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: November 27, 2020

From: Eric Bastings, MD
Division Director

Subject: Orphan Products Consult Request #2020-00029-EC
NDA 212690
Xywav™
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 (Serial Number)	**212690**
Sponsor:	**Jazz Pharmaceuticals, Inc**
Drug:	**Xywav (JZP-258)**
Approved Indication:	**Narcolepsy**
Material Received:	**Consultation Request**
Consultation Request Date:	**10/26/20**
Date Received By Reviewer:	**10/26/20**
Date Review Completed	**11/27/20**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Introduction

This consultation request has been received from the Office of Orphan Products Development, and follows a request to that office for the grant of orphan drug exclusivity for Xywav™.

Currently, Xywav™ (a low-sodium oxybate oral solution formulation containing a mixture of calcium, magnesium, potassium, and sodium oxybates) is approved for the treatment of cataplexy or excessive daytime sleepiness, in patients 7 years or older with narcolepsy. Another product approved for the same indication is Xyrem® (sodium oxybate oral solution). Xyrem® was initially approved, under NDA 21196, on July 17, 2002, whereas Xywav™ was initially approved, under NDA 212690, on July 21, 2020. One or more generic formulations of sodium oxybate oral solution have also been approved for the treatment of narcolepsy. All the aforementioned oxybate formulations are administered twice nightly, with the two nightly doses separated by an interval of 2.5 to 4 hours.

The active moiety in both Xywav™ and Xyrem® is oxybate (gamma-hydroxybutyric acid). The sponsor of both products is the same: Jazz Pharmaceuticals, Inc.

Orphan drug designation was originally granted to sodium oxybate by the Office of Orphan Products Development on November 7, 1994.

2. Text Of Consultation Request

The following section headings and text are copied from the consultation request from the Office of Orphan Products Development, dated October 26, 2020.

2.1 Background:

The Office of Orphan Products Development (OOPD) granted orphan drug designation to sodium oxybate on 11/07/94 for the treatment of narcolepsy. Sodium oxybate was originally approved for use in the treatment of narcolepsy on 7/17/02 under the trade name Xyrem. Xywav (calcium, magnesium, potassium, and sodium oxybates) was

approved on 7/21/20 for treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. At the time of this approval, the indication for Xyrem was identical. Since the active moiety in both Xyrem and Xywav is oxybate (gamma-hydroxybutyrate), the orphan drug designation granted in 1994 also applies to Xywav. The purpose of this consult request is to obtain the review division's input in order to help the OOPD determine eligibility for orphan drug exclusivity for Xywav.

Per the orphan drug regulations, since the active moiety, oxybate, was already approved for the same use or indication, in order to receive orphan drug exclusivity, Xywav must be clinically superiority to all previously approved oxybate products for the same indication, i.e. Xyrem. 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.

The sponsor for Xywav submitted a request to the OOPD on 4/24/20 for orphan drug exclusivity based on clinical superiority with regard to safety over Xyrem. The same request was also submitted to the NDA on the same date (see NDA 212690 eCTD Sequence Number 0009). In this document, the sponsor makes a case that Xywav provides greater safety because it provides a greatly reduced chronic sodium burden compared to Xyrem. To support their position, the sponsor has provided various references regarding a link between excess sodium intake and poor cardiovascular outcomes, as well as references to public health initiatives to decrease sodium intake. In addition, the sponsor notes that patients with narcolepsy often experience comorbidities such as metabolic disorders and obesity, hypertension, coronary heart failure, and myocardial infarction, which puts them at higher cardiovascular risk than the general population.

Furthermore, the sponsor notes that Xyrem's labeling has included warnings about Xyrem's high salt content and associated instructions for prescribers and patients since its initial approval. According to the sponsor, the recommended effective nightly dose of Xywav contains between 87 to 131 mg of sodium compared to 1,100 to 1,638 mg of sodium contained in a nightly dose of Xyrem. This equates to a sodium reduction of 1,013 to 1,507 mg per day relative to a patient started or maintained on oxybate therapy with Xyrem. To support that this reduction is clinically meaningful, the sponsor references several published meta-analyses of randomized controlled trials that reported lower systolic and diastolic blood pressure in patients with mean or median reductions in exposure to sodium that were similar to the reduction in sodium exposure associated with the use of Xywav instead of Xyrem. Other publications are referenced to support that a sodium reduction in this range is associated with a reduced risk of cardiovascular disease and hypertension.

