

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212690Orig1s000

PRODUCT QUALITY REVIEW(S)

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
	Grace Chiou	Julia Pinto
Drug Product		
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

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

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

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,

(b) (4) added the test at the Agency's request. (b) (4)

(b) (4), analytical methods for the product are similar to those for the drug substance. All noncompendial procedures are described and validated. The applicant performed a risk assessment for elemental impurities per ICH Q3D and provided data from development batches to justify exclusion of testing for elemental impurities from the specification.

Based on the stability data provided, the expiration dating period requested by the applicant, i.e., 60 months for product stored at controlled room temperature, is granted.

Labeling: Adequate

The original oxybate, Xyrem was approved in 2002 with label potency based on the sodium salt content, i.e., 0.5 g/mL (equivalent to 0.413 g/mL oxybate). Approval of Xyrem occurred prior to implementation of the USP Salt Policy (SP); however, an exception would likely be granted due to the high sodium content if the product had been reviewed after implementation of the SP. The mixed salt product is considered a new active ingredient; thus, the SP applies. This was noted and discussed with the applicant during development. In the initial NDA submission, the applicant requested an exception based on the potential for medication errors. In discussions between ONDP and DMEPA it was determined that application of the SP (b) (4) would result in the highest risk for medication errors. However, granting an exception to the SP and (b) (4) was also unacceptable due to potential medication errors. As an alternative, ONDP and DMEPA proposed expressing potency based on total salt content and including amounts of individual salts in Section 11 of the PI on the side panel of the container label. E.g., for container:

Principle Display Panel

TRADENAME

(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).

The acceptability of this approach was confirmed with the Office of Policy for Pharmaceutical Quality and the changes will be incorporated into final labeling.

Manufacturing: Adequate

The drug product manufacturing process consists of (b) (4)

(b) (4) Exhibit batches manufactured at the proposed commercial facility, Jazz Pharmaceutical Ireland Limited (JPIL) Athlone, were produced at commercial scale. The manufacturing process and controls are deemed adequate given the simple formulation.

All proposed commercial manufacturing and testing facilities are currently acceptable. It is noted that the Agency had not previously inspected the JPIL Athlone facility as a drug manufacturer and physical inspection was not possible due to the COVID-19 pandemic. Acceptability of the facility was determined based on review of an inspection report from the Irish Health Products and Regulatory Authority (HPRA) and documents requested from the applicant under 704(a)(4).

Microbiology: Adequate

The drug product is a nonsterile aqueous oral solution that will be diluted with water prior to use. The product does not contain antimicrobial agents; however, the formulation has inherent antimicrobial properties. The product specification includes microbial enumeration testing and absence of specified microorganisms appropriate per USP <1111> aqueous preparations for oral use. All microbiological tests for batch release and stability testing are deemed suitable for quality control.

Environmental: Adequate

The applicant claims a categorical exclusion under 21 CFR 25.31(b). Approval of the NDA will increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. The claim for categorical exclusion is granted.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Comments
Assay, stability	- x Formulation - x Container Closure - x Process Parameters	L	(b) (4)	Adequate	
Dosing accuracy	- x Dosing device - x Raw materials - x Formulation	L		Adequate	
Palatability	- x Formulation - x Raw Materials - x Process Parameters			Adequate	
Microbial limits	- x Formulation - x Raw materials - x Process parameters - x Scale/Equipment/Site	L		Adequate	
Leachables	- x Formulation - x Container Closure - x Raw materials	M		Adequate	

D. List of Deficiencies for Complete Response

Not applicable

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.

CMC Lead

Office of New Drug Products

Division of New Drug Products II

6/2/2020



Martha
Heimann

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CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: The PI and Medication Guide assessed in this review was submitted on April 4, 2020 and the bottle label was submitted on January 21, 2020. Based on the information provided, there are edits to be made to the labeling portion of this submission. A majority of these edits relate to the USP Salt Policy.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRADENAME™	
Established name(s)	(calcium (b) (4), potassium (b) (4), magnesium (b) (4), sodium (b) (4)) oral solution, CIII	Inadequate (calcium, magnesium, potassium, and sodium oxybates) oral solution
Route(s) of administration	Oral solution	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Oral solution, 0.5 g per mL	Inadequate Revise to "0.5 g/mL total salts" and include equivalency statement
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include	NA	NA

pharmacy bulk package and imaging bulk package.		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

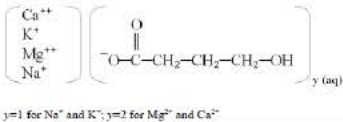
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Prepare both doses of TRADENAME prior to bedtime. Prior to ingestion, each dose of TRADENAME should be diluted with approximately ¼ cup (approximately 60 mL) of water in the provided pharmacy containers.	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	TRADENAME is a	Inadequate Revise to say "at a total salt concentration of 0.5 g per mL..."
Strength(s) in metric system	clear to slightly	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	opalescent oral solution at a concentration of 0.5 g per mL	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	(b) (4) (b) (4) (b) (4) equivalent to 0.413 g/mL of oxybate.	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3. Section 11 DESCRIPTION

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TRADENAME oral solution contains	Inadequate Revise to include appearance (i.e. "TRADENAME oral solution is a clear to slightly opaque solution that contains....")
Dosage form(s) and route(s) of administration	oxybate, a CNS depressant. The	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	chemical name of oxybate is gamma-hydroxybutyrate (GHB). TRADENAME contains a mixture of calcium oxybate, potassium oxybate, magnesium oxybate, and sodium oxybate equivalent to 0.5 g/mL, which corresponds to 0.413 g/mL oxybate. Each mL of TRADENAME contains: 0.234 g calcium oxybate, Ca(C ₄ H ₇ O ₃) ₂ ; 0.130 g potassium oxybate, K(C ₄ H ₇ O ₃); 0.096 g magnesium oxybate, Mg(C ₄ H ₇ O ₃) ₂ ; and 0.040 g sodium oxybate, Na(C ₄ H ₇ O ₃) in dissociated form in the solution.	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The inactive ingredients are sucralose and purified water.	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA

