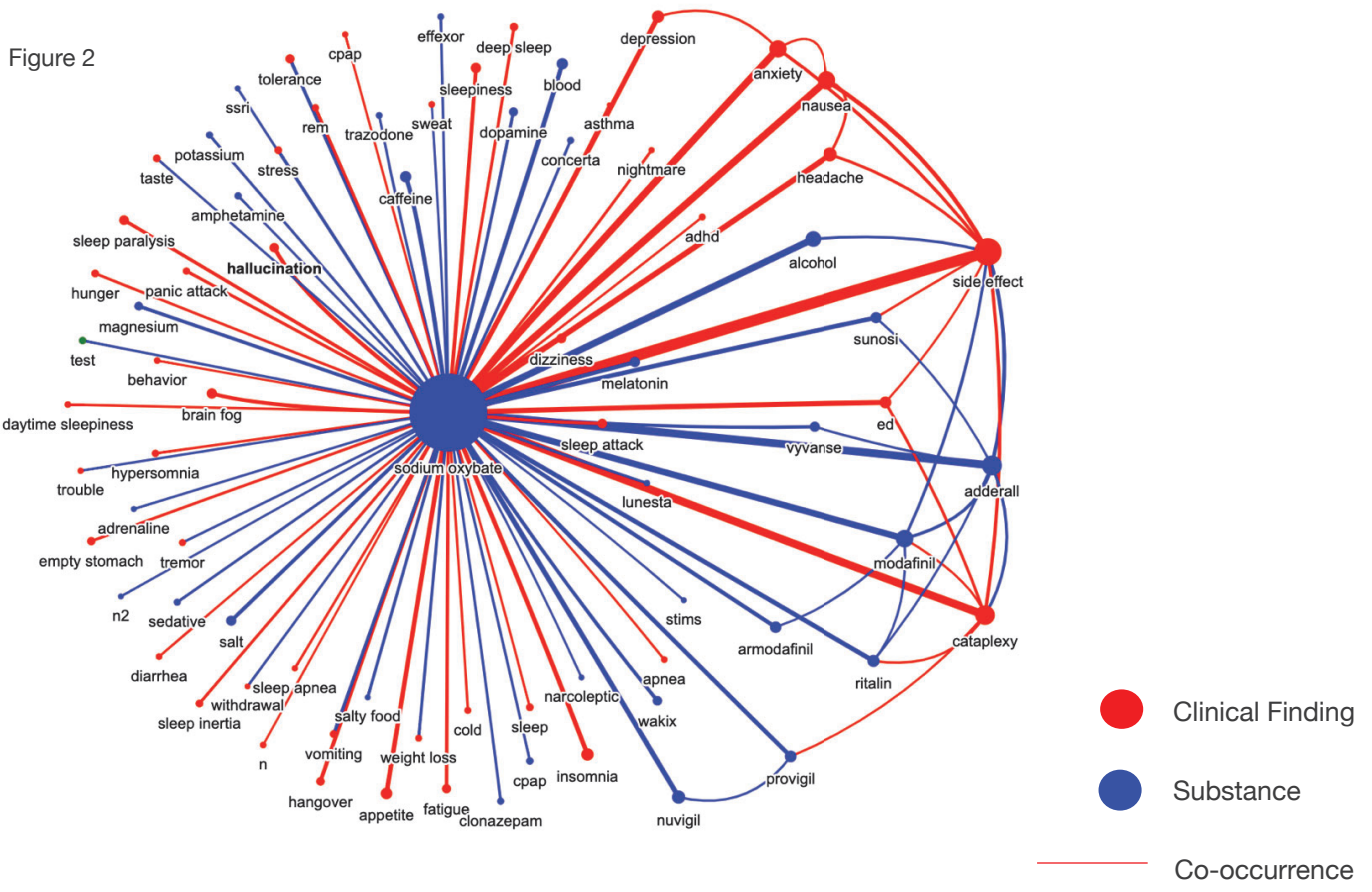
By using the state-of-the-art deep learning language model, we are able to extract the posts and sentences discussing the above issues. The table below shows the statistics of each issue identified. The second column lists the number of occurrences and frequency out of all sodium oxybate discussions (N=26,088). The third column is the number of distinct reddit users and its frequency out of all reddit users who have mentioned sodium oxybate (N=4,275).

