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*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

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# 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<sup>®</sup> 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

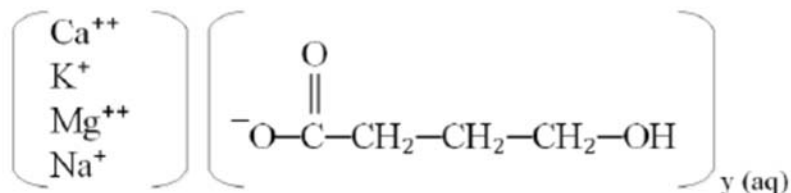
## 2.1 Drug

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 <sub>4</sub> H <sub>8</sub> O <sub>3</sub> , 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	$\text{Ca}(\text{C}_4\text{H}_7\text{O}_3)_2 \text{ (aq)}$
	Potassium Oxybate	$\text{KC}_4\text{H}_7\text{O}_3 \text{ (aq)}$
	Magnesium Oxybate	$\text{Mg}(\text{C}_4\text{H}_7\text{O}_3)_2 \text{ (aq)}$
	Sodium Oxybate	$\text{NaC}_4\text{H}_7\text{O}_3 \text{ (aq)}$

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

**Figure 1: Structural Formula, JZP-258 Drug Substance**

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

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).

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