

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212690Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type/Numbers	NDA 021196 NDA 212690
Action Date	July 21, 2020
OSE RCM #	2020-124 2020-1537
Reviewer Names	Yasmeen Abou-Sayed, PharmD Joan E. Blair, RN, MPH Shelly Harris, ScD, MPH
Acting Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	July 21, 2020
Subject	Evaluation REMS modification for Xyrem; Evaluation of REMS Submission for Xywav
Established Name	Sodium oxybate (Xyrem); calcium, magnesium, potassium, and sodium oxybates (Xywav)
Trade Name	Xyrem; Xywav
Name of Applicant	Jazz Pharmaceuticals, Inc.
Therapeutic Class	Central Nervous System (CNS) Depressant
Formulation	0.5g/ml sodium oxybate (Xyrem); 0.5 g/mL total salts equivalent to 234 mg/mL calcium oxybate, 96 mg/mL magnesium oxybate, 130 mg/mL potassium oxybate, and 40 mg/mL sodium oxybate equivalent to 0.413 g/mL of oxybate
Dosing Regimen	For Adult Patients: • Initiate dosage at 4.5 grams (g) per night orally, divided into two doses 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 g to 9 g per night orally

For Pediatric Patients:

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	There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg.					
20 kg to < 30	≤ 1 g	≤ 1 g	0.5 g	0.5 g	3 g	3 g
30 kg to < 45	≤ 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

Table of Contents

EXECUTIVE SUMMARY	4
1 Introduction	5
2 Background	5
2.1 PRODUCT INFORMATION.....	5
2.2 CURRENTLY APPROVED XYREM REMS	6
2.3 REGULATORY HISTORY	7
3 Therapeutic Context and Treatment Options.....	7
3.1 DESCRIPTION OF THE MEDICAL CONDITION.....	7
3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS	8
4 Benefit Assessment.....	8
5 Risk Assessment and Safe-Use Conditions	9
6 Expected Postmarket Use	10
7 Review of Proposed REMS	10
7.1 GENERAL	10
7.2 REMS GOAL.....	10
7.3 REMS DOCUMENT	11
7.4 REMS REQUIREMENTS.....	11
7.4.1 REMS Participant Requirements and Materials	11
7.4.2 REMS Materials and Key Risk Messages.....	11
7.5 REMS ASSESSMENT TIMETABLE	13
8 Supporting Document.....	13
9 REMS Assessment Plan	13
10 Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials	13
11 Discussion	15
12 Conclusions and Recommendations.....	16
13 Appendix	16
A. Xywav and Xyrem REMS Assessment Plan	16
B. Appended REMS Materials.....	23
14 References	24

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates the risk evaluation and mitigation strategy (REMS) for Xywav (calcium, magnesium, potassium, and sodium oxybates), submitted on January 21, 2020, and amended on July 7, 2020, July 13, 2020, July 16, 2020, and July 20, 2020 and the REMS modification for Xyrem (sodium oxybate), submitted on July 16, 2020 and amended on July 20, 2020. Jazz (the “Applicant”) submitted a New Drug Application (NDA) 212690 under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, for Xywav with the proposed indication for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. The reference listed drug Xyrem (sodium oxybate) is approved with a REMS with elements to assure safe use (ETASU) to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing misuse, abuse, and diversion of Xyrem.

The Applicant has proposed a REMS for Xywav and Xyrem. Xywav and Xyrem contain the same active moiety, have the same risks and will use the same risk mitigation strategies. The Applicant submitted a full REMS proposal, including REMS document, REMS supporting document, and all REMS appended materials, that incorporates Xywav into the existing Xyrem REMS forming the new Xywav and Xyrem REMS. In addition, the following new materials – *Xywav Patient Quick Start Guide*, *Xywav Brochure for Pediatric Patients and their Caregivers*, and *Xywav Prescription Form* were created, and an optional Takeback program for the return of unused drug was added.

