CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s000

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date:	July 7, 2020
To:	Vandna Kishore Regulatory Project Manager **Division of Neurology I**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	XYWAV (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate)
Dosage Form and Route:	oral solution, CIII
Application Type/Number:	NDA 212690
Applicant:	Jazz Pharmaceuticals

1 INTRODUCTION

On January 21, 2020, Jazz Pharmaceuticals submitted for the Agency's review an original New Drug Application (NDA) 212690 for XYWAV (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate). This NDA proposes the indication for the treatment of cataplexy and excessive daytime sleepiness in patients 7 years of age and older with narcolepsy. The reference listed drug for this NDA is XYREM (sodium oxybate).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology I on February 4, 2020 and February 5, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG), and Instructions for Use (IFU) for XYWAV (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate) oral solution, CIII.

2 MATERIAL REVIEWED

- Draft XYWAV (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate) MG and IFU received on January 21, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 22, 2020.
- Draft XYWAV (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate) Prescribing Information (PI) received on January 21, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 22, 2020.
- XYREM (sodium oxybate) comparator labeling dated October 26, 2018.

3 REVIEW METHODS

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

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

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

LONICE J CARTER
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REBECCA A FALTER
07/07/2020 08:03:39 AM

MARCIA B WILLIAMS
07/07/2020 10:13:13 AM

LASHAWN M GRIFFITHS
07/07/2020 06:18:55 PM

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

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

Memorandum

Date: July 07, 2020

To: Vandna Kishore, Regulatory Project Manager
Division of Neurology-I (DN-I)

Tracy Peters, PharmD, Associate Director for Labeling, (DN-I)

From: Rebecca Falter, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Xywav™ (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII

NDA: 212690

In response to DN-I's consult request dated February 5, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Xywav.

PI and Medication Guide/IFU: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DN-I (Vandna Kishore) on June 22, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide and IFU were sent under separate cover on July 7, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 19, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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REBECCA A FALTER
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 24, 2020
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 212690
Product Name and Strength:	Xywav (calcium, magnesium, potassium, sodium oxybates) oral solution, 0.5 g/mL
Applicant/Sponsor Name:	Jazz Pharmaceuticals Ireland Limited
OSE RCM #:	2020-132-2
DMEPA Safety Evaluator:	Justine Kalonia, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted the revised container label received on June 19, 2020 for Xywav. The Division of Neurology 1 (DN 1) requested that we review the revised container label for Xywav (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and memorandum.[a,b]

2 CONCLUSION

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

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[a] Kalonia J. Label and Labeling Review for Xywav (NDA 212690). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 11. RCM No.: 2020-132.
[b] Kalonia J. Label and Labeling Memorandum for Xywav (NDA 212690). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 17. RCM No.: 2020-132-1.

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/s/

JUSTINE H KALONIA
06/24/2020 08:44:29 AM

LOLITA G WHITE
06/24/2020 02:04:39 PM

M E M O R A N D U M

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

Date: June 21, 2020

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

Through: Dominic Chiapperino, Ph.D., Director
Controlled Substance Staff

From: Chad Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff

Subject: Gamma-hydroxybutyrate (JZP-258), NDA 212690
XYWAV oral solution, 0.5 g/mL
IND 49641
Indication(s): treatment of cataplexy and excessive daytime sleepiness (EDS) in Patients 7 years of age and older with narcolepsy
Sponsor: Jazz Pharmaceuticals Ireland Limited
PDUFA Goal Date: July 21, 2020

Materials Reviewed:

Abuse-related clinical data and labeling in NDA 212690

Table of Contents

I. EXECUTIVE SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Neurology Products 1 (DNP1) to evaluate the abuse potential of JZP-258 (proposed trade name: XYWAV) submitted by Jazz pharmaceuticals in NDA 212690. JZP-258 is an orally administered solution. The drug product is indicated for the treatment of cataplexy and excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. The recommended dose is 0.5 g/mL. According to the Sponsor, JZP-258 contains the active moiety oxybate (4-hydroxybutanoate), a central nervous system depressant, and belongs to the same pharmacologic class as Xyrem (sodium oxybate). Xyrem was first reviewed by CSS in 2001 (DARRTS entry by Michael Klein, 5/8/2001) and approved on July 17, 2002 for the treatment of cataplexy associated with narcolepsy. The Sponsor states that JZP-258 and Xyrem contain the same concentration of active ingredients (0.5 g/mL) and the same concentration of active moiety. The Sponsor is developing JZP-258 to reduce the sodium content of their product while retaining the treatment benefits of Xyrem. Xyrem is controlled in Schedule III (C-III) of the Controlled Substances Act (CSA).

JZP-258 is a new molecular entity. The mechanism of action of oxybate in the treatment of narcolepsy is unknown. It is hypothesized that the therapeutic effects of oxybate on the symptoms of narcolepsy (cataplexy and excessive daytime sleepiness [EDS]) are mediated through interactions with the B-subtype of the gamma-aminobutyric acid ($GABA_B$) receptors on noradrenergic and dopaminergic neurons, and thalamocortical neurons.

2. Conclusions

- JZP-258 contains the same active pharmaceutical ingredient (API) as Xyrem and in an equivalent amount
- JZP-258 may have a slightly longer time to reach maximum concentration (i.e., increased Tmax) and an approximately 20% lower peak concentration (decreased Cmax). Thus, the abuse potential of JZP-258 does not appear to be increased relative to Xyrem
- Clinical studies with JZP-258 did not appear to produce an adverse event (AE) profile demonstrating an increased abuse potential relative to Xyrem
- JZP-258 is labeled appropriately and nearly identical to Xyrem

3. Recommendations

Based on our findings, we recommend the following:

1. JZP-258 does not appear to have an increased abuse potential relative to Xyrem (C-III) and contains the same active moiety in an equivalent amount. Accordingly, JZP-258 should be controlled in schedule III of the Controlled Substances Act.

Sections of product labeling for JZP-258 related to abuse and dependence are similar to Xyrem labeling, appropriate, and appears as follows:

5.2 Abuse and Misuse

XYWAV is a Schedule III controlled substance. The active moiety of XYWAV, is oxybate also known as gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim). Because illicit use and abuse of GHB have been reported, physicians should evaluate patients for a history of drug abuse and follow them closely, particularly for signs of misuse or abuse of GHB (including but not limited to increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy) *[see Drug Abuse and Dependence (9.2)]*. If abuse is suspected, treatment with XYWAV should be discontinued.

XYWAV is available only through a restricted program under a REMS *[see Warnings and Precautions (5.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

TRADENAME is a Schedule III controlled substance under the Federal Controlled Substances Act. Non-medical use of TRADENAME could lead to penalties assessed under the higher Schedule I controls.

9.2 Abuse

The active moiety of TRADENAME, oxybate, produces dose-dependent central nervous system effects, including hypnotic and positive subjective reinforcing effects. The onset of effect is rapid, enhancing its potential for abuse or misuse.
The rapid onset of sedation, coupled with the amnestic features of oxybate, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).

Illicit GHB is abused in social settings primarily by young adults. Some of the doses estimated to be abused are in a similar dosage range to that used for treatment of patients with cataplexy. GHB has some commonalities with ethanol over a limited dose range, and some cross tolerance with ethanol has been reported as well. Cases of severe dependence and craving for GHB have been reported when the drug is taken around the clock. Patterns of abuse indicative of dependence include: 1) the use of increasingly large doses, 2) increased frequency of use, and 3) continued use despite adverse consequences.

Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g., increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy). Dispose of TRADENAME according to state and federal regulations. It is safe to dispose of TRADENAME down the sanitary sewer.

9.3 Dependence

There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the recommended dosage range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps,

tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal, visual hallucinations, agitation, and delirium. These symptoms generally abated in 3 to 14 days. In cases of severe withdrawal, hospitalization may be required. The discontinuation effects of TRADENAME have not been systematically evaluated in controlled clinical trials. In the clinical trial experience with Xyrem in narcolepsy/cataplexy patients at recommended doses, two patients
reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time. In the TRADENAME clinical trial in adult narcolepsy/cataplexy patients at recommended doses, one patient reported insomnia following abrupt discontinuation of TRADENAME.

Tolerance
Tolerance to TRADENAME has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended TRADENAME dosage regimen. Clinical studies of sodium oxybate in the treatment of alcohol withdrawal suggest a potential cross-tolerance with alcohol. The safety and effectiveness of TRADENAME in the treatment of alcohol withdrawal have not been established.

17 PATIENT COUNSELING INFORMATION

[relevant sections for abuse, dependence, and diversion risks]

Abuse and Misuse
Inform patients and/or caregivers that the active ingredient of XYWAV is gamma-hydroxybutyrate (GHB), which is associated with serious adverse reactions with illicit use and abuse *[see Warnings and Precautions (5.2)]*.