The approved labeling for Xywav and Xyrem suggests to the OOPD that the reduction in sodium content in Xywav is expected to be clinically meaningful. First, we note that the approved labeling for both Xyrem and Xywav indicate that fluid retention and hypertension have been observed in postmarketing experience with Xyrem. We also note that the approved labeling for Xyrem contains a Warning and Precaution regarding its use in patients with conditions such as heart failure, hypertension, or renal impairment due to the drug's high salt content. The approved labeling for Xywav does not contain a similar warning. In addition, we note that the orphan drug regulations use the specific example of the elimination of an ingredient that is associated with adverse effects as a way to adequately support clinical superiority by means of safety (see definitions below). Overall, the OOPD thinks the sponsor's argument for clinical superiority for Xywav may have merit.

2.2 Consult Questions

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

Question 2
Does the review division agree that Xywav provides greater safety in a substantial portion of the target population when compared to Xyrem? Please explain. (As a reminder, the orphan drug regulations do not require head-to-head studies for clinical superiority based on safety.)

Question 3
Is the review division aware of any other possible advantages or disadvantages of Xywav compared to Xyrem? If so, please elaborate.

2.3 Designation Statutes and 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.

4. Summary Of Sponsor Request For Orphan Drug Exclusivity

As stated in the previous section, the sponsor (i.e., Jazz Pharmaceuticals, Inc.) submitted a package containing a request for orphan drug exclusivity for Xywav™, also referred to as "JZP-258," to the Office of Orphan Products Development on April 24, 2020. A copy of that request package was submitted to NDA 212690 on the same day (the initial submission under that NDA was under review by the Agency at that time).

The following is a summary list of the key arguments and assertions by the sponsor in that request. Please see the full text of that request for more details.

- An excess sodium intake in human subjects is associated with an increase in blood pressure which, in turn, is a predictor of cardiovascular disease in the general population.

- The National Academies of Science, Engineering, and Medicine have concluded in an assessment entitled "*Dietary Reference Intakes for Sodium and Potassium at 65*," (2019) that "*there is moderate to high strength of evidence for both a causal relationship and intake-response relationship between sodium and several interrelated chronic disease indicators: cardiovascular disease, hypertension, systolic blood pressure, and diastolic blood pressure*."

- Many professional organizations have recommended a reduction of sodium intake as a public health goal. Health authorities, including this Agency, have made efforts to reduce the sodium content of consumer products including pharmaceutical products in an effort to reduce the daily intake of sodium. The upper limit for daily sodium consumption has been set at 2300 mg, with an optimal consumption limit of 1500 mg/day (however, a typical American diet already has a sodium content exceeding those limits).

- Narcolepsy may be associated with a higher risk of hypertension and other cardiovascular conditions.

- Xyrem® has a high salt content, as depicted in a table included in the Prescribing Information for that product (this table is also in the next section of this review).

Table 3
Approximate Sodium Content per Total Nightly Dose of Xyrem (g = grams)

Xyrem Dose	Sodium Content/Total Nightly Exposure
3 g per night	550 mg
4.5 g per night	820 mg
6 g per night	1100 mg
7.5 g per night	1400 mg
9 g per night	1640 mg

- The recommended total nightly doses of both Xyrem® and Xywav™ range from 6 grams to 9 grams: that range encompasses a range of 1100 to 1638 mg of sodium for Xyrem® versus 87 to 131 mg of sodium for Xywav™. Thus for patients taking a total Xyrem® dose or 6 to 9 grams nightly, a change to Xywav™ would result in a reduction in nightly sodium intake ranging from 1013 mg (for the 6 g dose) to 1507 mg (for the 9 g dose).

- Meta-analyses of randomized, controlled trials investigating the effects of dietary sodium restriction on blood pressure and cardiovascular morbidity, and publications interpreting the results of those trials indicate that a change in daily sodium intake similar to that which will occur if Xywav™ (JZP-258) is substituted for Xyrem® at the 6-9 gram nightly dose is likely to be associated with a reduction in cardiovascular morbidity.