Issue	Entry Count (Frequency) N=26,088	User Count (Frequency) N=4,275
Difficulties taking the second dose	635 (2.43%)	398 (9.31%)
Issues scheduling the two doses	14 (0.05%)	4 (0.33%)
Insomnia after doses	161 (0.62%)	134 (3.13%)
Skipped doses due to drinking	3 (0.01%)	3 (0.07%)
Binge eating or food craving after doses	13 (0.05%)	13(0.3%)
Timing meals	27 (0.1%)	26 (0.61%)
Total	715 (2.74%)	439 (10.29%)

The data show that there are 715 posts (2.74% of all sodium oxybate conversations) mentioning an issue when taking sodium oxybate. There were 439 distinct users (10.29% of total users) who mentioned sodium oxybate in their conversations. Please refer to Appendix B for comments from these patients.

Network Analysis

Using our CER tagger, we can build the co-occurrence network and examine the relationships between entities. We filtered conversations that mentioned (1) second dosage (e.g., second dose, 2nd, etc) and (2) sodium oxybate (e.g., xyrem, SO, etc) to build a unique co-occurrence network for all conversations discussing second doses of sodium oxybate. The sub-network is shown in Figure 2 below. The red nodes are clinical findings and blue nodes are substances. The size of the nodes corresponds to the total number of occurrences. Entities mentioned together in the same post/comments are connected by edges. The width of the edges corresponds to the number of co-occurrences; thicker edges imply stronger relationships.



Network analysis shows the top 20 most influential clinical finding nodes below, ordered by degree centrality.

- | | |
|--------------------------|------------------------|
| 1. side effect | 11. dizziness |
| 2. cataplexy | 12. appetite |
| 3. nausea | 13. sleepiness |
| 4. anxiety | 14. sleep attack |
| 5. headache | 15. hallucination |
| 6. ed (eating disorders) | 16. medication anxiety |
| 7. depression | 17. sleep paralysis |
| 8. insomnia | 18. tolerance |
| 9. hypersomnia | 19. empty stomach |
| 10. hangover | 20. panic attack |

The results show that the second dose of sodium oxybate results in not only physical issues such as nausea, headaches, dizziness, and hunger but also mental health issues like anxiety, panic, and depression.

Summary

In this report we evaluated the impact of sodium oxybate based on the analysis of social media data. The results show that the need to take the second dose of sodium oxybate creates various issues and disruption for the patients and their caregivers. These issues range from challenges with waking up to take the second dose to then struggling with getting back to sleep in some cases or dealing with daytime sleepiness in other instances. After taking sodium oxybate, patients also experience physical symptoms such as nausea, headaches, dizziness, and hunger as well as mental health challenges like anxiety, panic, and depression.

Appendix A

Words and synonyms used for concept

SO: oxybate, xyrem, xywav, jazz, nighttime med, ghb, gaba, date rape, gamma hydroxybutyrate, gamma-hydroxybutyrate

'Skip' verbs: skip, miss, skips, misses, skiping, missing, skipping, mising, skiped, missed

Alarm: alarm, fitbit, tracker, tracking

First dose: first dose, 1st dose, first xyrem, first xywav, 1st xyrem, 1st xywav, one dose, one-dose, single dose, single-dose

Second dose: second dose, 2nd dose, second xyrem, second xywav, 2nd xyrem, 2nd xywav, double dose, between dose

Slow release: once nightly, once-nightly, slow release, extended release, extend release, once per night, long acting, slow-release, extended-release, extend-release, once-per-night, long-acting

'Wake' verb: wake me up, woke me up, wakes up, wake up, woke up, waking up

'Sleep' verb: sleep over, slept over, sleep through, slept through, sleeping over, sleeping through, sleeps over, sleeps through

Alcohol: alcohol

Titration: titrat

Accident: miss work, miss school, missing work, missing school, missed work, missed school, accident

Appendix B

Quotes from the discussions

Difficulties taking the second dose

“I have difficulty waking up for a second dose too, even if I use an alarm and give myself a full 4 hours of sleep after the first dose (side note: excessive sleeping / oversleeping / hypersomnia has always been a part of my sleep problem / narcolepsy).”

“I cannot for the life of me seem to wake up for the second dose....”

“I struggle immensely with waking up to take a second dose and am at the point where I only take the first one and don't bother preparing the second.”

“Waking up to take a second dose is jarring and I hate the drugged feeling I get.”