XYWAV/XYREM REMS Program
XYWAV is available only through a restricted program called the XYWAV/XYREM REMS Program *[see Warnings and Precautions (5.3)]*. Inform the patient and/or caregiver of the following notable requirements:
• XYWAV is dispensed only by the central pharmacy
• XYWAV will be dispensed and shipped only to patients enrolled in the XYWAV/XYREM REMS Program

XYWAV is available only from the central pharmacy participating in the program. Therefore, provide patients and/or caregivers with the telephone number and website for information on how to obtain the product.

II. DISCUSSION

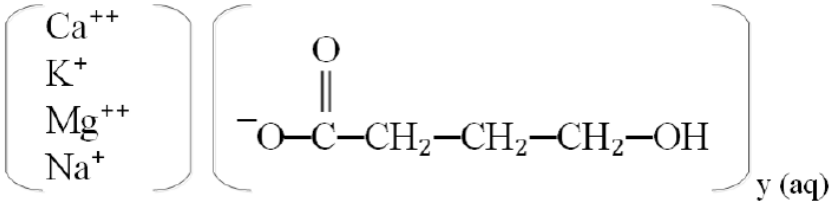
1. Chemistry

According to the Sponsor, JZP-258 drug substance consists of mixed oxybate salts (calcium, potassium, magnesium, and sodium). The molecular formula of the active moiety, oxybate, is $C_4H_8O_3$. The

molecular weight of oxybate (as its neutral species) is 104.10 g/mol. JZP-258 does not have a CAS number or IUPAC name.

JZP-258 does not have any chiral centers and the structure appears below:

Figure 1: Structural Formula, JZP-258 Drug Substance



where y=1 for Na^+ and K^+; y=2 for Mg^{2+} and Ca^{2+}.

The drug product formulation is an oral solution containing the oxybate salts active ingredient at a concentration of 0.5 g/mL, with only sucralose and purified water as excipients.

2. Clinical Pharmacology

Two studies (13-010 and JZP258-101) evaluated the bioavailability/bioequivalence (BE) of JZP-258 and characterized the basic pharmacokinetic (PK) properties of JZP-258, including food effects (both studies) and dose proportionality (only in Study 13-010) relative to Xyrem. Overall, relative to Xyrem, under fasting conditions JZP-258 had a slightly longer time to peak concentration (i.e., longer Tmax) and lower peak plasma concentration (i.e., decreased Cmax), with a similar area under the curve (AUC), and similar half-life. The Sponsor notes that JZP-258 met FDA bioequivalence criteria for AUC, but not Cmax.

Under fed conditions, exposure was decreased for both formulations while the half-life was unchanged. Food had a greater effect on the Cmax of Xyrem relative to JZP-258 (~40% reduction for Xyrem compared to ~25% for JZP-258). In addition, food increased the time to Tmax for Xyrem and not JZP-258. The Sponsor notes that JZP-258 met bioequivalence criteria for Xyrem under fed conditions.

Based on the PK studies, the clinical pharmacology of JZP-258 is similar to Xyrem and thus pharmacodynamic abuse-related effects predicted to be similar to Xyrem. See the clinical pharmacology review for additional discussion.

3. Clinical Studies

The clinical development program for JZP-258 included four studies: three phase 1 bioavailability bioequivalence (BA/BE) studies (Studies 13-010, JZP258-101, and 15-003) and a Phase 3 study (study 15-006). Each of these studies was assessed for abuse-related AEs and briefly summarized below:

Study 13-010: "An Open-Label, Randomized Crossover Study to Evaluate the Pharmacokinetics of Oxybate Formulations in Healthy Subjects, Bioavailability, Bioequivalence, and Food Effect Following Administration."

This study was divided into two phases. The first phase examined the bioavailability and bioequivalence (BA/BE) of JZP-258 compared to Xyrem under fasting and fed conditions (phase 1). The second study phase (phase 2) evaluated the BA/BE of two admixtures of JZP-258 and Xyrem at different ratios. A range of N=35-36 subjects completed phase 1 of the study and n=23-24 completed phase 2. Relative to Xyrem, mean oxybate concentration time profiles were similar under fasted conditions, although values for JZP-258 were lower for the first 1.5 hours. Overall, both JZP-258 and the admixtures produced slightly delayed Tmax and Cmax values relative to Xyrem.

Abuse-related adverse events judged as "related" to study drug by the Investigator from both phases of the study are shown below in Table 1.

Table 1: Abuse-related AEs from Study 13-010

Part 1, food-effect study

System Organ Class Preferred term	Fasting JZP* n=35 (%)	Fed JZP n=36 (%)	Fasting Xyrem n=36 (%)	Fed Xyrem n=36 (%)	Overall subjects n= 36 (%)	Number of Events
Somnolence	25 (71.4%)	27 (75%)	32 (88.9%)	27 (75%)	35 (97.2%)	134
Euphoric Mood	5 (14.3%)	2 (5.6%)	4 (11.1%)	1 (2.8%)	8 (22.2%)	13
Disturbance in Attention	2 (5.7%)	3 (8.3%)	3 (8.3%)	3 (8.3%)	8 (22.2%)	11
Feeling of relaxation	3 (8.6%)	2 (5.6%)	3 (8.3%)	1 (2.8%)	9 (25%)	9
Feeling Drunk	1 (2.9%)	2 (5.6%)	2 (5.6%)	3 (8.3%)	7 (19.4%)	9
Restlessness	2 (5.7%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	3 (8.3%)	4
Confusional State	1 (2.9%)	0 (0.0%)	2 (5.6%)	0 (0.0%)	3 (8.3%	3
Emotional Disorder	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)	2 (5.6%)	2
Irritability	1 (2.9%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	2 (5.6%)	2
Hypervigilance	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	1

*JZP and Xyrem were administered as a 4.5g dose

Part 2 admixture study

System Organ Class Preferred term	Fasting 2.5 g JZP + Xyrem 2g Subjects n=23 (%)	Fasting 3.75 g JZP + Xyrem 0.75g Subjects n=23 (%)	Fasting Xyrem 4g Subjects n=23 (%)	Fasting JZP 2.25 g Subjects n=23 (%)	Overall subjects n= 24(%)	Number of Events
Somnolence	20 (87.0%)	17 (77.3%)	18 (78.3%)	11 (47.8%)	24 (100.0%)	93
Feeling of Relaxation	2 (8.7%)	1 (4.5%)	1 (4.3%)	3 (13.0%)	4 (16.7%)	7
Euphoric mood	1 (4.3%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	2 (8.3%)	2
Feeling Drunk	1 (4.3%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	2 (8.3%)	2
Feeling abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	1 (4.2%)	1
Irritability	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	1 (4.2%)	1
Disturbance in Attention	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	1 (4.2%)	1
Confusional state	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1
Disinhibition	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1
Restlessness	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	1 (4.2%)	1

As seen in the tables above, in both parts of the study somnolence was the most commonly reported AE. This might be expected for a drug indicated for treatment of cataplexy and excessive daytime sleepiness, where the therapeutic effect is derived from the promotion of sleep. Though a formal statistical analysis of abuse-related AEs was not performed, JZP-258 did not appear to produce an increase in AEs relative to Xyrem.

Study JZP258-101: "An Open-Label, Randomized, Crossover, Phase 1 Study to Evaluate the Pharmacokinetics, Bioavailability, and Bioequivalence Following Administration of Oxybate Formulations in Healthy Subjects"

According to the Sponsor, the primary objective of this study was to assess the relative bioavailability and bioequivalence of JZP-258 oral solution versus Xyrem when taken with 60 or 240 mL water under fasting or fed conditions. This was an open-label, within-subjects study evaluating JZP-258 and Xyrem, each dosed at 500 mg/mL. Secondary outcome measures evaluated food effects and safety and tolerability. Forty two (n=42) subjects aged 18-45 were assessed in the completer population. To evaluate PK effects, blood samples were taken predose, and 10, 20, 30, 45, 60, and 75 minutes postdose, and at 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, and 8 hours postdose following each treatment.

The PK analyses demonstrated that relative to Xyrem, JZP-258 had decreased exposure. This was demonstrated by the fact that across all conditions (e.g., fast vs fed, and 60 vs. 240 mL of water) JZP-258 generally produced lower PK values at equivalent doses. For example, in every condition, JZP-258 had a reduced Cmax, AUC, and increased Tmax (i.e., longer time to Cmax). Across the conditions, both drugs had roughly equivalent t½ values. The Sponsor reports AEs were similar between JZP-258 and Xyrem and that "no clinically import differences in AEs were observed between JZP-258 and Xyrem." Common AEs (incidence ≥5%) included somnolence, dizziness, nausea, headache, fatigue, paresthesia, vertigo, euphoric mood, feeling drunk, feeling hot, and limb discomfort.