- 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®.

5. Efficacy And Safety Of Xywav™ Compared With Xyrem® As Described In Prescribing Information

There are no head-to-head comparisons of the efficacy and safety of Xywav™ with that of Xyrem® described in the Prescribing Information for the products.

To supplement what is stated in this consultative review, I have provided links to the current approved Prescribing Information for both products.

- The current Prescribing Information for Xywav™ is available at:

  https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212690s000lbl.pdf

- The current Prescribing Information for Xyrem® is available at:

  https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021196s032lbl.pdf

The comparative efficacy and safety of the two products to the extent that is apparent from the Prescribing Information for each will be summarized next.

5.1 Comparative Efficacy Of Xywav™ and Xyrem®

No prospectively-designed head-to-head comparisons of the efficacy of Xyrem® and Xywav™ have been performed.

Retrospective comparisons of the efficacy of the two products using data from the pre-approval clinical trials described in the product label are confounded by many factors. Nonetheless the efficacy of the two products, Xywav™ and Xyrem®, in treating cataplexy and excessive daytime sleepiness in narcolepsy appears to be broadly similar.

5.2 Comparative Safety Of Xywav™ and Xyrem®

As already stated, no head-to-head comparisons of the safety and tolerability of Xywav™ and Xyrem® have been conducted. Neither have the effects on cardiovascular morbidity of a change in regimen from Xyrem® to Xywav™ (for the treatment of cataplexy or excessive daytime sleepiness in patients with narcolepsy, 7 years and older), been investigated in a prospectively-designed clinical trial.

However, the observed safety profiles of the two products as described in the Prescribing Information and in prior clinical reviews, for each, do not have substantial differences.

The only readily-evident potential reason for a difference in the safety of the two products is the higher sodium content of Xyrem® relative to Xywav™.

5.2.1 Pertinent Sections Of Prescribing Information

The sections of the Prescribing Information that are most pertinent to this review are described below, but other sections of the Prescribing Information, Medication Guide, and Risk Evaluation and Mitigation Strategy (REMS) for this product also contain text that may be relevant.

5.2.1.1 Xyrem®

5.2.1.1.1 Dosage Forms And Strengths

The following text has been extracted from Section 3 (DOSAGE FORMS AND STRENGTHS) of the Prescribing Information.

> Xyrem is a clear to slightly opalescent oral solution, in a concentration of 0.5 g per mL (0.5 g/mL of sodium oxybate equivalent to 0.413 g/mL of oxybate).

Please also see Section 11 (DESCRIPTION) of the Prescribing Information for Xyrem® for additional information regarding the composition of this product.

5.2.1.1.2 Warnings and Precautions

The following text has been extracted from Section 5 (WARNINGS AND PRECAUTIONS) of the Prescribing Information.

> **5.8 Use in Patients Sensitive to High Sodium Intake**
>
> 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.
>
> **Table 3**
> **Approximate Sodium Content per Total Nightly Dose of Xyrem (g = grams)**

Xyrem Dose	Sodium Content/Total Nightly Exposure
3 g per night	550 mg
4.5 g per night	820 mg
6 g per night	1100 mg
7.5 g per night	1400 mg
9 g per night	1640 mg

5.2.1.2 Xywav™

5.2.1.2.1 Dosage Forms And Strengths

The following text has been extracted from Section 3 (DOSAGE FORMS AND STRENGTHS) of the Prescribing Information.

> XYWAV is a clear to slightly opalescent oral solution at a total salt concentration of 0.5 g per mL. Each mL contains 0.5 g of total salts present as 0.234 g calcium oxybate, 0.096 g magnesium oxybate, 0.13 g potassium oxybate, and 0.04 g sodium oxybate (equivalent to 0.413 g total oxybate).

Please also see Section 11 (DESCRIPTION) of the Prescribing Information for Xywav™ for additional information regarding the composition of this product.

5.2.1.2.2 Warnings and Precautions

There is no text in Section 5 of the Prescribing Information for Xywav™, that corresponds to the text of Section 5.8 of the Prescribing Information for Xyrem® that is copied above.