“It's been a miracle drug for me. It completely turned my life around but I'm having the darnedest time waking up for the second dose.”

“Part of the problem was a ton of anxiety about waking up for the second dose without disturbing my partner.”

Alcohol and food

“No alcohol with Xyrem unless somebody else is going home with you and will make sure you wait the appropriate amount of time.”

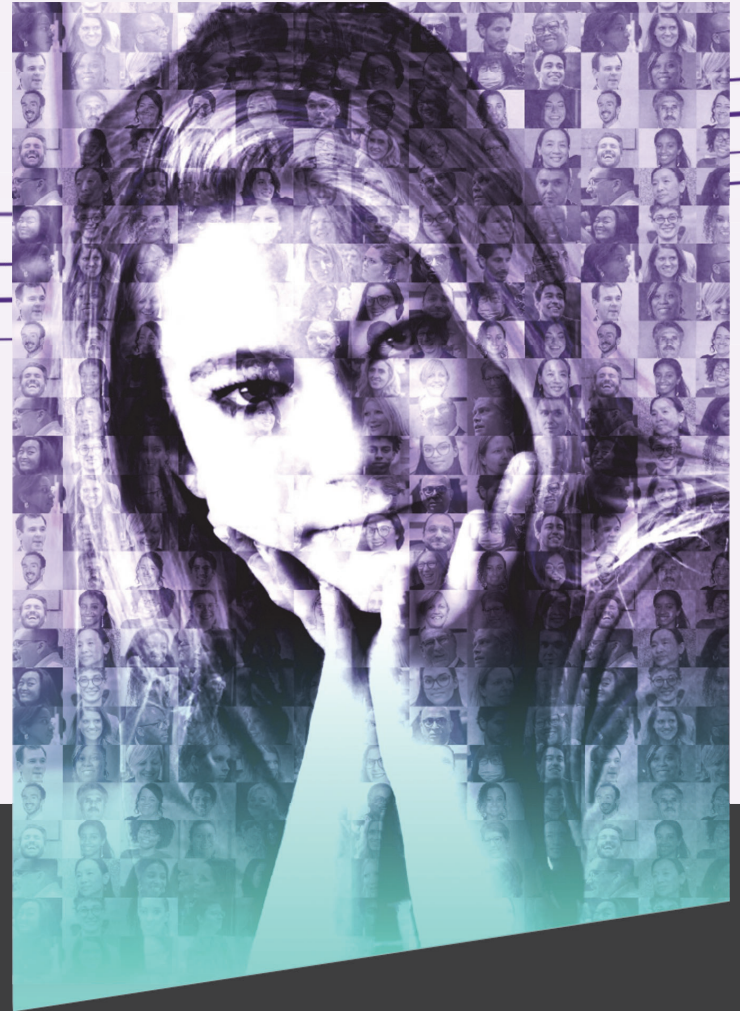
“If I want to drink I skip it that night.”

“I take my first dose, the second it kicks in, I feel like I'm starving so I nibble on my premade meal.”

“Strangely enough, after taking my first dose, if I stay awake for more than a half hour I find myself becoming ravenous, even if I've eaten full meals throughout the day.”

UNDERSTANDING PATIENT EXPERIENCE WITH OXYBATE THERAPY

Survey Results
November 16, 2022



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OBJECTIVES & CRITERIA



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Research Objectives and Screening Criteria

The purpose of this research is to better understand patient experience with taking oxybate therapy (Xyrem® or Xywav®) for narcolepsy.

The following are the criteria to participate in the survey:

- Age \geq 18 years
- Living in the United States
- Patient or caregiver of a patient with a narcolepsy diagnosis
- Currently taking or have previously taken oxybate therapy like Xyrem® or Xywav®

FINDINGS



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Survey Respondent Data

Total Respondents
N=87

Group
Patient: 85
Caregiver: 2

Gender (patients)
Female: 64
Male: 19
Intersex: 1
Prefer not to answer: 1

Diagnoses
Type 1 with Cataplexy: 44
Type 2 without Cataplexy: 39
Unsure: 2

Medications
Currently taking Xyrem®: 19
Previously taken Xyrem®: 34
Currently taking Xywav®: 45
Previously taken Xywav®: 11

Frequency of missing the second dose

When asked: during the time you have been on your oxybate therapy (Xyrem or Xywav), have you accidentally missed your 2nd dose, a majority (75%) of the 85 patients who responded reported this experience.

