CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	212690
Supporting document/s:	1, 12
Applicant's letter date:	1/21/2020, 5/4/2020
CDER stamp date:	1/21/2020, 5/4/2020
Product:	JZP-258 (calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate), oral solution, 0.5 g/mL Trade name: XYWAV
Indication:	Treatment of cataplexy and excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy
Applicant:	Jazz Pharmaceuticals
Review Division:	DN I
Reviewer:	Melissa Banks-Muckenfuss, PhD
Supervisor:	Lois Freed, PhD
Acting Division Director:	Eric Bastings, MD
Project Manager:	Vandna Kishore, RPh

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Jazz Pharmaceuticals has developed JZP-258, a mixed salt oxybate oral solution, as a lower sodium alternative to Xyrem® sodium oxybate oral solution for the treatment of cataplexy or excessive daytime sleepiness (EDS) in pediatric (7 years of age and older) and adult patients with narcolepsy. Xyrem contains 1.638 g of sodium per 9 g dose, while JZP-258 contains 131 mg of sodium, 642 mg of potassium, 687 mg of calcium, and 182 mg of magnesium per 9 g dose.

1.2 Brief Discussion of Nonclinical Findings

This NDA is primarily supported by cross-reference to the nonclinical pharmacology, PK, and toxicology sections of NDA 21-196 for Xyrem (sodium oxybate; Jazz Pharmaceuticals). The sponsor submitted a PK study, a dose-ranging toxicity study, and a GLP 3-month bridging toxicity study of JZP-258 by oral administration in dogs (see the nonclinical reviews under IND 49641, dated June 02, 2014 and January 28, 2017). Generally, the toxicities observed with JZP-258 were comparable to those observed with sodium oxybate (see original Xyrem review by Dr. Rosloff, dated February 2, 2001).

1.3 Recommendations

1.3.1 Approvability

There is no objection to the approval of NDA 212-690 for JZP-258 for the treatment of EDS or cataplexy in narcolepsy in adults and children 7 years and older.

1.3.3 Labeling

The nonclinical sections of the current Xyrem labeling should be utilized for JZP-258.

2 Drug Information

2.1 Drug

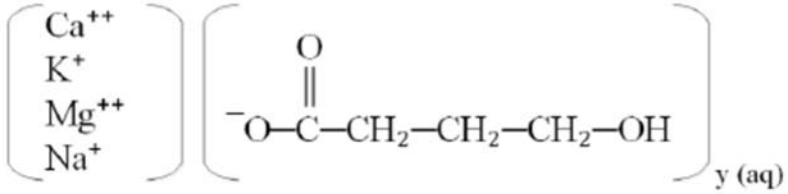
Generic Name:	Calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate
Code Name	JZP-258
Chemical Name	Calcium, potassium, magnesium and sodium salts of 4-hydroxybutanoic acid.
Molecular Formula/Molecular Weight	oxybate is $C_4H_8O_3$, with MW= 104.1 g/mol [from the sponsor's submission, below]

Table 1: Drug Substance Components

Drug Substance	Component	Molecular Formula
Dissociated Drug Substance Salts	Calcium Oxybate	$Ca(C_4H_7O_3)_{2\,(aq)}$
	Potassium Oxybate	$KC_4H_7O_{3\,(aq)}$
	Magnesium Oxybate	$Mg(C_4H_7O_3)_{2\,(aq)}$
	Sodium Oxybate	$NaC_4H_7O_{3\,(aq)}$

Structure or Biochemical Description [from the sponsor's submission, below]

Figure 1: Structural Formula, JZP-258 Drug Substance



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

Pharmacologic Class Central Nervous System (CNS) depressant

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 49,641 sodium oxybate
NDA 21-196 sodium oxybate, Xyrem

2.3 Drug Formulation

JZP-258 is a mixed (sodium, potassium, calcium, and magnesium) salt oral solution; see the sponsor's Table 1, below. The concentration of the oxybate active moiety is identical for Xyrem and JZP-258; both contain 0.413 g/mL oxybate (4-hydroxybutanoic acid).

Table 1: Cation Composition per 9 Gram Dose of JZP-258

Formulation	Cation Concentration, mg			
	Sodium	Potassium	Calcium	Magnesium
JZP-258	131	642	687	182
Xyrem	1638	0	0	0

Source: CSR 13-010\Table 2.