No significant adverse events (SAEs) or deaths occurred. Abuse-related AEs are tabulated and summarized below in table 2. Only AEs that were categorized by the Sponsor as "related" to study drug are shown.

Table 2: Abuse-related AEs from study JZP 258-101*

System Organ Class Preferred term	JZP-258 + 60mL water (fasting) n= 47 (%)	Xyrem + 60 mL water (fasting) n= 47 (%)	JZP + 60 mL water (fed) n= 46 (%)	Xyrem + 60 mL water (fed) n= 46 (%)	JZP + 240 mL water (fasting) n= 47 (%)	Xyrem + 240 mL water (fasting) n= 47 (%)	Overall** n=48 (%)
Somnolence	39 (83%)	41 (87%)	34 (73%)	33 (71.7%)	38 (80.9%)	37 (78.7%)	47 (97.9%)
Euphoric Mood	6 (12.8%)	2 (4.3%)	3 (6.5%)	2 (4.3%)	1 (2.1%)	1 (2.1%)	11 (22.9%)
Feeling Drunk	4 (8.5%)	4 (8.5%)	2 (4.3%)	1 (2.2%)	3 (6.4%)	4 (8.5%)	8 (16.7%)
Disturbance in Attention	2 (4.3%)	3 (6.4%)	1 (2.2%)	1 (2.2%)	1 (2.1%)	0 (0.0%	5 (10.4%)
Depression	0 (0.0%	0 (0.0%	0 (0.0%	1 (2.2%)	3 (6.4%)	3 (6.4%)	5 (10.4%)
Feeling of Relaxation	0 (0.0%	1 (2.1%)	1 (2.2%)	0 (0.0%	1 (2.1%)	2 (4.3%)	4 (8.3%)
Feeling Abnormal	2 (4.3%)	2 (4.3%)	0 (0.0%	0 (0.0%	0 (0.0%	0 (0.0%	4 (8.3%)
Confusional State	0 (0.0%	0 (0.0%	0 (0.0%	0 (0.0%	2 (4.3%)	1 (2.1%)	2 (4.2%)
Agitation	1 (2.1%)	1 (2.1%)	0 (0.0%	0 (0.0%	0 (0.0%	0 (0.0%	2 (4.2%)
Memory Impairment	0 (0.0%	0 (0.0%	0 (0.0%	0 (0.0%	0 (0.0%	1 (2.1%)	1 (2.1%)

* Both JZP-258 and Xyrem were dosed as 4.5g

** AEs are shown as a percentage of subjects experiencing an AE. Subjects may have had the same AE on multiple occasions

Similar to study 13-010, somnolence was the most commonly observed abuse-related AE. In the treatment arms receiving 60mL water (i.e., JZP vs. Xyrem after dosing with 60mL water), euphoric mood AEs were three times more prevalent with JZP-258 than Xyrem (2 vs. 3 incidents), however, the low occurrence overall (i.e., 12.% vs. 4.3%) is not amenable to clear interpretation. Overall, abuse-related AEs did not appear to differ between Xyrem and JZP-258 to a substantial degree.

Study 15-003: "A Randomized, Double-Blind, Crossover Taste Testing Study in Healthy Subjects Comparing JZP-258 and Placebo"

According to the Sponsor, the objective of this study was to compare the taste of JZP-258 to placebo for sameness. Sixty eight subjects (n=68) completed the study and were included in the safety evaluation. In the study, subjects underwent a screening period where they had to discriminate salt water vs. distilled water to be eligible for the main portion of the study. Eligible subjects were enrolled in a 4-sequence, 4-period, 2-treatment, crossover study and randomized into one of the following four treatment sequences:

	Replicate 1		Replicate 2	
Sequence	Period 1 (Pair 1)	Period 2 (Pair 2)	Period 3 (Pair 3)	Period 4 (Pair 4)
1	TRT A/TRT A	TRT A/TRT B	TRT B/TRT A	TRT A/TRT A
2	TRT A/TRT A	TRT B/TRT A	TRT A/TRT A	TRT A/TRT B
3	TRT A/TRT B	TRT A/TRT A	TRT A/TRT A	TRT B/TRT A
4	TRT B/TRT A	TRT A/TRT A	TRT A/TRT B	TRT A/TRT A

Treatment A: JZP-258 oral solution (500 mg/mL; 9 mL [4.5 g] JZP-258 diluted with 60 mL water)
Treatment B: Placebo (9 mL placebo diluted with 60 mL water)
TRT = Treatment

The Sponsor describes the study procedures as follows:

On Day 1, two liquids were rated for sameness in duplicate by each subject as follows:

- Treatment A and Treatment B twice, in different replicates, or
- Treatment A and Treatment A twice, in different replicates

Treatment pairs were tested in 2 replicates. In each sequence, Replicate 1 contained the first 2 pairs of test liquids. Replicate 2 contained the second 2 pairs of test liquids. Replicates 1 and 2 contained the same 2 pairs of test liquids; however, the order of the pairs could have been different. One hour after breakfast and brushing of teeth, each subject was asked to taste the first liquid of the pair and then remember that taste so that he/she could compare that liquid for sameness to the second liquid.
An hour later, the subject tasted the second liquid and rated the liquid for sameness to the prior liquid of the pair. Subjects rated the sameness of each pair of test liquids (X, Y) by answering "Yes" or "No" to the following question: "Does liquid Y taste the same as liquid X?" An hour following the taste test of the first pair of liquids (Replicate 1, Period 1), the second pair of liquids was tested (Replicate 1, Period 2).

One hour after lunch and the brushing of teeth, the sequence was repeated with subjects beginning Replicate 2 and tasting another two pairs of liquids an hour apart (periods 3 and 4). Only 30 mL of the sample solution was administered. The Sponsor states that subjects were told that "test samples were to be tasted not consumed." The specifics of this study procedure are not clear, but they imply that only

miniscule amounts of JZP-258 were administered to subjects to avoid producing a pharmacological effect that might influence the discrimination.

A total of 8 treatment-emergent adverse events were reported by 8 subjects (11.8%). Headache and myalgia were reported in 2 subjects (2.9%) each. All other TEAEs were reported for 1 (1.5%) subject each and included migraine, somnolence, nausea, and fatigue. All TEAEs were considered unrelated to study treatment, of mild severity, and resolved by the end of the study. Of these, somnolence was the only abuse-related AE recorded. In the absence of euphoria, the AEs do not appear to suggest a signal for abuse, however, no comparator data are available. Nonetheless, if study procedures were appropriately followed by subjects (i.e., taste samples were not consumed and no drug was administered), the AE results of this study are irrelevant, as they were not due to a pharmacological effect.

Study 15-006: "A Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of the Efficacy and Safety of JZP-258 in Subjects with Narcolepsy with Cataplexy"

This was a phase 3 safety and efficacy study and the primary objective was to evaluate the efficacy of JZP-258 in the treatment of cataplexy in subjects with narcolepsy. Secondary measures evaluated the efficacy of JZP-258 in the treatment of excessive daytime sleepiness (EDS) in subjects with narcolepsy and the evaluation of safety in subjects with both narcolepsy and cataplexy. The study was divided into two parts: a two week, double-blind, placebo controlled randomized-withdrawal portion followed by a 6 month (24 week) open-label extension. A total of 201 subjects (n=201) were evaluated as part of the safety evaluation. Four groups of subjects were enrolled in the study based on their medication status prior to entering the study:

- Group 1 (subjects receiving a stable dose of Xyrem for at least 2 months prior to screening): Subjects were switched from Xyrem to JZP-258 (gram for gram) and remained on this JZP-258 dose for a minimum of 2 weeks. If needed, the dose of JZP-258 could have been titrated during the subsequent 8 weeks to a stable, tolerable, and effective dose.

- Group 2 (subjects receiving a stable dose of Xyrem and an additional anticataplectic [defined as a tricyclic antidepressant (TCA), serotonin-norepinephrine reuptake inhibitor (SNRI), selective serotonin reuptake inhibitor (SSRI), atomoxetine, or other] for at least 2 months prior to screening). Subjects were switched from Xyrem to JZP-258 (gram for gram) and remained on this JZP-258 dose for a minimum of 2 weeks. Following this 2-week period, subjects were tapered off the additional anticataplectic over a minimum period of 2 weeks and up to 8 weeks. If needed, the dose of JZP-258 could have been further titrated to a stable, tolerable, and effective dose during this 8-week period.

- Group 3 (subjects receiving a non-Xyrem anticataplectic and Xyrem-naive at screening): Subjects were titrated to a tolerable dose of JZP-258 over a minimum of 2 weeks at the start of this period. After initial JZP-258 titration, subjects were tapered off other anticataplectics over a minimum of 2 weeks and up to 8 weeks. If needed, the dose of JZP-258 could have been further titrated to a stable, tolerable, and effective dose during this 8-week period.

