Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32-5271
Silver Spring, MD 20993

Jazz Pharmaceuticals, Inc.
2005 Market Street, Suite 2100
Philadelphia, PA 19103

Attention: Arthur Merlin d'Estreux
US Agent for Jazz Pharmaceuticals Ireland Limited
Arthur.MerlindEstreux@jazzpharma.com

Re: Orphan-drug designation DRU-1994-858

Dear Mr. Merlin d'Estreux:

This letter refers to your orphan drug calcium, magnesium, potassium, and sodium oxybates which was designated pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) on November 7, 1994, for "treatment of narcolepsy." We also refer to the letter from the Center for Drug Evaluation and Research, dated July 21, 2020, granting marketing approval of your New Drug Application for XYWAV™ (calcium, magnesium, potassium, and sodium oxybates) (hereinafter Xywav). In addition, reference is made to the letter dated April 24, 2020 from Jazz Pharmaceuticals, Inc. to the Office of Orphan Products Development (OOPD) requesting that orphan-drug exclusivity for Xywav be recognized upon marketing approval. Lastly, reference is made to the letter dated April 19, 2021 from Jazz Pharmaceuticals to the OOPD requesting to expedite recognition of orphan-drug exclusivity for Xywav.

Jazz Pharmaceuticals Ireland Limited is entitled to seven years of orphan-drug exclusive approval pursuant to section 527 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360cc) for Xywav (calcium, magnesium, potassium, and sodium oxybates) indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. The seven-year exclusive approval began on July 21, 2020, the date of approval of the New Drug Application (NDA #212690). The scope of orphan-drug exclusive approval is described under 21 CFR 316.31.

In accordance with section 527(e)(2) of the FD&C Act (21 U.S.C. 360cc(e)(2)), FDA's summary of the clinical superiority finding will be posted at https://www.fda.gov/orphan.

As the holder of exclusivity, the sponsor is required to assure the availability of sufficient quantities of this drug to meet the needs of patients. Failure to do so could result in the withdrawal of the drug's exclusive approval as stipulated under 21 CFR 316.36(b).

Congratulations on obtaining orphan-drug exclusivity. Should you have any questions regarding this exclusivity, please contact our office at 301-796-8660 or by email at orphan@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Director
Office of Orphan Products Development

Nicole Wolanski

Digitally signed by Nicole Wolanski

Date: 6/24/2021 11:46 AM EDT
GUID: 13313

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Avadel CNS Pharmaceuticals, LLC
16640 Chesterfield Grove Road, Suite 200
Chesterfield, MO 63005

Attention: Jennifer Gudeman, PharmD
Vice President, Clinical & Medical Affairs
jgudeman@avadel.com

Re: Sodium Oxybate for the Treatment of Narcolepsy

Dear Dr. Gudeman:

This letter responds to your letter dated December 8, 2020, about sodium oxybate for the treatment of narcolepsy. You requested that the Office of Orphan Products Development (OOPD) in the Food and Drug Administration (FDA) refrain from recognizing orphan-drug exclusivity for Xywav (calcium, magnesium, potassium, and sodium oxybates), approved on July 21, 2020, for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

After careful consideration, OOPD has determined that Xywav is eligible for orphan-drug exclusivity,[1] because Xywav is clinically superior to the same drug[2] previously approved for the same use or indication.[3] Specifically, Xywav is clinically superior[4] to Xyrem (sodium oxybate) by means of greater safety, because Xywav provides a greatly reduced chronic sodium burden compared to Xyrem. 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. We respond to the arguments in your December 8, 2020, letter below. Please

[1] In your December 8, 2020, letter you state, "As of the date of this letter, no such additional period of exclusivity is identified for Xywav in the FDA database, indicating an FDA determination that Xywav is indeed the 'same drug' as Xyrem and, as such, not clinically superior." This is incorrect. At the time of your letter, FDA had not yet determined whether Xywav is clinically superior to Xyrem, and thus had not yet determined whether Xywav is eligible for orphan-drug exclusivity.
[2] *See* 21 CFR 316.3(b)(14).
[3] *See* Sec. 527(c)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); *see also* 21 CFR 316.34(c).
[4] *See* Sec. 527(c)(2) of the FD&C Act; *see also* 21 CFR 316.3(b)(3).

note that this determination is limited to Xywav's eligibility for orphan-drug exclusivity and FDA has not yet evaluated the impact of Xywav's orphan-drug exclusivity on the new drug application (NDA) you submitted for your sodium oxybate product. FDA will evaluate the arguments that you submitted in your NDA on December 15, 2020, regarding the clinical superiority of your product over any same drug that currently has orphan-drug exclusivity for the indication for which you are seeking approval.

First, your letter argues that there is no clinical or real-world evidence showing that the sodium content of Xyrem increases cardiovascular risks in patients with narcolepsy. You reference a paper by Avidan and Kushida published in Sleep Medicine in 2020 to support that there is no clinical or real-world evidence showing that the sodium content of Xyrem increases cardiovascular risks in patients with narcolepsy.[5] That paper is a literature review and the authors conclude that exisiting evidence does not support that exposure to sodium oxybate leads to increased cardiovascular risk in patients with narcolepsy. However, as acknowledged by the authors, this possibility has never been adequately investigated since there have been no studies that have been prospectively designed to specifically investigate whether the administration of Xyrem at recommended doses is associated with adverse cardiovascular outcomes, either in the wider population with narcolepsy or in subgroups of patients with narcolepsy who have co-existing medical conditions. Nevertheless, 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. The National Academies of Sciences, Engineering and Medicine, an authoritative national body in the United States, has recommended in an official publication titled "Dietary Reference Intakes for Sodium and Potassium" that daily salt intake in individuals 14 years and older be restricted to 2300 mg or less.[6] The National Academies have also stated that there is evidence that a reduction in sodium intake has a beneficial effect on the risk of cardiovascular disease, the risk of hypertension, systolic blood pressure and diastolic blood pressure in the general population.[7] In addition, the US Department of Agriculture's publication titled "Dietary Guidelines for Americans 2020-2025" also supports the recommendations of the National Academies.[8]