The goal of the XYWAV and XYREM REMS is to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of XYWAV and XYREM by:

1. Informing prescribers, pharmacists, and patients of:
 - a. The risk of significant CNS and respiratory depression associated with XYWAV and XYREM
 - b. The contraindication of use of XYWAV and XYREM with sedative hypnotics and alcohol
 - c. The potential for abuse, misuse, and overdose associated with XYWAV and XYREM
 - d. The safe use, handling, and storage of XYWAV and XYREM
2. Ensuring that pharmacy controls exist prior to filling prescriptions for XYWAV and XYREM that:
 - a. Screen for concomitant use of sedative hypnotics and other potentially interacting agents
 - b. Monitor for inappropriate prescribing, misuse, abuse, and diversion of XYWAV and XYREM
 - c. Notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion

DRM finds the proposed Xywav and Xyrem REMS to be acceptable for approval. This REMS proposal, if approved, will require a modification to the existing Xyrem REMS (NDA 021196) to the new Xywav and Xyrem REMS.

The Timetable for submission of assessments of the Xywav and Xyrem REMS remains the same as that approved on February 27, 2015 in the Xyrem REMS. The REMS Assessment Plan was changed to capture metrics for both products in this REMS.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Xywav (calcium, magnesium, potassium, and sodium oxybates). Jazz Pharmaceuticals, Inc. (Jazz) submitted a New Drug Application (NDA) 212690 under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, for Xywav with the proposed indication for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.¹ This application is under review in the Division of Neurology 1 (DN1). The reference listed drug is Xyrem (sodium oxybate) NDA 021196. Xyrem is approved with a REMS to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of Xyrem. The Applicant has proposed a REMS for Xywav and Xyrem, as these products contain the same active moiety, have the same risks and will have the same goals and REMS requirements. A corresponding REMS modification submitted as a prior approval supplement (PAS) 34 for Xyrem is under review in DN1, to incorporate Xywav into the existing Xyrem REMS forming the Xywav and Xyrem REMS.² The applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Xywav and Xyrem outweigh the risks.³

2 Background

2.1 PRODUCT INFORMATION

Xywav (calcium, potassium, magnesium, and sodium oxybates) oral solution contains the active moiety oxybate (4-hydroxybutanoate), a central nervous system depressant, and belongs to the same pharmacologic class as Xyrem® (sodium oxybate), a Schedule III controlled substance. Oxybate is also known as gamma-hydroxybutyrate (GHB), an endogenous compound and metabolite of the neurotransmitter gamma-amino butyric acid (GABA_B), that acts as a potent central nervous system (CNS) depressant. Oxybate is a CNS depressant, however, the exact mechanism of action of oxybate in the treatment of narcolepsy is unknown. It is hypothesized that the therapeutic effects of Xywav on the symptoms of narcolepsy (cataplexy and EDS) are mediated through GABA_B actions during sleep at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.

Xywav is a non-new molecular entity, submitted under section 505(b)(2) of the Food, Drug, and Cosmetic Act (FDCA).^a The intent of the Xywav formulation is to reduce sodium content by replacing most of the sodium with other cations, i.e., calcium, potassium, and magnesium.

Although Xyrem and Xywav both contain the same concentration of the active moiety and have the same dosing regimen^b; the products were not deemed bioequivalent. Therefore, the Applicant was required to perform a clinical study to demonstrate efficacy of Xywav.⁴

The dosing for Xywav aligns with current Xyrem dosing. The recommended starting dose in adult patients is 4.5 grams (g) per night administered orally in two equal divided doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later. The dose should be increased by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dose range of 6 to 9 g per night orally. Doses higher than 9 g per night have not been studied in either Xyrem or Xywav and

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

should not ordinarily be administered. Xywav is also proposed for use in pediatric patients, and the proposed dosing regimen in the table below aligns with current Xyrem dosing.