- Group 4 (subjects not receiving treatment with an anticataplectic at screening [hereafter referred to as naïve]): Subjects were initiated and titrated with JZP-258 over a minimum of 2 weeks and up to 8 weeks to achieve a stable, tolerable, and effective dose during this period.

According to the Sponsor, the majority of subjects (79.6%) experienced at least one TEAE and half were judged by the Investigator to be related to study drug. Five SAEs were reported and no deaths were documented. The most frequently reported TEAEs during treatment with JZP-258 (≥ 5% of subjects overall) were Headache, Nausea, Dizziness, Cataplexy, Nasopharyngitis, Decreased Appetite, Influenza, Diarrhea, and Vomiting. Adverse events occurred most frequently in the Nervous System, Disorders SOC. Table three below displays abuse-related AEs from study 15-006.

Table 3: Abuse-related AEs from study 15-006, adapted from Sponsor Table 14.3.1.3.1 from study report 15-006

	Pre-randomization Group				
System Organ Class Preferred term	Xyrem only n=52 n(%)	Xyrem + other anticataplectic (n=23) n(%)	non-Xyrem anticataplectic (n=36) n(%)	naive n=90 n(%)	Total n= 201
Headache	10 (19.2%)	3 (13.0%)	8 (22.2%)	24 (26.7%)	45 (22.4%)
Irritability	0 (0.0%)	2 (8.7%)	1 (2.8%)	3 (3.3%)	6 (3.0%)

No AEs of euphoria were observed. Moreover, AE analyses are confounded by the fact that the Sponsor excluded placebo-related AEs from the study report and by the fact that subjects were titrated to different doses of JZP-258. However, "headache" in the absence of euphoria is not generally considered to be representative of abuse. The only other abuse-related AE that observed was "irritability," which occurred in less than 5% of study participants.

4. Regulatory Issues and Labeling

The Sponsor has included an extensive description of their Risk Evaluation and Mitigation Strategy (REMS). The REMS appears substantially similar to the Xyrem REMS, and, according to the Sponsor, is designed to "mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of [TRADENAME] and XYREM." Broadly, this is done by informing prescribers, pharmacists, and patients of the risks of JZP-258 (e.g., CNS depression, concomitant use of JZP and CNS depressants, potential for abuse and misuse, and handling and storage). The REMS also outlines pharmacy controls of JZP-258.

Abuse- and dependence-related labeling sections of the JZP-258 label are similar to Xyrem labeling and are shown in Section I, Recommendations.

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

/s/

CHAD REISSIG
06/21/2020 10:43:07 AM

DOMINIC CHIAPPERINO
06/21/2020 08:49:45 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 17, 2020
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 212690
Product Name and Strength:	Xywav (calcium, magnesium, potassium, sodium oxybates) oral solution, 0.5 g/mL
Applicant/Sponsor Name:	Jazz Pharmaceuticals Ireland Limited
OSE RCM #:	2020-132-1
DMEPA Safety Evaluator:	Justine Kalonia, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted the revised container label received on June 4, 2020 for Xywav. Division of Neurology 1 (DN 1) requested that we review the revised container label and PI, MG, and IFU labeling for Xywav (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 ASSESSMENT

Table 1 below includes the identified medication error issues with the revised container label our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 1. Identified Issues and Recommendations for Jazz Pharmaceuticals Ireland Limited (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION

[a] Kalonia J. Label and Labeling Review for Xywav (NDA 212690). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 11. RCM No.: 2020-132.

Table 1. Identified Issues and Recommendations for Jazz Pharmaceuticals Ireland Limited (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	A logo was added to the container label in close proximity to the controlled substance status symbol.	The logo detracts from the controlled substance status symbol.	Revise or relocate the logo in a manner such that is does not obscure or detract from the controlled substance symbol (for example, to the bottom of the PDP, or to the side panel).

3 CONCLUSION

The revised container label is unacceptable from a medication error perspective. We provide recommendations to Jazz Pharmaceuticals Ireland Limited to address our concerns in Table 1 above. We ask that the Division convey Table 1 in its entirety to Jazz Pharmaceuticals Ireland Limited so that recommendations are implemented prior to approval of this NDA.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JUNE 4, 2020

Draft Labeling (PI, MG, and IFU):

- Track changes the Draft Labeling available at: \\cdsesub1\evsprod\nda212690\0015\m1\us\proposed-jzp258-uspi04junrespnsannotated.pdf
- Clean proposed Draft Labeling available at: \\cdsesub1\evsprod\nda212690\0015\m1\us\proposed-jzp258-uspi04junrespnsclean.pdf

Container label

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

/s/

JUSTINE H KALONIA
06/17/2020 01:30:45 PM

LOLITA G WHITE
06/17/2020 01:49:08 PM

DANIELLE M HARRIS
06/17/2020 02:18:44 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 11, 2020
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 212690
Product Name and Strength:	Xywav[a] (calcium, magnesium, potassium, sodium oxybates) oral solution, 0.5 g/mL
Product Type:	Multiple-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Jazz Pharmaceuticals Ireland Limited (Jazz)
FDA Received Date:	January 21, 2020
OSE RCM #:	2020-132
DMEPA Safety Evaluator:	Justine Kalonia, PharmD
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Deputy Director:	Danielle Harris, PharmD

[a] The proposed proprietary name Xywav was found conditionally acceptable on March 23, 2020.

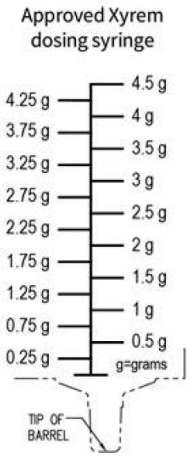
1 REASON FOR REVIEW

As part of the application review process for Xywav (calcium, magnesium, potassium, sodium oxybates) oral solution, the Division of Neurology 1 (DN 1) requested that we review the proposed Xywav Prescribing Information (PI), Medication Guide (MG), and Instructions for Use (IFU), and container label for areas of vulnerability that may lead to medication errors.

2 BACKGROUND

2.1 PRODUCT INFORMATION

Jazz markets Xyrem under NDA 021196 for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with Narcolepsy. Xyrem contains 0.5 g/mL of sodium oxybate (equivalent to 0.413 g/mL of oxybate). The strength expression on the principal display panel is 0.5 g/mL and users measure the dose using an oral syringe labeled with doses in grams (see image below).



Jazz developed Xywav under NDA 212690 as a lower sodium alternative to Xyrem for the same indication. The proposed product contains the same active moiety (oxybate) but is formulated with different active ingredients. Xywav 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).

2.2 REGULATORY HISTORY

On May 1, 2013, the United States Pharmacopeia (USP) Salt Policy became effective requiring all new drug product monographs for products containing an active ingredient that is a salt to use the active moiety, instead of the name of the salt, and base the strength of the product on the active moiety. FDA guidance entitled *Naming of Drug Products Containing Salt Drug*

Substances[b] describes how products with active ingredients that are salts may be affected by CDER's implementation of the USP Salt Policy, and how CDER intends to apply exceptions to the policy. Jazz met with the Agency to discuss the product development plan, including the appropriate established name and strength expression of the proposed product.

During the Type B Face-to-Face Pre-NDA Meeting for Xywav on October 2, 2019[c], Jazz proposed (b) (4) The Agency indicated that labeling the product in this manner would be unacceptable (b) (4)

The Agency acknowledged the sponsor's concerns with respect to potential medication errors; however, the Agency also noted (b) (4) may also result in medication errors. FDA informed the sponsor that they may request an exception to the USP Salt Policy, if adequately supported by clinical or safety considerations.

Additionally, during this Type B meeting on October 2, 2019, we requested the Applicant submit a comprehensive use-related risk analysis, comparative analyses, and justification for not submitting the human factors validation study to the Agency for review under this IND if they determined that human factors validation study does not need to be submitted for this product.

On December 11, 2019, under IND 049641 the Applicant submitted a proactive risk assessment, comparative analysis of Instructions for Use, post marketing data, previous Human Factors (HF) results report to validate the oral dosing syringe, and a request for an exception to the USP Salt Policy to support their marketing application.

On January 21, 2020, Jazz submitted NDA 212690 for agency review.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A

[b] Guidance for Industry: Naming of Drug Products Containing Salt Drug Substances. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf.

[c] Kishore, Vandna. Type B Pre-NDA Meeting Minutes for JZP-258. Silver Spring (MD): FDA, CDER, OND, DNP (US); 2019 OCT 30. IND 049641.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
ISMP Newsletters	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other: Human Factors Data Previously Submitted	E
Labels and Labeling	F
N/A=not applicable for this review *We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance	

4 FINDINGS AND RECOMMENDATIONS

As part of our review of this NDA, DMEPA carefully reviewed the Applicant's request for exception to the USP Salt Policy, taking into consideration the medication error safety concerns associated with labeling the product with either:

(b) (4)

(2) a strength expression based on the active ingredients (i.e., calcium, magnesium, potassium, and sodium oxybates).