The recommended dose for both Xyrem and Xywav is 6 g to 9 g per night. Xyrem doses of 6 g to 9 g per night would have a sodium content that ranges from 1100 mg to 1638 mg. That led to the labeling for Xyrem to contain a Warning and Precaution regarding use in patients that are sensitive to high sodium intake. For patients already taking Xyrem at these doses, a change to Xywav at the same total nightly doses would result in a reduction in total nightly sodium intake ranging from 1013 mg (for the 6 g dose) to 1507 mg (for the 9 g dose). The labeling for Xywav does not contain the same Warning and

[5] A.Y. Avidan & C.A. Kushida (2020), *The Sodium in Sodium Oxybate: Is There Cause for Concern?,* Sleep Medicine 75:497-501.
[6] Available at https://www.nationalacademies.org/our-work/review-of-the-dietary-reference-intakes-for-sodium-and-potassium.
[7] *See* https://www.nationalacademies.org/news/2019/03/sodium-and-potassium-dietary-reference-intake-values-updated-in-new-report.
[8] Available at https://www.dietaryguidelines.gov/sites/default/files/2020-12/Dietary_Guidelines_for_Americans_2020-2025.pdf.

Precaution given the reduced sodium content of this drug. Thus, the sodium reduction from Xyrem to Xywav is significant under the guidelines referenced above. In addition, a higher prevalence of comorbidities such as hypertension, obesity, hyperlipidemia, and glucose intolerance has been reported in association with narcolepsy.[9] The reduction in chronic sodium burden with Xywav would be expected to be beneficial to all patients with narcolepsy, especially those with comorbidities that put them at increased risk of cardiovascular disease.

Second, your letter argues that the connection between sodium intake and adverse health outcomes has been largely disproven. As stated above, the paper by Avidan and Kushida published in Sleep Medicine in 2020 does not disprove the connection between sodium intake and adverse health outcomes, because the possibility that the sodium content of Xyrem increases cardiovascular risks in patients with narcolepsy has not been adequately studied to draw that conclusion. You also cite publications by O'Donnell, et al.[10] and Moore. et al.[11] to support your argument that the connection between sodium intake and adverse health outcomes has been largely disproven. The conclusions by the authors of these publications contrast sharply with what is stated in the recent publication by the National Academies and with the latest dietary guidelines published by the US Department of Agriculture, discussed above. The statements by the National Academies and US Department of Agriculture are authoritative and based on the latest consensus opinions of experts in the field. 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.

Third, your letter argues that there is no basis to conclude that reduced sodium in a sodium oxybate product will provide greater effectiveness, greater safety, or a major contribution to patient care. You point to an article by R.K. Bogan, et al.[12] and argue that "while the authors identified that the groups already receiving Xyrem had a modest increased systolic and diastolic blood pressure at baseline compared to groups not receiving Xyrem, no rates of increased blood pressure were reported in the Xywav-treated group after switching, presumably because no difference was observed." However, your presumption that no increases in blood pressure were observed in patients after switching to Xwyav because they were not reported is speculative. The authors of the paper stated that a rigorous evaluation of changes in blood pressure with Xywav in patients previously treated with Xyrem was not performed because it was outside the scope of the study. The authors also pointed out that the impact on cardiovascular disease risk of the reduction in sodium content in Xywav in patients previously treated with Xyrem could not be assessed because the duration of the study was very short.

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[9] *See* https://www.sciencedirect.com/science/article/abs/pii/S1389945717315587.
[10] M. O'Donnell, et al., (2020), Salt and Cardiovascular Disease: Insufficient Evidence to Recommend Low Sodium Intake, European Heart Journal 41: 3363-73.
[11] L.L. Moore, et al. (2018), Low Sodium Intakes are Not Associated with Lower Blood Pressure Levels Among Framingham Offspring Study Adults, The FASEB Journal 31(S1).
[12] R.K. Bogan, et al. (2020), Efficacy and Safety of Calcium, Magnesium, Potassium, and Sodium Oxybates (Lower-Sodium Oxybate [LXB]; JZP-258) in a Placebo-Controlled, Double-Blind, Randomized Withdrawal Study in Adults with Narcolepsy with Cataplexy, Sleep (electronic publication ahead of print).

Finally, we are not responding to your arguments about major contribution to patient case, because OOPD will only consider major contribution to patient care "where neither greater safety nor greater effectiveness has been shown,"[13] and here, greater safety has been shown.

In conclusion, Xywav is clinically superior to Xyrem by means of greater safety, because Xywav provides a greatly reduced chronic sodium burden compared to Xyrem. Xywav is eligible for orphan-drug exclusivity. Under 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.[14] If a subsequent same drug is clinically superior to Xywav, it will not be considered to be the same drug, [15] and not subject to the orphan-drug exclusivity for Xywav. As stated above, FDA has not yet evaluated whether your sodium oxybate product is clinically superior to any same drug that currently has orphan-drug exclusivity for the indication for which you are seeking approval.

Should you have any questions, please contact our office at 301-796-8660 or by email at orphan@fda.hhs.gov.

Sincerely,

Nicole L. Wolanski, CAPT, USPHS
Acting Director
Office of Orphan Products Development

[13] 21 CFR 316.3(b)(3)(iii).
[14] *See* Sec. 527(a) of the FD&C Act; *see also* 21 CFR 316.31.
[15] *See* 21 CFR 316.3(b)(14)(i).