6. Reviewer's Summary Comments

This request for a consultative review from the Office of Orphan Product Development is regarding a request for orphan drug exclusivity for Xywav™.

Currently, Xywav™ (a low-sodium oxybate oral solution formulation containing a mixture of calcium, magnesium, potassium, and sodium oxybates) and Xyrem® (sodium oxybate oral solution) are both approved for the treatment of cataplexy or excessive daytime sleepiness, in patients 7 years or older with narcolepsy. The active moiety in both Xywav™ and Xyrem® is oxybate (gamma-hydroxybutyric acid). Xywav™ is also named "JZP-258" in recent communications between the sponsor and Agency.

Orphan drug designation was originally granted to sodium oxybate by the Office of Orphan Products Development on November 7, 1994. The current request for orphan drug exclusivity for Xywav™ is based on that product having greater safety than Xyrem® based on the much lower sodium content of the former product.

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.

Adequate support for this view is provided in the request for orphan exclusivity submitted by the sponsor on April 24, 2020, which discusses the above in much greater detail.

7. Consult Questions From Office Of Orphan Products Development And Division Of Neurology 1 Responses

7.1 Question 1

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

Division of Neurology 1 Response:

There is no evidence available to suggest that the efficacy of Xywav™ may be substantially different from that of Xyrem®.

7.2 Question 2

Does the review division agree that Xywav provides greater safety in a substantial portion of the target population when compared to Xyrem? Please explain. (As a reminder, the orphan drug regulations do not require head-to-head studies for clinical superiority based on safety.)

Division of Neurology 1 Response:

We agree that Xywav™ provides greater safety than Xyrem® in a substantial proportion of patients for whom both Xywav™ and Xyrem® are indicated. The sodium content of Xywav™ at the recommended doses of 6 to 9 grams nightly is much less than the sodium content of Xyrem® at the same doses. Although the safety of Xyrem® and Xywav™ have not been compared head-to-head in clinical trials, the available evidence from other sources, including the data that has been submitted by the sponsor, indicates that 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. This view is explained further above in this review.

7.3 Question 3

Is the review division aware of any other possible advantages or disadvantages of Xywav compared to Xyrem? If so, please elaborate.

Division of Neurology 1 Response:

We are unaware of any other possible advantages or disadvantages that Xywav™ may have compared to Xyrem®.

Ranjit B. Mani -S

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Ranjit B. Mani, M.D.
Clinical Reviewer and Supervisory Lead

Eric P. Bastings -S

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

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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: March 8, 2021

From: Eric Bastings, MD
Division Director

Subject: Orphan Products Consult Request #2020-00029-EC
NDA 212690
Xywav™
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 (Serial Number)	**212690**
Sponsor:	**Jazz Pharmaceuticals, Inc.**
Product:	**Xywav (JZP-258)**
Proposed Indication:	**Narcolepsy**
Material Submitted:	**Consultation Request**
Consultation Request Date:	**1/8/21**
Date Received By Reviewer:	**1/11/21**
Date Review Completed:	**3/8/21**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This consultation request has been received from the Office of Orphan Products Development, and is related to a letter to that office requesting that the Agency refrain from granting orphan drug exclusivity for Xywav™.

Currently, Xywav™ (a low-sodium oxybate oral solution formulation containing a mixture of calcium, magnesium, potassium, and sodium oxybates) is approved for the treatment of cataplexy or excessive daytime sleepiness, in patients 7 years or older with narcolepsy. Another product approved for the same indication is Xyrem® (sodium oxybate oral solution). Xyrem® was initially approved, under NDA 21196, on July 17, 2002, whereas Xywav™ was initially approved, under NDA 212690, on July 21, 2020. One or more generic formulations of sodium oxybate oral solution have also been approved for the treatment of narcolepsy. All the aforementioned oxybate formulations are administered twice nightly, with the two nightly doses separated by an interval of 2.5 to 4 hours.

The active moiety in both Xywav™ and Xyrem® is oxybate (gamma-hydroxybutyric acid). The sponsor of both products is the same: Jazz Pharmaceuticals, Inc.

Orphan drug designation was originally granted to sodium oxybate by the Office of Orphan Products Development on November 7, 1994.