The sponsor stated that the amount of each cation in the maximum recommended daily dose (i.e., 9 g/ night in adults, and up to 9 g/ night in children on a weight basis) is within the US dietary intake guidelines for adults (see the sponsor's Table 2, below).

Table 2: Cation Content in the Maximum Recommended Daily Dose (9 g/night) of JZP-258 [a]: Relationship to Dietary Reference Intake [b]

Cation	Amount of Cation (mg)	Dietary Reference Intake (RDA or AI) (mg)	% of Dietary Reference Intake [d]	mEq of Cation
Na^+	131	1500-2400 [c]	9%	5.7
K^+	642	4700	14%	16.4
Ca^{++}	687	1000-1300	69%	17.1
Mg^{++}	182	320-420	57%	7.5

AI = adequate intake; IOM = Institute of Medicine; RDA = recommended dietary allowance.

[a] 9 g JZP-258 equivalent to maximum recommended daily dose of Xyrem (9 g)

[b] As set by the Institute of Medicine, includes the following: (1) RDA, the daily dietary intake level of a nutrient considered sufficient by the Food and Nutrition Board to meet the requirements of 97% of healthy individuals in each life-stage and gender group; calcium is presented as RDA and (2) AI, recommended average daily nutrient intake level, based on experimentally derived intake levels or approximations of observed mean nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate; sodium and potassium are presented as AIs as no RDAs are available.

[c] The IOM's RDA for Na^+ is 1500 mg. Other sources allow intake up to 2400 mg (British Heart Foundation, UK). The full range is provided here for completeness, but the IOM's RDA of 1500 mg was used as the standard.

[d] Lower end of recommended exposure range was used for % dietary reference intake calculation to provide a conservative estimate of daily salt exposure.

Source: Module 2.7.1.1.

The amounts of each cation in Table 2 are also within the US dietary guidelines for children, except for magnesium in the youngest children (i.e., 7 to 8 year olds). The recommended daily allowance (RDA) for magnesium is 130 mg in children 4 to 8 years old. However, the weight-based dosing for a 7 to 8 year old child (i.e., average weight of approximately 20 to 30 kg; see the sponsor's Table 3, below) would contain approximately 121 mg of magnesium at the maximum recommended dose of 6 g. The tolerable upper limit for magnesium, based on magnesium from non-food sources, is 5 mg/kg or ~110 mg for children 4-8 years of age (NIH Magnesium Fact Sheet for Health Professionals, March 24, 2020). As noted by the sponsor, intake of excess magnesium generally results in diarrhea, which is monitorable.

Table 3: Recommended Initial JZP-258 Dosage for Patients 7 Years of Age and Older

Patient Weight	Initial Dosage		Maximum Weekly Dosage Increase		Maximum Recommended Dosage	
	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.

2.4 Comments on Novel Excipients

JZP-258 is formulated as [(b) (4)]% drug substance with [(b) (4)]% (w/w) sucralose [(b) (4)] and [(b) (4)]% water.

2.5 Comments on Impurities/Degradants of Concern

The impurity profile and limits for the JZP-258 drug substance were identified as the same as those for Xyrem.

2.6 Proposed Clinical Population and Dosing Regimen

JZP-258 is being developed for the same indication and patient populations as Xyrem (i.e., the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy). See the sponsor's dosing table in **Drug Formulation**, above.

3 Studies Submitted

3.1 Studies Reviewed

None.

3.3 Previous Reviews Referenced

Nonclinical review for NDA 21-196, Barry Rosloff, PhD, February 2, 2001
Nonclinical review for NDA 21-196, Supplement 30, Melissa Banks-Muckenfuss, PhD October 24, 2018
Nonclinical reviews under IND 49641, June 2, 2014 and January 28, 2017

6 General Toxicology

The sponsor conducted non-GLP dose-ranging toxicity (MTD-estimating) and PK studies, and a GLP bridging toxicity studies in beagle dogs. These studies were previously reviewed and are briefly summarized below.

In a non-GLP oral MTD dose-ranging toxicity study in dogs (study 1301-007; see P/T review dated 6/2/14), an acute dose of 600 mg/kg JZP-258 was determined to be an MTD. JZP-258 (0, 150, 350, and 600 mg/kg) was orally administered for 7 days (N=2/sex/group) in the repeated dose phase. Body weight losses (4-14%) were observed, as were hematological alterations (e.g., ~10% reductions in hemoglobin and hematocrit in MD and HD males).