Statement of being sterile (if applicable)	NA	NA
Pharmacological/therapeutic class	CNS depressant	Adequate
Chemical name, structural formula, molecular weight	The chemical structure is:  y=1 for Na⁺ and K⁺; y=2 for Mg²⁺ and Ca²⁺	Inadequate Revise to include molecular weights. Note, chemical names and formulas are provided above.
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	None provided	None provided

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	TRADENAME contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).	Adequate
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	NA	NA

1.2.3 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) Strength(s) in metric system Available units (e.g., bottles of 100 tablets) Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	TRADENAME is a clear to slightly opalescent oral solution. 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 and has a child-resistant cap. One 180 mL bottle NDC 68727-150-01	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Dispense in tight containers. Solutions prepared following dilution should be consumed within 24 hours.	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	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).	Inadequate Replace "-" with "to" to avoid confusion with minus sign
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information about child-resistant packaging	The pharmacy provides two empty containers with child-resistant caps with each TRADENAME shipment.	Adequate

1.2.4 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Jazz Pharmaceuticals, Inc. Palo Alto, CA 94304	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): The information provided for patient labeling appears acceptable.

3.0 STRUCTURED PRODUCT LABELING (SPL)

Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:68727-150	
Route of Administration	ORAL	DEA Schedule	CIII	
Active Ingredient/Active Moiety				
Ingredient Name	Basis of Strength	Strength		
SODIUM OXYBATE (UNII: 7G33012534) (4-HYDROXYBUTANOIC ACID - UNII:30IW36W5B2)	SODIUM OXYBATE	0.5 g in 1 mL		
Calcium Oxibate (UNII: 8W24SYD6Z1) (4-HYDROXYBUTANOIC ACID - UNII:30IW36W5B2)	Calcium Oxibate	0.5 g in 1 mL		
Potassium Oxibate (UNII: 88NKF3HRT) (4-HYDROXYBUTANOIC ACID - UNII:30IW36W5B2)	Potassium Oxibate	0.5 g in 1 mL		
Magnesium Oxibate (UNII: G983HLV265) (4-HYDROXYBUTANOIC ACID - UNII:30IW36W5B2)	Magnesium Oxibate	0.5 g in 1 mL		
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68727-150-01	180 mL in 1 BOTTLE, PLASTIC, Type 0: Not a Combination Product	(b) (4) 2020	
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA212699	(b) (4) 2020		

Assessment of Carton and Container Labeling: Adequate

The carton and container labeling is adequate, pending the Applicant's acceptance of the revisions noted above in red.

ITEMS FOR ADDITIONAL ASSESSMENT

Adequate. The Structured Product Labeling does not include excipients and the UNII codes. This is a minor edit and will be addressed later in labeling discussions. Pending the Applicant's acceptance of the revisions noted above in red and the Structured Product Labeling comment, the labeling information is adequate.

Overall Assessment and Recommendation:

This application is recommended for approval per labeling/labels perspective once the following changes have been made to the label.



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Chiou

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Julia
Pinto

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CHAPTER VII: MICROBIOLOGY

Product Information	XYWAV [®] is indicated for treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.
NDA Number	212690
Assessment Cycle Number	01
Drug Product Name / Strength	XYWAV [®] (Calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate) Oral solution, 0.5 g/ mL
Route of Administration	Oral solution
Applicant Name	Jazz Pharmaceuticals Ireland Limited Fifth Floor, Waterloo Exchange, Dublin, Ireland D04E5W7
Manufacturing Site	Jazz Pharmaceuticals Ireland Limited Monksland, Athlone, Roscommon Ireland N37AX84
Method of Sterilization	Not applicable (Non-sterile)

Assessment Recommendation: Adequate

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: N/A

Assessment Summary: Bulk solution is prepared by (b) (4)

(b) (4) Drug product is filled into 6 oz round amber two-piece (b) (4) bottle with a (b) (4) child resistant/ (b) (4) closure with (b) (4) press-in-bottle-adapter (PIBA).

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
0001	01/21/2020
0010	04/24/2020

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks: This is an eCTD submission. IR was conveyed to the applicant on 4/10/2020. Response received on 4/24/2020 was incorporated in the review.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

Supporting Documents: None

Select Number of Approved Comparability Protocols: 0

S DRUG SUBSTANCE

Assessment: Not applicable

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product- XYWAV® (Calcium oxybate, potassium oxybate, magnesium oxybate, sodium oxybate) 0.5 g/ mL is a non-sterile aqueous oral solution.

Drug product composition- XYWAV® 0.5 g/ mL oral solution:

Component	Pharmaceutical function	Quality standard	Amount per g solution	Amount % w/w
JZP-258 Drug substance*	Active ingredient	In-house		(b) (4)
Sucralose				(b) (4)
Purified Water (b) (4)				

*Drug substance is an aqueous solution containing 0.5 g/ mL mixed oxybate salts

Description of container closure system: 6 oz round amber two-piece (b) (4) bottle with a (b) (4) child resistant/ (b) (4) closure with (b) (4) a press-in-bottle-adapter (PIBA).

Assessment: {Adequate}

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product microbiological quality.

P.2 PHARMACEUTICAL DEVELOPMENT

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