An earlier consultation was completed by this Division (in response to a request from the Office of Orphan Products Development), that was related to the current request for orphan drug exclusivity for Xywav™. That consultation request was made on October 26, 2020, and was completed on November 27, 2020. Please see the text of that consultation request for further details.

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2. Text Of Consultation Request

The full text of the consultation request is copied verbatim below.

(b) (4)

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[redacted]

(b) (4)

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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. Reviewer's Background Comments

In this section, this reviewer has summarized several subjects that are pertinent to this consultation request.

The current approved Prescribing Information for Xyrem® and Xywav™ have been referenced in this section. I have therefore provided links to the current approved Prescribing Information for both products.

- The current approved Prescribing Information for Xyrem® is available at the following link.

  https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021196s032lbl.pdf

- The current approved Prescribing Information for Xywav™ is available at the next link.

  https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021196s035,212690s001s002lbl.pdf

3.1 Sodium Content Of Xyrem® And Xywav™ And Its Implications

3.1.1 Xyrem®

3.1.1.1 Dosage Forms And Strengths

The following text has been extracted from Section 3 (DOSAGE FORMS AND STRENGTHS) of the Prescribing Information.

> Xyrem is a clear to slightly opalescent oral solution, in a concentration of 0.5 g per mL (0.5 g/mL of sodium oxybate equivalent to 0.413 g/mL of oxybate).

Please also see Section 11 (DESCRIPTION) of the Prescribing Information for Xyrem® for additional information regarding the composition of this product.

3.1.1.2 Dosage And Administration

As stated in Section 2 of the current Prescribing Information for Xyrem®, the effective dose range for Xyrem® is 6 to 9 grams per night in 2 divided doses, in adults.

Please refer to the sponsor's table in the next section. Xyrem® doses of 6 to 9 grams per night would have a sodium content that ranges from 1100 to 1638 mg.

3.1.1.3 Warnings and Precautions

The following text has been extracted from Section 5 (WARNINGS AND PRECAUTIONS) of the Prescribing Information.

> **5.8 Use in Patients Sensitive to High Sodium Intake**
>
> 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.
>
> **Table 3**
> **Approximate Sodium Content per Total Nightly Dose of Xyrem (g = grams)**

Xyrem Dose	Sodium Content/Total Nightly Exposure
3 g per night	550 mg
4.5 g per night	820 mg
6 g per night	1100 mg
7.5 g per night	1400 mg
9 g per night	1640 mg

3.1.2 Xywav™

3.1.2.1 Dosage Forms And Strengths

The following text has been extracted from Section 3 (DOSAGE FORMS AND STRENGTHS) of the Prescribing Information.

> XYWAV is a clear to slightly opalescent oral solution at a total salt concentration of 0.5 g per mL. Each mL contains 0.5 g of total salts present as 0.234 g calcium oxybate, 0.096 g magnesium oxybate, 0.13 g potassium oxybate, and 0.04 g sodium oxybate (equivalent to 0.413 g total oxybate).

Please also see Section 11 (DESCRIPTION) of the Prescribing Information for Xywav™ for additional information regarding the composition of this product.

3.1.2.2 Dosage And Administration

As stated in Section 2 of the current Prescribing Information for Xywav™, the recommended dose range for Xywav™ is 6 to 9 grams per night in 2 divided doses.

Based on data previously made available to this reviewer, Xywav™ doses of 6 to 9 grams per night would have a sodium content that ranges from 87 to 131 mg.

Thus for patients already taking a total Xyrem® dose of 6 grams or 9 grams nightly, a change to Xywav™ at the same total nightly dose, 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).

3.1.2.3 Warnings and Precautions

Unlike the corresponding section of Prescribing Information for Xyrem®, this section of the Xywav™ label contains no text pertaining to its use in patients who are sensitive to a high sodium intake, which is unsurprising given the sodium content of Xywav™.

3.2 Xyrem® And Adverse Cardiovascular Outcomes

There are no studies that have been prospectively designed to specifically investigate whether the administration of Xyrem® at doses recommended in the Prescribing Information 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 (e.g., hypertension or obesity) that may predispose to such outcomes. Moreover, the controlled clinical trials of Xyrem® that are described in the Prescribing Information for that drug have been of too short a duration and have exposed too few patients to Xyrem® to enable such outcomes to be investigated.