Using principles of Failure Mode and Effects Analysis, we considered errors that may occur at various points in the medication use process for both options, taking into consideration that Xywav users are likely to have experience with the currently marketed Xyrem product, including the oral syringe that is labeled in gram dosing increments and supplied with Xyrem.

(b) (4)

Alternatively, our evaluation of option (2), labeling the product with a strength expression based on active ingredients did not identify the same medication error concerns. In this option, the expression of strength, dose, and oral syringe markings would all be identical to that of Xyrem, minimizing risks associated with transitioning patients to the proposed product or use of the wrong syringe for dose measurement. Taking into consideration the user interfaces would be the same between the two products, Xywav and Xyrem, and no new or unique risks

are introduced with this option, we determined that results of a HF validation study are not needed to be submitted to support this option (See Appendix E).

We discussed the benefits and risks of both options with the Division of Neurology 1 (DN1), the Division of Risk Management (DRM), and the Office of Pharmaceutical Quality (OPQ) and recommended the proposed product is labeled in accordance with option 2 above.

Taking into consideration our recommendations for the safe use of the product, OPQ and the Office of Policy for Pharmaceutical Quality (OPPQ) recommended the established name and strength appear as "calcium, magnesium, potassium, and sodium oxybates 0.5 g/mL," and provided additional recommendations for the container label:

PDP:
Xywav
(calcium, magnesium, potassium, and sodium oxybates) oral solution
*0.5 g/mL total salts

Side Panel:
*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).

We agree with these recommendations and have incorporated them into our comments to the applicant (see Table 3).

Tables 2 and 3 below include the identified medication error issues with the submitted PI, MG, IFU, and container label, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	We note that the placeholder, "TRADENAME" is included throughout the PI, MG, IFU, and the container label.	The proposed proprietary name, Xywav, was found conditionally acceptable on March 23, 2020.[d]	Replace the placeholder, "Tradename" with the conditionally acceptable proprietary name, "Xywav", wherever it appears.

[d] Kalonia J. Proprietary Name Review for Xywav (NDA 212690). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 23. OSE RCM No.: 2020-37463829.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The first temperature numerals are missing the units symbols (C and F) and uses a hyphen where the word 'to' would provide more clarity.	Each numeric value should have a corresponding unit of measure to decrease risk of wrong technique medication error.	Revise the sentence: "TRADENAME should be stored between 20°-25°C (68°-77°F); excursions permitted between 15°and 30°C (59°and 86°F)." to read: ""TRADENAME should be stored between 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)"
2.	The NDC number for the proposed product is not easily identifiable in Section 16 (How Supplied/ Storage and Handling).	The NDC number should be included in Section 16 of the PI per 21 CFR 201.57(c)(17). As currently presented it may be overlooked.	We recommend revising Section 16 to move the NDC number for the proposed product closer to the information about the bottle. For example, you may move it directly under "One (b) (4) mL bottle", or address this by some other means.

Table 3. Identified Issues and Recommendations for Jazz Pharmaceuticals Ireland Limited (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s)			
1.	We note that the placeholder, "TRADENAME" is included on the container label and throughout the PI, MG, and IFU.	The proposed proprietary name, Xywav, was found conditionally acceptable on March 23, 2020.[e]	Replace the placeholder, "Tradename" with the conditionally acceptable proprietary name, "Xywav", wherever it appears.

[e] Kalonia J. Proprietary Name Review for Xywav (NDA 212690). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 23. OSE RCM No.: 2020-37463829.

Table 3. Identified Issues and Recommendations for Jazz Pharmaceuticals Ireland Limited (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The statement (b) (4) [redacted] can be improved.	To ensure consistency with the Physician Labeling Rule (PLR) formatted Prescribing Information.	Revise the statement: (b) (4) [redacted] to read "Recommended Dosage: See prescribing information."
3.	The 'Rx only' statement appears more prominent than other information on the PDP.	Per our guidance, the proprietary name, established name, product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP[f].	Ensure the 'Rx only' statement does not compete in prominence with the aforementioned critical information. Consider decreasing the font size and relocating the 'Rx only' statement to the top or bottom of the PDP or address this concern by other means.
4.	We note that the principal display panel (PDP) is cluttered. The established name may be revised for accuracy of information and the equivalency statement may be placed on the side panel to reduce clutter. The salts should be listed in alphabetical order and the counterion does not need to be listed more	It is difficult to readily locate and understand critical safety information (e.g., equivalency statement, warnings) presented on the PDP.	Revise the proprietary name, established name, and statement of strength on the PDP as shown below. Move the equivalency statement to the side panel as shown below. PDP: Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution *0.5 g/mL total salts

[f] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Table 3. Identified Issues and Recommendations for Jazz Pharmaceuticals Ireland Limited (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	than once in the sequence of salts.		<u>Side Panel:</u> *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).
5.	The first temperature numerals are missing the units symbols (C and F) and uses a hyphen where the word 'to' would provide more clarity.	Each numeric value should have a corresponding unit of measure to decrease risk of wrong technique medication error.	Revise the sentence: "Store at 20°-25°C (68°-77°F)." to read: "Store at 20°C to 25°C (68°F to 77°F)."

5 CONCLUSION

We have determined that results of a HF validation study are not needed to be submitted as part of the NDA for the proposed indication. However, our evaluation of the proposed Xywav PI, MG, IFU, and container labels identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Jazz Pharmaceuticals Ireland Limited so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Xywav that Jazz Pharmaceuticals Ireland Limited submitted on January 21, 2020.

<table>
<tr><th colspan="2">Table 4. Relevant Product Information for Xywav</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>calcium, magnesium, potassium, sodium oxybates</td></tr>
<tr><td>Indication</td><td>Treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.</td></tr>
<tr><td>Route of Administration</td><td>oral</td></tr>
<tr><td>Dosage Form</td><td>oral solution</td></tr>
<tr><td>Strength</td><td>0.5 g/mL[g]</td></tr>
<tr><td>Dose and Frequency</td><td>
Table 1: Recommended Adult TRADENAME Dose Regimen (g = grams)
<table>
<tr><th>If a Patient's Total Nightly Dose Is:</th><th>Take at Bedtime:</th><th>Take 2.5 to 4 Hours Later:</th></tr>
<tr><td>4.5 g per night</td><td>2.25 g</td><td>2.25 g</td></tr>
<tr><td>6 g per night</td><td>3 g</td><td>3 g</td></tr>
<tr><td>7.5 g per night</td><td>3.75 g</td><td>3.75 g</td></tr>
<tr><td>9 g per night</td><td>4.5 g</td><td>4.5 g</td></tr>
</table>
Note: Unequal dosages may be required for some patients to achieve optimal treatment.
Table 2: Recommended Initial TRADENAME Dosage for Patients 7 Years of Age and Older*
<table>
<tr><th rowspan="2">Patient Weight</th><th colspan="2">Initial Dosage</th><th colspan="2">Maximum Weekly Dosage Increase</th><th colspan="2">Maximum Recommended Dosage</th></tr>
<tr><th>Take at Bedtime:</th><th>Take 2.5 to 4 Hours Later:</th><th>Take at Bedtime:</th><th>Take 2.5 to 4 Hours Later:</th><th>Take at Bedtime:</th><th>Take 2.5 to 4 Hours Later:</th></tr>
<tr><td><20 kg**</td><td colspan="6">There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg.</td></tr>
<tr><td>20 kg to <30 kg</td><td>≤1 g</td><td>≤1 g</td><td>0.5 g</td><td>0.5 g</td><td>3 g</td><td>3 g</td></tr>
<tr><td>30 kg to <45 kg</td><td>≤1.5 g</td><td>≤1.5 g</td><td>0.5 g</td><td>0.5 g</td><td>3.75 g</td><td>3.75 g</td></tr>
<tr><td>≥45 kg</td><td>≤2.25 g</td><td>≤2.25 g</td><td>0.75 g</td><td>0.75 g</td><td>4.5 g</td><td>4.5 g</td></tr>
</table>
* For patients who sleep more than 8 hours per night, the first dose of TRADENAME may be given at bedtime or after an initial period of sleep.
**If TRADENAME is used in patients 7 years of age and older who weigh less than 20 kg, a lower starting dosage, lower maximum weekly dosage increases, and lower total maximum nightly dosage should be considered.
Note: Unequal dosages may be required for some patients to achieve optimal treatment.
</td></tr>
<tr><td>How Supplied</td><td>One 180 mL bottle</td></tr>
</table>

[g] The actual potency based on active moiety is 0.413 g/mL (active moiety; oxybate). The Applicant requested an exception to the salt policy. The decision is pending and final expression of potency has not been determined.