These patients were then asked: approximately how frequently do you experience this issue? Of this group, 65% miss the second dose once a month or more often.

Frequency	% (N=64)
A few times a week	17%
Once a week	20%
Once a month	28%
Every 6 months	25%
Once a year	5%
Less frequently than once a year	5%

Injuries resulting from waking to take second dose

To better understand the patient experience we asked: during the time you have been on your oxybate therapy (Xyrem or Xywav), have you experienced injuries (such as falling) after waking to take your second dose?

Almost one-third (32%) of the survey respondents have experienced injuries after waking to take the second dose of oxybate therapy.

Of this group, the chart to the right shows the frequency of injuries with 33% experiencing issues once a month or more often.

Frequency	% (N=27)
A few times a week	7%
Once a week	7%
Once a month	19%
Every 6 months	22%
Once a year	19%
Less than once a year	26%

Injuries resulting from waking to take second dose

When asked: please provide us with some additional details about this (for example, describe injuries, how the event happened, seriousness, etc.), many patients reported falling or bumping into things resulting in bumps, bruises, and black eyes. Pulled muscles, stitches, and the need for physical therapy due to a neck and shoulder injury have occurred. One person experienced confusion resulting in taking the second dose too soon which led to a trip to the ER. Another suffered multiple concussions thus impacting their ability to function as well as their mental health.

“[I received] frequent minor injuries (mild bumps and bruises). I have had several concussions that caused more serious issues and required treatment from a concussion clinic due to lingering concussion symptoms and periodic re-injury due to additional concussions under the same circumstances. Overall, the concussions have taken a big toll on my overall functioning and mental health.”

“Knocked over CPAP onto floor and walked around confused bumping into the wall and/or stubbing toes looking for second dose & forgetting it was next to the bed all along.”

“I got up to use the bathroom, fell asleep on the toilet and fell off, slamming my head on doorjamb of bathroom door.”

“I’ve fallen out of bed when I sat up to take the 2nd dose. I hurt my neck and shoulder and needed physical therapy.”

Dose Timing: Taking the second dose more than 4 hours after the first

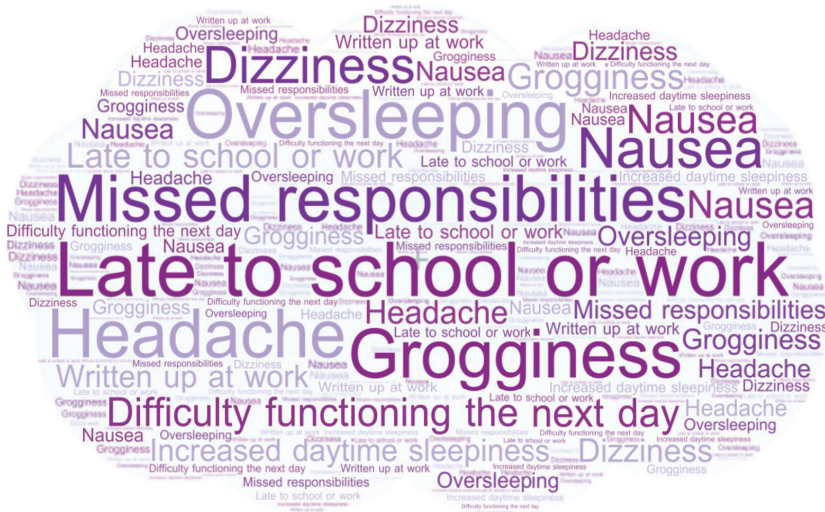
More than half (59%) of the 85 survey respondents have taken the second dose of oxybate therapy more than 4 hours after the first dose. These data were derived when we asked: during the time you have been on your oxybate therapy (Xyrem or Xywav), have you taken your second dose more than 4 hours after your first dose?

Of those taking the second dose more than four hours after the first, this is occurring once a month or more for almost three quarters (74%) of these patients.

Frequency	% (N=50)
A few times a week	6%
Once a week	14%
Once a month	54%
Every 6 months	12%
Once a year	6%
Less than once a year	8%

Impact of taking the second dose more than 4 hours after the first

When asked: please describe any impact or issues you typically experience due to taking your second dose 4+ hours after your first dose, we learned about the disruption it causes. The biggest impact is missing activities or missing/being late to school and work which has resulted in disciplinary action or termination for some patients. Many report grogginess and difficulty functioning the next day.