3.3 Salt Intake And Cardiovascular Disease

Please refer to the publication by the US Department of Agriculture entitled "*Dietary Guidelines for Americans 2020-2025*" published in December 2020, which is available at the following link.

https://www.dietaryguidelines.gov/sites/default/files/2020-12/Dietary_Guidelines_for_Americans_2020-2025.pdf

The following is stated on Page 46 (of 159) of the above guidelines.

"Sodium is an essential nutrient primarily consumed as salt (sodium chloride). Healthy eating patterns limit sodium to the Chronic Disease Risk Reduction (CDRR) levels defined by the National Academies—1,200 mg/day for ages 1 through 3; 1,500 mg/day for ages 4 through 8; 1,800 mg/day for ages 9 through 13; and 2,300 mg/day for all other age groups. The CDRR for sodium was established using evidence of the benefit of reducing sodium intake on cardiovascular risk and hypertension risk."

The publication by the National Academies cited above is summarized in a news release dated March 5, 2019, which is available at the link below.

https://www.nationalacademies.org/news/2019/03/sodium-and-potassium-dietary-reference-intake-values-updated-in-new-report

A link to the same publication in full is available in the body of that news release.

The following text is extracted from the above news release.

"There is sufficient evidence to characterize the relationship between sodium intake and risk of chronic disease. Therefore, the committee established a chronic Disease Risk Reduction Intake (CDRR) for sodium using evidence of the beneficial effect of reducing sodium intake on cardiovascular disease risk, hypertension risk, systolic blood pressure, and diastolic blood pressure. Reductions in intakes that exceed the sodium CDRR are expected to reduce chronic disease risk within the apparently healthy population. For individuals ages 14 and older, the CDRR recommendation is to reduce sodium intakes if above 2,300 mg per day."

Thus, an authoritative national body in the United States has recommended in an official publication that daily salt intake in individuals 14 years and older be restricted to 2300 mg or less. The National Academies have also stated that there is evidence that a reduction is 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.

3.4 Co-Morbidities Associated With Narcolepsy

A higher prevalence of hypertension, obesity, hyperlipidemia, and glucose intolerance has been reported in association with narcolepsy, in addition to other medical and psychiatric disorders. An example of a publication describing such co-morbidities is available at the link below.

https://www.sciencedirect.com/science/article/abs/pii/S1389945717315587

4. Consult Questions From Office Of Orphan Products Development And Division Of Neurology 1 Responses

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(b) (4)

4.5 Question 5

Are there any other issues not addressed above or in the previous consult that DN1 would like the OOPD to consider in its determination of orphan drug eligibility for Xywav?

Division of Neurology 1 Response:

No.

Ranjit B. Mani -S

Digitally signed by Ranjit B. Mani -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ranjit B. Mani -S, 0.9.2342.19200300.100.1.1=1300122852
Date: 2021.03.08 10:38:17 -05'00'

Ranjit B. Mani, M.D.
Clinical Reviewer and Supervisory Lead

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

Eric P. Bastings -S

Digitally signed by Eric P. Bastings -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300158815, cn=Eric P. Bastings -S
Date: 2021.03.08 13:51:31 -05'00'

rbm
cc:
HFD-120
IND

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Office of Orphan Products Development

Exclusivity Memorandum

Date:	6/23/21
From:	Theodore Garnett, PhD, Health Science Administrator Roberta Szydlo, RPh, MBA, Senior Program Management Officer Roberta T. Szydlo -S3 Digitally signed by Roberta T Szydlo -S3 Date: 2021 09 30 17:12:31 04'00'
Through:	Henry Startzman III, MD, Director, Orphan Drug Designation Program Henry H. Startzman -S Digitally signed by Henry H Startzman -S Date: 2021 09 30 12:31:49 04'00' Aaron Friedman, JD, Senior Regulatory Counsel Aaron R. Friedman -S Digitally signed by Aaron R Friedman -S Date: 2021 09 30 17:07:19 04'00' Nicole Wolanski, Acting Director, Office of Orphan Products Development
To File #:	DRU-1994-858
Name of drug or biologic:	Xywav (calcium, magnesium, potassium, and sodium oxybates)
Orphan designation:	Treatment of narcolepsy
Designation date:	11/7/1994
Sponsor name:	Jazz Pharmaceuticals
NDA, sNDA, BLA, or sBLA #:	NDA 212690
Approval date:	7/21/2020