	Each prescription includes one bottle of TRADENAME with attached press in bottle adaptor, an oral measuring device (plastic syringe), and a Medication Guide. The pharmacy provides two empty containers with child-resistant caps with each TRADENAME shipment. Each amber bottle contains TRADENAME oral solution at a concentration of 0.5 g/mL
Storage	TRADENAME should be stored between 20°-25°C (68°-77°F); excursions permitted between 15°and 30°C (59°and 86°F) (see USP Controlled Room Temperature). Dispense in tight containers. Solutions prepared following dilution should be consumed within 24 hours.
Container Closure	child-resistant cap

APPENDIX E. HUMAN FACTORS DATA PREVIOUSLY SUBMITTED

December 11, 2019 submission containing Human Factors Data under IND 049641:

- Human Factors Development Plan: \\cdsesub1\evsprod\ind049641\0356\m5\53-clin-stud-rep\535-rep-effic-safety-stud\narcolepsy\5354-other-stud-rep\human-factors\5354-human-factors-development-plan.pdf
- Human Factors Validation Study of Xyrem Dispenser: \\cdsesub1\evsprod\ind049641\0356\m5\53-clin-stud-rep\535-rep-effic-safety-stud\narcolepsy\5354-other-stud-rep\human-factors-engine\human-factors-validation-study-of-xyrem-dispenser.pdf
- Request for Exception to USP Salt Policy for Naming of JZP-258: \\cdsesub1\evsprod\ind049641\0356\m1\us\1114-request-for-exception-to-usp-salt-policy.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[h] along with postmarket medication error data, we reviewed the following Xywav labels and labeling submitted by Jazz Pharmaceuticals Ireland Limited received on January 21, 2020.

- Container label
- Instructions for Use (image not shown)
- Medication Guide (image not shown)
- Prescribing Information (image not shown)

F.2 Label and Labeling Images

Container label

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

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/s/

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06/11/2020 11:22:29 AM

DANIELLE M HARRIS
06/11/2020 11:50:34 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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PEDIATRIC LABELING REVIEW

From:	Carolyn L. Yancey, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Shetarra Walker, MD, MSCR, Acting Team Leader, DPMH John J. Alexander, MD, MPH, Deputy Director, DPMH
NDA Number:	212690
Sponsor:	Jazz Pharmaceuticals, Incorporated
Drug:	XYWAV (calcium, potassium, magnesium, and sodium oxybates oral solution)
Drug Class:	Central Nervous System (CNS) depressant
Dosage Form and Route of Administration:	Oral solution (0.5 g/mL)
Dosing Regimen:	<u>For Adult Patients</u> • Initiate dosage at 4.5 grams (g) per night orally, divide into two doses • Titrate to effect in increments of 1.5 g per night at weekly intervals (0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) • Recommended dosage range: 6 g to 9 g per night orally <u>For Pediatric Patients</u> • The recommended starting dosage, titration regimen, and maximum total nightly dosage are based on body weight.
Proposed Indication:	For the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years and older with narcolepsy.
Consult Request:	The Division of Neurology-1 (DN1) requests DPMH Pediatric Team review of pediatric labeling for new drug application (NDA) 212690, XYWAV (calcium, potassium, magnesium, and sodium oxybates oral solution) by Jazz Pharmaceuticals Ireland Limited (Jazz), via a 505(b)(1) regulatory pathway based on bioequivalence (BE) and bioavailability (BA) to Xyrem (sodium oxybate) oral solution by the

same manufacturer. Proposed labeling is in the Physician Labeling Rule (PLR) format and Pregnancy and Lactation Labeling Rule (PLLR) format received on January 21, 2020. DN1 also requests DPMH assistance on preparation for the Pediatric Review Committee (PeRC) Meeting. The consult is due on June 21, 2020 (dated January 31, 2020).

Background

JZP-258 (calcium, potassium, magnesium, and sodium oxybates oral solution) contains oxybate, also known as gamma-hydroxybutyrate (GHB), that is an endogenous compound and metabolite of the neurotransmitter gamma-amino butyric acid ($GABA_B$). Oxybate is a CNS depressant, however, the exact mechanism of action of oxybate in the treatment of narcolepsy is unknown. The applicant claims that the therapeutic effects of JZP-258 on cataplexy and EDS in narcolepsy are mediated through $GABA_B$ actions during sleep at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.[1]

Labeling under this review is for JZP-258 (XYWAV) proposed for the treatment of cataplexy or EDS in patients 7 years and older with narcolepsy. Sodium oxybate is a drug of abuse potential and therefore, a Schedule I controlled substance under the Federal Controlled Substances. NDA 212690, submitted on January 21, 2020 with redemption of a Rare Disease Priority Review Voucher (BLA 125610), includes four clinical studies detailed later in this review. Jazz is the manufacturer of Xyrem (NDA 21196), FDA-approved in October 2018 for the same indication cited above, and the license-holder with right-of-reference to Xyrem which is relevant to the JZP-258 clinical development program.

Xyrem labeling includes a boxed warning on dose-dependent response for CNS and respiratory depression. Xyrem treatment is associated with obtundation and clinically significant respiratory depression, even at recommended therapeutic doses. Xyrem and JZP-258 are associated with serious side effects including apnea, depression, and confusion, and prescribers are cautioned against concurrent use of Xyrem with other CNS depressants. Based on the known safety risks with Xyrem and the potential for abuse and misuse, an approved Risk Evaluation and Mitigation Strategy (REMS) for Xyrem includes elements to assure safe use, i.e., prescriber education, patient education, and pharmacy controls with instructions on proper dosing and administration to mitigate incorrect dosing and related medication errors.[2]

The to-be-marketed JZP-258 aqueous solution contains 0.413 g/milliliter (mL) of oxybate (active moiety) equivalent to a 0.5 g/mL mixture of calcium, potassium, magnesium, and sodium oxybates. The proposed JZP-258 dosing is based on a reduced sodium content alternative to Xyrem [sodium oxybate oral solution (500 mg/mL)] known for its high sodium content. JZP-258 and Xyrem contain the same concentration of active ingredient (0.5 g/mL) and the active moiety, oxybate (0.413 g/mL). However, by comparison of the sodium content, a single nightly dose of Xyrem contains 1,640 mg of sodium versus a single nightly dose of JZP-258 containing 87 to 131 mg sodium.[2] Xyrem is initiated at a low dose and gradually titrated at weekly intervals to an effective dose. The applicant proposes JZP-258 labeling with the same dosing and administration as Xyrem.

Salt Concentration in JZP-258

The concentration of salt in JZP-258 is different from the salt concentration in Xyrem oral solution (sodium oxybate). The applicant proposes that JZP-258 (b) (4)

[1] NDA 212690 XYWAV (calcium, potassium, magnesium, and sodium oxybates oral solution), proposed labeling, Section 12 Clinical Pharmacology, subsection 12.1 Mechanism of Action (dated January 21, 2020), page 15 of 34.
[2] NDA 212690 XYWAV (calcium, potassium, magnesium, and sodium oxybates oral solution), Module 1.11.4 Request for Exemption to USP Salt Policy for Naming JZP-258, p2-3 of 12.

(b) (4)

per Chemistry Manufacturing and Controls, Martha Heimann, Ph.D., the established name for JZP-258 will be calcium, potassium, magnesium, and sodium oxybates oral solution.[2]

Reviewer Comment: CMC underscored that the risk of prescribing and medication errors associated with (b) (4) .[3]

Pediatric Research Equity Act Requirements

Under the Pediatric Research Equity Act (PREA), (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Orphan Drug Designation (Number 94-858 pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 USC 360bb) was granted on November 7, 1994 for Jazz Pharma gamma hydroxybutyrate (oxybate) for the "treatment of narcolepsy". Therefore, JZP-258 is exempt from requirements under PREA and submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication.

JZP-258 Bioequivalence, Bioavailability, Safety, and Efficacy Studies

The clinical development program for JZP-258 consists of four clinical studies: supplemental studies JZP-258-13-010, JZP-258-101, and JZP-258-15-003, each a Phase 1 study in healthy adult subjects, and pivotal Phase 3 study 15-006 in adults with cataplexy and EDS in narcolepsy.

- Study JZP-258-13-010 is an open label (OL), randomized (R), crossover study investigating relative BE and BA of JZP-258 and Xyrem under fasted and fed conditions. A dosing water volume of 60 mL (labeled administration of Xyrem) was used in this BE/food effects assessment. This study demonstrated that JZP-258 is BE to Xyrem based on area under the plasma concentration-time curve (AUC) but is not BE for maximum concentration (C_{max}). JZP-258 demonstrated ~20% lower C_{max} compared to Xyrem in fasting conditions.

