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APPLICATION NUMBER:

212690Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology

Integrated Clinical Pharmacology Review

NDA Number	212690 Sequence Number 0001
Link to EDR	\\CDSESUB1\evsprod\NDA212690\212690.enx
Submission Date	01/21/2020
Submission Type	505(b)(1) Application – Priority review
Brand Name	XYWAV™
Generic Name	JZP-258
Dosage Form and Strength	Solution (0.5 g/ml), for oral administration
Proposed Indication	Treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy
Proposed Dose/regimen	Adults: Initiate dosage at 4.5 g per night orally divided into two equal doses taken 2.5 to 4 hours apart • 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 to 9 g per night orally. Pediatric patients (7 years of age and older) The recommended starting dosage, titration regimen and maximum total nightly dosage are based on body weight
Applicant	Jazz Pharmaceuticals Ireland Limited.
Associated IND	49641
OCP Review Team	Gopichand Gottipati Ph.D., Atul Bhattaram, Ph.D., Sreedharan Sabarinath, Ph.D.
OCP Final Signatory	Mehul Mehta, Ph.D.

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List of Abbreviations

AE	Adverse event
AUC	Area under the concentration-time curve
AUCinf	AUC from time 0 to extrapolated to infinity
AUClast	AUC from time 0 to last measurable concentration
CI	Confidence intervals
Cmax	Maximum (peak) drug concentration
FDA	Food and drug administration
LLOQ	Lower limit of quantification
NDA	New Drug Application
PK	Pharmacokinetics
Tmax	Time of maximum (peak) drug concentration
USPI	United States package insert

1 Executive Summary

Jazz Pharmaceuticals Ireland Limited submitted this original 505(b)(1) New Drug Application (NDA 212690) seeking approval for XYWAV™ (JZP-258) for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. JZP-258 is a 0.5 g/mL aqueous solution of mixture of calcium, potassium, magnesium, and sodium salts of oxybate; equivalent to 0.413 g/mL oxybate. Xyrem® (sodium oxybate) oral solution (also marketed by the same applicant) was approved by the Food and Drug Administration (FDA) for the treatment of cataplexy in narcolepsy (07/17/2002) and excessive daytime sleepiness (11/18/2005) in adults, and subsequently in pediatric patients 7 years and above for both indications (10/26/2018).

The proposed adult JZP-258 dosing recommendations are to initiate JZP-258 at 4.5 g per night orally in two equally divided doses taken 2.5 to 4 hours apart, and 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), not exceeding total nightly dose of 9 g. The proposed JZP-258 pediatric dosing recommendations for initiation, titration regimen and maximum total nightly dosage are based on body weight. These recommendations are identical to those included in US package insert (USPI) for Xyrem®[1].

The application package includes two relative bioavailability/bioequivalence studies, 13-010 and JZP258-101, in healthy subjects comparing JZP-258 with Xyrem® and a phase 3 double-blind, placebo-controlled randomized withdrawal study (15-006) in adult patients with narcolepsy. In addition, population PK and exposure-response analyses were included in this submission. This NDA relies on the approved product Xyrem (also from the same applicant) for dosing recommendations for intrinsic and extrinsic factors.

The primary focus of this review is to evaluate the dosing recommendations for JZP-258 with regards to food-intake.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) recommends the approval of JZP-258 for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adult and pediatric populations at doses listed below. (b) (4) The first dose of JZP-258 should be administered at least 2 hours after meals, just as it is recommended in the USPI for Xyrem.

Key review issues with specific recommendations and comments are summarized below.

[1] USPI for Xyrem accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021196s030lbl.pdf

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