Approved indication:	XYWAV is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.		
Is the approval within scope of designation?	**Yes ☒ No ☐**		
Comments:	The approval of XYWAV (calcium, magnesium, potassium, and sodium oxybates) for the indication above is within the scope of orphan drug designation #1994-858 for the treatment of narcolepsy.		
Has the same drug or biologic been previously approved?	**Yes ☒ No ☐**	**Is the drug or biologic a New Molecular Entity (NME) or New Biological Entity (NBE)?**	**Yes ☐ No ☒**
Comments:	According to the Clinical Review for Xywav dated July 21, 2020, the sponsor developed Xywav to be a low-sodium alternative to their other drug, Xyrem (sodium oxybate), which was originally approved by the Agency on July 17, 2002 under NDA 21196 (see page 7). Xywav and Xyrem both contain the same active moiety which is oxybate (also known as gamma hydroxybutyrate) (see page 6 and 7 of the Clinical Review). Therefore, Xywav is not a new molecular entity.		
Has the same drug or biologic already been approved for the same indication?	**Yes ☒ No ☐**		
Comments:	As noted above, Xyrem and Xywav contain the same active moiety. Xyrem was originally approved on July 17, 2002, for the treatment of cataplexy in narcolepsy. Subsequent efficacy supplements approved on November 18, 2005, and October 26, 2018, respectively, expanded the approved use of Xyrem to include the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy (see page 7 of the Clinical Review). Therefore, the indications for Xyrem and Xywav are currently identical which means that the same drug has been previously approved for the same indication.		
Has clinical superiority been demonstrated?	**Yes ☒ No ☐ Not Applicable ☐**		
Comments:	Since the same drug has been previously approved for the same indication, Xywav must be clinically superior to Xyrem in order to be eligible for orphan drug exclusivity. Sec. 527(c)(1) of the FD&C Act; 21 CFR 316.34(c). Clinical superiority 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) through greater effectiveness, greater safety in a substantial portion of the target population, or in unusual cases, by making a major contribution to patient care. Sec. 527 (c)(2) of the FD&C Act; 21 CFR		

316.3(b)(3).

The sponsor for Xywav submitted a request to the OOPD on April 24, 2020 for orphan drug exclusivity for Xywav based on clinical superiority with regard to safety over Xyrem. The same request was also submitted to the NDA on the same date (NDA 212690 eCTD Sequence Number 0009). In this document, the sponsor asserted that Xywav provides greater safety because it provides a greatly reduced chronic sodium burden compared to Xyrem. Specifically, a daily dose of Xyrem adds 1,100 to 1,638 mg of sodium to each patient's daily sodium intake. A daily dose of Xywav contains 87 to 131 mg of sodium, thus reducing the sodium burden by 1.5 grams (92%) at the highest dose. The sponsor argues that reducing the sodium burden is important because excess sodium intake is associated with poor cadiovascular outcomes. The amount of sodium reduction from Xyrem to Xywav is associated with clinically meaningful reductions in blood pressure and cardiovasular disease. In addition, the sponsor noted that patients with narcolepsy often experience comorbidities such as metabolic disorders and obesity, hypertension, coronary heart failure, and myocardial infarction, which puts them at higher cardiovascular risk than the general population. Furthermore, the sponsor noted that Xyrem's labeling has included warnings about its high salt content and associated instructions for prescribers and patients since its initial approval.

The OOPD consulted with the Division of Neurology 1 (DN1) to help determine if Xywav is clinically superior to Xyrem. In their consult response dated Nov. 27, 2020, DN1 agreed that Xywav is clinically superior because it provides greater safety than Xyrem in a substantial proportion of patients for whom both Xywav and Xyrem are indicated. DN1 noted that although the safety of Xyrem and Xywav have not been compared in a head-to-head manner, "the available evidence from other sources, including the data that has been submitted by the sponsor, indicates that 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." Specifically, DN1 stated the following:

"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."