- Study JZP-258-101 is an OL, R, crossover study investigating relative BE and BA of JZP-258 and Xyrem under fasted conditions. Study JZP-258 evaluated a dosing water volume of 240 mL and pharmacokinetics (PK) only for the 4.5 g dose for both JZP-258 and Xyrem. This study demonstrated that JZP-258 provides a lower C_{max} with a longer median T_{max} than Xyrem. Both JZP-258 and Xyrem have a lower C_{max} and AUC after a high-fat meal relative to fasting conditions. The magnitude of food effect with JZP-258 was numerically smaller than with Xyrem. Dosing water volume (60 mL versus 240 mL) had no significant impact on relative BA/PK of oxybate for JZP-258 or Xyrem.

- Study 15-003 is a R, double-blind (DB), placebo-controlled (PBO-C) crossover study comparing taste of JZP-258 with PBO. Study results demonstrated that 82% of healthy subjects could not distinguish between JZP-258 and PBO oral solutions (this study was conducted to evaluate the PBO to be used in study 15-006).

- Study 15-006 is a two-part R, DB, PBO-C, R withdrawal study to evaluate efficacy and safety in adult patients with cataplexy and EDS in narcolepsy followed by an optional 24-week, OL extension study

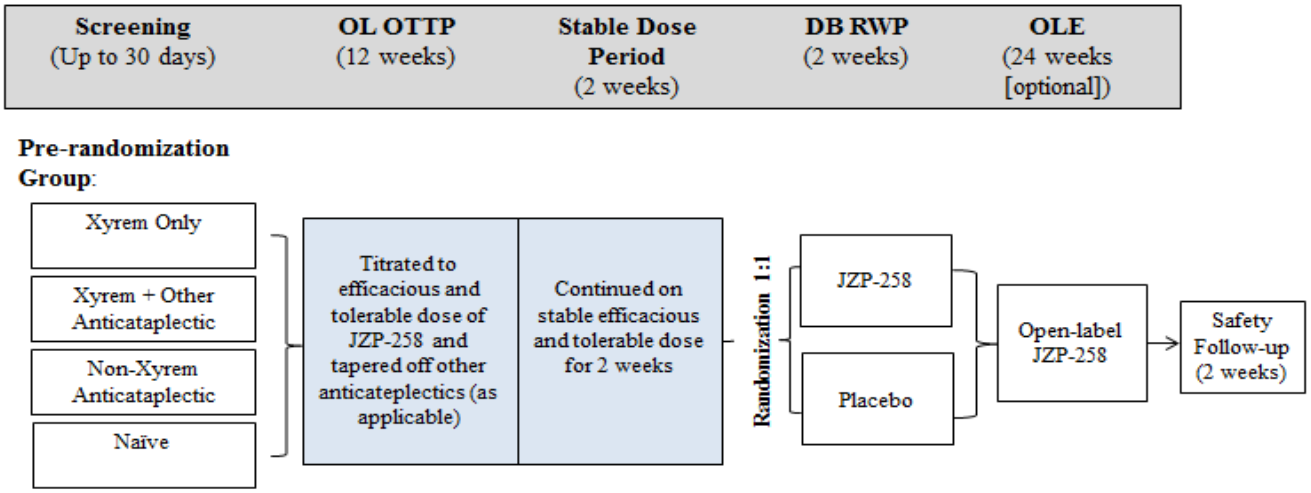
[3] United States Pharmacopeia, Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations, USP General Chapter 1121.

(see **Figure 1** on the next page). JZP-258 dosing is based on 0.5 g/mL mixture of calcium, potassium, magnesium, and sodium oxybates. Study 15-006 enrolled 201 subjects, median age 38 years, and majority female (61%). At study entry, 52 subjects were being treated with Xyrem, 23 with Xyrem plus other anti-cataplectic, 36 with a non-Xyrem anti-cataplectic, and 90 were treatment-naïve. All subjects started treatment with JZP-258 in a 12-week OL, optimized treatment and titration period (OTTP) followed by a 2-week stable dose period then 2-week DB, PBO, R withdrawal period (see **Figure 1** on the next page). The primary efficacy endpoint is the change in the average weekly number of cataplexy attacks from 2 weeks of the Stable Dose Period to 2 weeks of the DB, randomized withdrawal period. A key secondary efficacy endpoint is the change in the Epworth Sleepiness Scale (ESS) score from the end of the Stable Dose Period to the end of the DB, randomized withdrawal period.

Study 15-006 achieved the primary efficacy endpoint demonstrating clinical efficacy of JZP-258 for treatment of cataplexy and EDS in narcolepsy. Patients randomized to PBO during the DB randomized withdrawal period showed significant increase (worsening) in the average weekly number of cataplexy attacks compared with subjects randomized to continue treatment with JZP-258 (median [first quartile (Q1), third quartile (Q3): 2.35 [0.00, 11.61] versus 0.0 [-0.49, -1.75], respectively.[4] The estimated median difference [JZP258 - PBO] was [Confidence Internal (CI): -3.308 [-6.044, -1.500]; $p < 0.0001$ using a nonparametric rank-based on an analysis of covariance model.[4] There was no change in the median average weekly number of cataplexy attacks in patients who remained on JZP-258 during the DB randomized withdrawal period. The JZP-258 dose initiation and titration method demonstrated 74% of subjects (149/201) achieved a tolerable and efficacious dose of JZP-258 upon entering the stable dose period. Subgroup analyses showed a trend in the change in the average weekly number of cataplexy attacks from 2 weeks of the stable dose period to the 2 weeks of the DB randomized withdrawal period, favoring JZP-258 over PBO.

Subjects randomized to PBO during the DB randomized withdrawal period showed a significant increase (worsening) in the ESS score compared with subjects randomized to continue treatment with JZP-258 (median [first quartile (Q1), third quartile (Q3): 2.0 [0.0, 5.0] versus 0.0 [-1.0, 1.0], respectively. There was no change in the median ESS score in subjects remaining on JZP-258 treatment during the DB randomized withdrawal period. In the OL extension study in subjects who were naïve to narcolepsy treatment at study entry, the median weekly number of cataplexy attacks generally decreased through Week 8 of the OL OTTP and then, remained similar through the end of the stable dose period, demonstrating efficacy during these periods.

Figure 1. Study 15-006 Schema



[4] NDA 212-690 JZP-258 (calcium, potassium, magnesium, and sodium oxybates oral solution), Module 2.7.3 Summary of Clinical Efficacy, 2.3.1 Primary Efficacy Endpoint, page 19-20 of 44.

Source Reference: NDA 212690 JZP-258, Module 2.7.3 Summary of Clinical Efficacy, Section 1.2 Overview of Clinical Efficacy Study 15-006, page 10 of 44.

Dosing in Pediatric Patients

The totality of clinical efficacy and PK data for JZP-258 in adults and Xyrem in adult and pediatric patients supports inclusion of pediatric patients 7 years and older in the indication for JZP-258 with the same dosing regimen as in Xyrem product labeling for pediatric patients with narcolepsy. Population PK (PPK) modeling and exposure-response (E-R) analyses using predicted PK versus observed response were used to characterize the PK and pharmacodynamic (PD) relationship for JZP-258 versus Xyrem. As with Xyrem, dosing is weight-based for JZP-258 and gradually titrated based on efficacy and tolerability. Once a new stable dose of JZP-258 is achieved, it may be taken with or without food. Patients treated with Xyrem oral solution may be switched to JZP-258 oral solution at the same gram-for-gram dose and regimen including waiting at least 2 hours after eating before taking the medicine and evaluation for optimum efficacy and tolerability. Dose adjustment may be needed to achieve the desired clinical response.

Table 1. Recommended Initial JZP-258 Dosage for Patients 7 Years of Age and Older

	Initial Dosage		Maximum Weekly Dosage Increase		Maximum Recommended Dosage	
Patient Weight	Take at Bedtime:	Take 2.5 to 4 Hours Later:	Take at Bedtime:	Take 2.5 to 4 Hours Later:	Take at Bedtime:	Take 2.5 to 4 Hours Later:
< 20 kg[a]	There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg.					
20 kg to < 30 kg	≤ 1 g	≤ 1 g	0.5 g	0.5 g	3 g	3 g
30 kg to < 45 kg	≤ 1.5 g	≤ 1.5 g	0.5 g	0.5 g	3.75 g	3.75 g
≥ 45 kg	≤ 2.25 g	≤ 2.25 g	0.75 g	0.75 g	4.5 g	4.5 g

JZP-258 may be given at bedtime or after an initial period of sleep.

[a] If JZP-258 is used in patients 7 years of age and older who weigh less than 20 kg, a lower starting dosage, lower maximum weekly dosage increases, and lower total maximum nightly dosage should be considered.