“Extended brain fog caused frequent late arrivals at work resulting in termination.”

“Missed morning activities and impacting of my daily life things for sure...it has gotten me in serious trouble from time to time where I've gotten written up because of my tardiness.”

“Ruined my work and life schedule because I was too groggy. I also couldn't drive, so had to cancel events. I've also shown up to work meetings more groggy than I wanted to be.”

Dose Timing: Taking the second dose less than 2.5 hours after the first

A smaller group has taken the second dose less than 2.5 hours after the first dose. The information was gleaned by asking: during the time you have been on your oxybate therapy (Xyrem or Xywav), have you taken your 2nd dose less than 2.5 hours after the first dose?

We then asked: you indicated that you have taken your 2nd dose less than 2.5 hours after the first dose. Approximately how frequently do you experience this issue? This is occurring once a month or more often for almost two fifths (39%) of these patients.

Frequency	% (N=18)
A few times a week	6%
Once a week	11%
Once a month	22%
Every 6 months	11%
Once a year	28%
Less than once a year	22%

Impact of taking the second dose less than 2.5 hours after the first

Upon asking: please describe any impact or issues you typically experience due to taking your second dose less than 2.5 hours after the first dose, a few patients expressed fear and anxiety about taking the doses too close together. Another small group spoke of confusion and disorientation when taking the oxybate therapy within 2.5 hours of the first dose. Others shared experiences of physical discomfort or illness, including headaches, dizziness, and upset stomach. For one patient, this impacted their ability to do things the next day and for another, they experienced EDS. Two patients felt the efficacy was decreased which led to them purposely take the second dose within 2 to 3 hours of the first. Another finds it useful and with no negative impact to take the second dose after only 2 hours.

“I was terrified once I looked at the clock and realized what I had done, ended up in the ER courtesy of my mom knocked out and with a respiration rate of 5 breaths per minute.”

“Increased emotions, severe digestive upset, headache, increased EDS, and worsening of symptoms.”

“I always take my first dose at 10 and my second at 12, it works the best for me and I haven’t noticed any bad symptoms. I wake up when I need to and taking the second dose after 2 hours has been the most successful for me to wake up.”

Additional issues reported

In response to the question: please provide details about other issues you experienced during the time you have been on your oxybate therapy (Xyrem or Xywav), a few patients spoke of experiencing serious mental health issues including depression. One person experienced suicidal thoughts and another experienced paranoia. Others mentioned the following issues: bed wetting, racing heart, light sensitivity, night sweats, muscle spasms, acid reflux, hand tremor, and nighttime cravings and eating problems in between doses. A few spoke of the need to experiment with the dosage amounts in order to get the desired effects. And another small group report a decrease in efficacy over time.

“I experienced extreme anxiety/depression for 4-6 hours after awakening from Xyrem. This is an extreme side effect that is not talked about or addressed.”

“The bottles and measuring and diluting and waking up in the middle of the night for dose two just feels so wrong. I'm on a dose now that definitely gives me a better quality sleep and less daytime sleepiness, but all it takes is sleeping through my second dose to screw everything up again. I feel like I'm on a rollercoaster, which then impacts my mental health. There has to be a better way to dose this!!”

“Xyrem made me want to rip my own skin off. Xywav left me feeling very ill in the mornings, so much that I could barely take care of my children.”

Belief that a once-nightly dose would be safer

As a final question, we asked: please indicate the extent to which you agree or disagree with the following statement: "I believe that a single bedtime dose of sodium oxybate, in a pre-measured packet, would be safer for me to take than the currently available versions, due to avoiding a 2nd, middle-of-the-night dose." The majority (76%) of these patients either strongly agree or agree.

	% (N=87)
Top 2 Box	76%
Strongly agree	46%
Agree	30%
Neither agree nor disagree	11%
Disagree	6%
Strongly disagree	7%

"I am awaiting approval of once nightly sodium oxybate because no other medicinal or lifestyle regimens have allowed me to complete my ADLs without significant struggle. I am so sad that I cannot spend the time I would like to with my 4 year old son and husband due to my EDS, and am not able to take Xyrem anymore due to missing the second dose too frequently due to shutting off my alarms, and going back to sleep, or hallucinating and thinking I took my second dose when I really did not."

"Accidentally poured a liquid that wasn't plain water into the cup. Accidentally poured water into another different medication bottle ruining an entire month script."



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