CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212690Orig1s000

PRODUCT QUALITY REVIEW(S)

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RECOMMENDATION: Approval

NDA 212690

Review #1

Drug Product Name	XYWAV (calcium, magnesium, potassium and sodium oxybates) oral solution
Dosage Form	Solution
Strength	0.5 g/mL Total Salts comprised of: 0.234 g/mL calcium oxybate 0.130 g/mL potassium oxybate 0.096 g/mL magnesium oxybate 0.040 g/mL sodium oxybate (Equivalent to 0.413 g/mL oxybate)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Jazz Pharmaceuticals Ireland Limited
US agent, if applicable	Jazz Pharmaceuticals, Inc.

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Gaetan Ladouceur	Donna Christner
Drug Product	Grace Chiou	Julia Pinto
Manufacturing	Joanne Wang	Frank Wackes
Microbiology	Hemlata Tamta	Nandini Bhattacharya
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Florence Aisida	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

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SUBMISSIONS REVIEWED

Submission	Document Date	Disciplines Affected
SD-01, Original NDA	1/21/2020	All
SD-03, Response to IR	2/4/2020	Manufacturing
SD-04, Response to IR	2/11/2020	Drug Product
SD-05, Response to IR	3/31/2020	Drug Product
SD-06, Response to IR	4/3/2020	Drug Product
SD-10, Response to IR	4/24/2020	Drug Substance, Drug Product, Microbiology

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QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	III		(b) (4)	N/A [1]	--	
	III			N/A [1]	--	
	III			N/A [1]	--	
	III			N/A [1]	--	
	III			N/A [1]	--	
	III			N/A [1]	--	

[1] Adequate information in NDA

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
NDA	21196	Approved NDA held by Jazz Pharmaceuticals for Xyrem® (sodium oxybate) oral solution
IND	49641	Development of Xyrem and the proposed mixed oxybate salts product

2. CONSULTS

Not applicable

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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The Office of Product Quality (OPQ) review team recommends that the Agency **Approve** NDA 212690 for XYWAV (calcium, magnesium, potassium, and sodium oxybates) oral solution. From a quality perspective, the application provides adequate information to ensure that the Applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Sodium oxybate (sodium gamma-hydroxybutyrate) was approved in under NDA 21196 in 2002 as Xyrem® (sodium oxybate) oral solution 0.5 g/mL. Xyrem is indicated for treatment of cataplexy or excessive daytime sleepiness (EDS) in patients with narcolepsy. The current holder NDA 21196, Jazz Pharmaceuticals, is seeking approval for an oxybate "mixed salts" oral solution (JZP-258) as a follow-on to the approved product. Due to the high doses used, the Xyrem formulation results in high sodium intake (maximum dose of 9 g sodium oxybate/night is equivalent to 1640 mg sodium). The intent of the JZP-258 formulation is to reduce sodium content by replacing most of the sodium with other cations, i.e., calcium, potassium, and magnesium. By adjusting the relative amounts of each cation, the applicant developed a product that contains the same concentration of the active moiety, oxybate (0.413 g/mL) and a total salt concentration of 0.5 g/mL. Note that although Xyrem and JZP-258 are both simple aqueous solutions that contain the same concentration of the active moiety; the products are not bioequivalent. Therefore, the applicant was required to perform a clinical study to demonstrate efficacy.

Proposed indication(s) including intended patient population	Treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy
Duration of treatment	Chronic
Maximum daily dose	9 g/day
Alternative methods of administration	None

B. Quality Assessment Overview

The proposed product contains an active moiety with a simple chemical structure in a nonsterile aqueous solution. Based on the initial risk assessment, the product was classified as low risk for all critical attributes except palatability and leachables,

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