Note: Unequal dosages may be required for some patients to achieve optimal treatment.

Source Reference: NDA 212690 JZP-258 Oral Solution, Module 2.7.3 Summary of Clinical Efficacy, Table 10, page 38 of 44

The applicant proposes inclusion of pediatric patients 7 years and older in labeling for JZP-258 with dosing and administration recommendations similar to that of Xyrem. FDA agreed (Pre-NDA Meeting dated October 30, 2019) that available data from Xyrem will be sufficient to support a pediatric indication for JZP-258 if the efficacy findings in adults are similar between JZP-258 and Xyrem.

Reviewer Comments: JZP-258 contains the same active moiety at the same concentration (0.413 g/mL) as Xyrem, therefore, JZP-258 dosing recommendations are based on dosing information for Xyrem. As cited earlier in this review, population PK of Xyrem and E-R analyses support the same dosage regimen for JZP-258 and Xyrem in pediatric patients 7 years and older. The main PK difference between JZP-258 and Xyrem is ~ 20% lower C_{max} for JZP-258 under fasted conditions. However, the two oral solutions are BE under fed conditions suggesting that JZP-258 has a lesser food effect. Regarding adverse reactions, there appear to be lower incidences of nausea and vomiting with JZP-258.

DPMH notes that the oral dosing syringe that patients will use to draw up an appropriate dose is graduated in grams rather than milliliters for consistency with labeled Xyrem dosing instructions. It is recommended that the JZP-258 product require a product-specific syringe with dose markings modified to match its different dose levels based on the strength of oxybate. DPMH defers to Clinical Pharmacology, Clinical, and

the Division on Medication Error Prevention and Analysis on recommendations for the XYWAV syringe.

DPMH Pediatric Labeling Recommendations
The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population compared with the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric population. As with Xyrem, XYWAV (calcium, potassium, magnesium, and sodium oxybates oral solution) is indicated for treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy. The Xyrem boxed warning informing on CNS depression and abuse and misuse is retained in XYWAV labeling and the Xyrem REMS will include XYWAV under the same restricted distribution program.

Section (2.2) Pediatric Dosing Information details weight-based dosing in patients weighing at least 20 kg. Reported serious adverse reactions with Xyrem are cross-referenced to Warnings and Precautions (5.4), (5.5), (5.6), and (5.7). Section (6.1) Clinical Trials Experience retains safety information based on the pediatric clinical trial with Xyrem. Section (8.4) Pediatric Use informs prescribers that safety and effectiveness of XYWAV in the treatment of cataplexy or EDS in pediatric patients 7 years and older with narcolepsy were established by the Xyrem pediatric clinical trial. Section 12.3 Specific Populations, *Pediatric Patients,* informs on population PK model analyses demonstrating that body weight is the major intrinsic factor affecting oxybate PK following Xyrem or XYWAV administration, and that XYWAV has similar PK characteristics (supra-dose proportionality) as Xyrem in pediatric patients, therefore supporting the same dose regimen as Xyrem and a 1-to-1 dose-switch from Xyrem to XYWAV in pediatric patients.

This review focuses on labeling sections and revisions that directly address pediatric use. These recommendations are based on the DN1 substantially complete proposed XYWAV labeling as of May 19, 2020 which is in PLR/PLLR format. DPMH's recommended information to be added to the labeling is underlined. Information to be deleted has a ~~strikethrough~~. Comments and rationale for DPMH's recommendations to the labeling are in *italics*.

HIGHLIGHTS OF PRESCRIBING INFORMATION

XYWAV (calcium (b) (4), potassium (b) (4), magnesium (b) (4), and sodium oxybates) oral solution), CIII
Initial U.S. Approval 2020

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XYWAV is (b) (4) indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

Reviewer Comments: DPMH agrees with revisions to the established name reflecting the salts and retaining the same Indication and Usage language in Xyrem labeling that informs on the lower pediatric age limit for use of XYWAV.

2 DOSAGE AND ADMINSITRATION

2.2 Pediatric Dosing Information

For pediatric patients (7 years of age and older), XYWAV is administered orally twice per night. The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight, as specified in Table 2. The dosage may be gradually titrated based on efficacy and tolerability.

Reviewer Comments: For details, see Table 2: Recommended Initial XYWAV Dosage for Patients 7 Years of Age and Older in the substantially complete labeling. DPMH defers to Clinical Pharmacology regarding pediatric dosing information on XYWAV.

8 USE IN SPECIAL POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of XYWAV in the treatment of cataplexy or excessive daytime sleepiness in pediatric patients (7 years of age and older) with narcolepsy have been established. XYWAV has not been studied in a pediatric clinical trial. Efficacy is based on a pediatric study of administration of sodium oxybate (b) (4) *[see Adverse Reactions (6.1)]*, and a study of adults showing similar treatment effect of XYWAV with sodium oxybate *[see Clinical Studies (14), Cataplexy and Excessive Daytime Sleepiness (EDS) in Adult Narcolepsy (14.1)]*. (b) (4)

In the pediatric clinical trial with (b) (4) administration of sodium oxybate in patients with narcolepsy, serious adverse reactions of central sleep apnea and oxygen desaturation documented by polysomnography evaluation; suicidal ideation in one patient; neuropsychiatric reactions including acute psychosis, confusion, and anxiety; and parasomnias, including sleepwalking, have been reported *[see Warnings and Precautions (5.4, 5.5, 5.6, 5.7) and Adverse Reactions (6.1)]*.

Safety and efficacy of XYWAV (b) (4) in pediatric patients below the age of 7 years have not been studied.

Juvenile Animal Toxicity Data

In a study in which sodium oxybate (100, 300, or 900 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 21 through 90), mortality was observed at the two highest doses tested. Deaths occurred during the first week of dosing and were associated with clinical signs (including decreased activity and respiratory rate) consistent with the pharmacological effects of the drug. Reduced body weight gain in males and females and delayed sexual maturation in males were observed at the highest dose tested. The no-effect dose for adverse effects in juvenile rats is associated with plasma exposures (AUC) less than that at the maximum recommended human dose (9 g/night).

Reviewer Comments: DPMH recommends retaining (8.4), as written in the listed product, Xyrem labeling and inserting the Trade Name, XYWAV, as appropriate.

DPMH Actions and Labeling Recommendations

DPMH reviewed Jazz Pharmaceuticals, Incorporated proposed labeling for XYWAV (calcium, potassium, magnesium, and sodium oxybates oral solution) and participated in meetings with the DN1 Clinical Team from March to May 2020. The most recent proposed labeling revisions per DPMH are dated May 19, 2020. DPMH labeling recommendations were provided in track changes for DN1 consideration to revise labeling to align with the listed drug labeling for Xyrem and to conform to the *Draft Guidance for Industry and*

Review Staff on Pediatric Labeling.[5] DPMH's input will be reflected in the final labeling and the action letter from the DN1. Should this product be approved, final labeling will be negotiated with the applicant, and may differ from recommendations in this DPMH labeling review.

[5] *Draft Guidance for Industry and Review Staff* - Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling, February 2013

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/s/

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Memo To File

Date	4/14/2020
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Vandna Kishore, Regulatory Project Manager Ranjit Mani, M.D., Medical Officer and Team Leader Division of Neurology 1 Office of Neuroscience
NDA #	212690
Applicant	Jazz Pharmaceuticals
Drug	Calcium/potassium/magnesium/sodium oxybate oral solution
NME	No
Proposed Indication	Treatment of cataplexy or excessive daytime sleepiness in patients $\geq$ 7 years of age with narcolepsy
Consultation Request Date	3/5/2020
Summary Goal Date	5/21/2020
Priority/Standard Review	Priority
Action Goal Date	7/21/2020
PDUFA Date	7/21/2020

A consult to conduct inspections was received from the Division of Neurology 1 (DN1) on 3/5/2020 that identified the following clinical investigators for Good Clinical Practice (GCP) inspections: Drs. Corser (Site 1454, United States) and Feldman (Site 1356, United States). An inspection assignment was issued on 3/6/2020 and the plans to conduct GCP inspections were scheduled by the Office of Regulatory Affairs (ORA).

At the current time, the COVID-19 global pandemic has significantly limited our ability to conduct on-site GCP inspections. As a result, and in an effort to protect the health, safety, and welfare of FDA employees and study staff, the need for planned inspections in support of NDA #212690 was reevaluated. Following discussions between OSI and DNI, a decision was made that assessment of the application could proceed without GCP inspections. OSI will, therefore, be unable to determine if Protocol 15-006 was conducted adequately and whether the study data are reliable in support of the proposed indication at this time.

{See appended electronic signature page}

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Good Clinical Practice Assessment Branch
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OSI/GCPAB Program Analyst/Yolanda Patague

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/s/

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