In the PK study, the sponsor tested single oral gavage doses of 0, 75, and 150 mg/kg JZP-258 or Xyrem in male and female dogs. Systemic exposures were similar after administration of JZP-258 or Xyrem; see the sponsor's summary Table 1, below.

Table 1. Study 1301-008: Mean (CV%) Oxybate Pharmacokinetic Parameter Estimates After Administration of Single Oral Doses of JZP-258 and Xyrem at 75 and 150 mg/kg in Beagle Dogs (n =10 males and n =10 females)

Treatment	Dose (mg/kg)	C_{max} (µg/mL)	C_{max}/Dose (µg·kg/mL/mg/kg)	T_{max} (h)	AUC_{0-4h} (µg·h/mL)	AUC/Dose (µg·h·kg/mL/mg)	AUC Ratio (JZP-258/ Xyrem)
JZP-258	75	98.9 (18)	1.32	0.5 (0.33-1.0)	112 (27)	1.50	1.01
	150	212 (16)	1.41	0.75 (0.5-1.5)	389 (25)	2.59	1.07
Xyrem	75	100 (23)	1.34	0.5 (0.33-1.0)	111 (29)	1.48	NA
	150	197 (23)	1.31	0.75 (0.33-1.0)	365 (31)	2.43	NA

AUC = area under the concentration-time curve; AUC_{0-4h} = area under the concentration-time curve from time 0 to 4 hours postdose; C_{max} = maximum concentration; CV% = percent coefficient of variation; T_{max} = time to C_{max} as median (range)

A 3-month GLP bridging toxicity study in dogs (Study 1301-009) was conducted testing oral doses of 0, 300, 600, 1000 (500 mg/kg BID) JZP-258 as well as 600 mg/kg sodium oxybate (Xyrem). Generally, the toxicities demonstrated with sodium oxybate and JZP-258 appeared similar. CNS signs occurred (e.g., head shaking) in one HD JZP-258 male that appeared Cmax-related based on timing. Dose-dependent abnormal salivation was reported, as well as altered feces and emesis. Mild hematological alterations (i.e., slight RBC parameters reductions) that had previously been observed in the dose-ranging study were also observed in the bridging study. Glandular atrophy was observed in several organs (e.g., salivary glands, GI tract), which was also noted to have occurred in the original dog toxicity studies for Xyrem (see Dr. Rosloff's review of Xyrem, dated 2/2/01). It is noted that atrophy of the submucosal glands of the stomach (pyloric, glandular) were of minimal severity in the LD and MD JZP-258-dosed animals as well as Xyrem-dosed animals and mild severity in the HD JZP-258 -dosed animals; this change was not reported in the original Xyrem study. Although difficult to assess based on the number of animals used in nonrodent studies, the severity of the glandular atrophy may have been slightly increased with the JZP-258. The pathologist indicated

that the histopathological alterations generally correlated with increased salivation (particularly in males), which appeared to resolve during the 2-week recovery period (the glandular atrophy did not show resolution). The toxicological importance of the minimal mineralization of the ovary that occurred in 2 HDF was unclear, and no similar finding was reported in recovery animals. The NOAELs were 600 mg/kg/day for JZP-258 and sodium oxybate (Xyrem) for 91 days. The small safety margin for adverse CNS effects (noted in a single male, ~3-fold) was not an unexpected toxicity for the oxybate active moiety.

11 Integrated Summary and Safety Evaluation

The sponsor has developed JZP-258 (mixed oxybate salts) as a lower sodium alternative to Xyrem (sodium oxybate) for the treatment of cataplexy or EDS in narcolepsy; oxybate (4-hydroxybutanoic acid) is the active moiety in both formulations. This NDA is primarily supported by cross-reference to the nonclinical pharmacology, PK, and toxicology sections of NDA 21-196 for Xyrem (sodium oxybate; Jazz Pharmaceuticals). Xyrem was recently approved for the treatment of cataplexy or EDS in pediatric patients (7 years and older) with narcolepsy in 2018.

12 Appendix/Attachments

References

Dietary Reference Intakes for Calcium and Vitamin D. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Ross AC, Taylor CL, Yaktine AL et al., editors. Washington (DC): National Academies Press (US); 2011.

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/

MELISSA K BANKS-MUCKENFUSS
06/08/2020 10:55:21 PM

LOIS M FREED
06/09/2020 03:12:06 PM
I concur.