The OOPD concurs with DN1's consult response. The orphan drug regulations, within the definition of "clinically superior," provide that "the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects" is an eample of greater safety. 21 CFR 316.3(b)(3)(ii). Although sodium is not eliminated in Xywav, the amount is substantially reduced such that it is likely to be clinically meaningful for

patients, especially since they will be receiving the drug chronically for their condition. In addition, a substantial portion of patients with narcolepsy have comorbidities for which limiting excess sodium intake is particulary important.

(b) (4)

The OOPD consulted with DN1 (b) (4). In their consult response dated March 8, 2021, DN1 concludes (b) (4) not alter what they stated in their earlier consult reponse provided to OOPD on Nov. 27, 2020. DN1's consult response notes the following as background:

- The recommended dose for both Xyrem and Xywav is 6 g to 9 g per night. For patients already taking Xyrem at this dose, a change to Xywav at the same total nightly dose 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 Xyrem contains a Warning and Precaution regarding use in patients that are sensitive to high sodium intake. The labeling for Xywav does not contain the same Warning and Precaution given the reduced sodium content of this drug.
- There are no studies that have been prospectively designed to specifically investigate whether the administration of Xyrem at recommended doses is associated with adverse CV outcomes, either in the wider population with narcolepsy or in subgroups of patients with narcolepsy who have co-existing medical conditions, such as hypertension or obesity, that may predispose them to such outcomes. Moreover, the controlled clinical trials of Xyrem that are described in the labeling for that drug have been of too short a duration and have exposed too few patients to Xyrem to enable such outcomes to be investigated.
- 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 (https://www.nationalacademies.org/our-work/review-of-the-dietary-

reference-intakes-for-sodium-and-potassium). 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. In addition, the US Department of Agriculture's publication titled "Dietary Guidelines for Americans 2020-2025" also supports the recommendations of the National Academies.

- A higher prevalence of co-morbidities such as hypertension, obesity, hyperlipidemia, and glucose intolerance has been reported in association with narcolepsy.

(b) (4)

DN1 also reviewed publications by O'Donnell et al (European Heart Journal 2020; 41:3363-3373) and Moore et al (FASEB Journal 2018; 31:1-3 [abstract only]) (b) (4) DN1 notes that 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 which are discussed above. According to DN1, statements by the National Academies and US Department of Agriculture are authoritative and based on the latest consensus opinions of experts in the field. In addition, DN1 reiterates the statement in their previous consult response to OOPD that "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." Furthermore, DN1 states that the recent conclusions of the National Academies and the guidelines published by the US Department of Agriculture regarding daily salt intake and its relationship to cardiovascular morbidity represent the current expert consensus and as such, DN1 accepts them. DN1 further notes that until these conclusions are overturned by an expert body, (b) (4)

(b) (4)

	[redacted] (b) (4) [redacted] (b) (4) Under the orphan drug regulations, the OOPD will only consider major contribution to patient care "where neither greater safety nor greater effectiveness has been shown." 21 CFR 316.3(b)(3)(iii). Because Jazz has demonstrated that Xywav provides greater safety than Xyrem, [redacted] (b) (4) The OOPD concurs with DN1's consult response and agrees that the reduced sodium in Xywav makes it clinically superior to Xyrem based on greater safety in a substantial portion of the target population. The OOPD notes that the term "substantial portion" does not necessarily mean the drug provides greater safety in **all or most** of the indicated population in order for it to be considered clinically superior. At a minimum, the reduction in chronic sodium burden with Xywav would be expected to be beneficial to patients with narcolepsy and comorbidities that put them at increased risk of CV disease.
Recommendation:	**Recognize Exclusivity: Yes ☒ No ☐** The approved indication for Xywav is within scope of orphan drug designation #94-858 for treatment of narcolepsy. Xywav and Xyrem contain the same active moiety and are approved for the identical indication. Xywav is clinically superior to Xyrem with regard to safety. Therefore, the sponsor is eligible for orphan exclusivity for Xywav indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

Additional comments (optional): Note that an interim draft of this memo was inadvertently filed in Nexus on 6/24/2021. This memo is the correct version and supersedes the memo filed 6/24/2021.