Table 1 – Xywav and Xyrem Dosage for Pediatric 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	There is insufficient information to provide specific dosing recommendations for patients who weigh less than 20 kg.					
20 kg to < 30	≤ 1 g	≤ 1 g	0.5 g	0.5 g	3 g	3 g
30 kg to < 45	≤ 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

2.2 CURRENTLY APPROVED XYREM REMS

Xyrem was approved in 2002 with a Risk Minimization Action Plan (RiskMAP) that required the following:

- Prescribers enrolled in the RiskMAP in order to prescribe Xyrem
- Patients enrolled in the RiskMAP in order to receive Xyrem
- A single, central, specialty pharmacy dispensed Xyrem only via direct shipment to an enrolled patient pursuant to a prescription written by an enrolled prescriber

Xyrem was identified as a product deemed to have in effect an approved REMS because there were elements to assure safe use in effect on the effective date of the Food and Drug Administration Amendments Act of 2007 (FDAAA). The REMS was approved on February 27, 2015 consisting of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The goal of the Xyrem REMS is to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of Xyrem by: ^{c,d}

1. Informing prescribers, pharmacists, and patients of:
 - The risk of significant CNS and respiratory depression associated with XYREM.
 - The contraindication of use of XYREM with sedative hypnotics and alcohol.
 - The potential for abuse, misuse, and overdose associated with XYREM.

^c The goal of mitigating diversion in this REMS refers to preventing the sale or transfer of the drug outside the framework of the REMS in order to mitigate the risks of central nervous system depression, respiratory depression, abuse, and misuse.

^d The goal of mitigating diversion in this REMS refers to preventing the sale or transfer of the drug outside the framework of the REMS in order to mitigate the risks of CNS depression, respiratory depression, abuse, and misuse.

- The safe use, handling, and storage of XYREM.
2. Ensuring that pharmacy controls exist prior to filling prescriptions for XYREM that:
- Screen for concomitant use of sedative hypnotics and other potentially interacting agents.
 - Monitor for inappropriate prescribing, misuse, abuse, and diversion of XYREM.
 - Notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion.

The ETASU in the Xyrem REMS include:

- Healthcare providers who prescribe Xyrem must be certified by reviewing the training materials and enrolling in the REMS.
- The pharmacy that dispenses Xyrem must be specially certified by reviewing the training materials. Pharmacists who dispense Xyrem must counsel new patients and those restarting treatment after 6 months or longer. They also need to document patient and prescriber behavior that may be indicative of abuse, misuse, or diversion.
- Patients who receive Xyrem must review the educational materials and be enrolled in the REMS by their provider.

2.3 REGULATORY HISTORY

The following is a summary of the regulatory history relevant to this review:

- 6/30/2020: The Agency held a teleconference with the Applicant to notify them of the need to modify the Xyrem REMS, to align with the proposed Xywav and Xyrem REMS.
- 7/16/2020: The Applicant submitted a REMS modification for Xyrem NDA 021196 under prior approval supplement (PAS) 34, in response to the June 30, 2020 teleconference with the Agency on June 30, 2020, to update the REMS materials to incorporate Xywav into the existing REMS materials, and to add new REMS materials specific to Xywav, including the *Xywav Patient Quick Start Guide*, *Xywav Brochure for Pediatric Patients and their Caregivers*, and *Xywav Prescription Form*.
- 7/17/2020: The Agency provided feedback on the Applicant's 7/16/2020 submissions (the REMS modification for Xyrem and REMS amendment for Xywav), including revisions to the REMS materials to align with the proposed Prescribing Information (PI) for both products, and updates to the REMS assessment plan.
- 7/20/2020: The Applicant submitted REMS amendments, consisting of a full REMS proposal, to NDAs 021196 and 212690, Xywav, incorporating the Agency's comments from 7/17/2020.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Narcolepsy is a chronic neurological disorder characterized by EDS, cataplexy (attacks of loss of muscle tone precipitated by emotional gestures lasting for several minutes), sleep paralysis and hypnagogic

hallucinations.^{e,5} The prevalence of narcolepsy with cataplexy is between 25 and 50 per 100,000 people (incidence 0.74 per 100,000 patient years).^{f,6} Narcolepsy patients, compared to the general US population, have a higher incidence of obstructive sleep apnea (50-68%)⁷; major depressive disorder (17%), social anxiety disorder (21%), and panic disorder (12%).⁸ Pediatric narcolepsy is associated with several co-morbid conditions, including metabolic diseases (including diabetes), obesity, precocious puberty and psychiatric comorbidities.⁹

In pediatric patients diagnosed with narcolepsy, the onset of narcolepsy symptoms was noted in as many as 11.7% of children prior to age 5¹⁰, and 59% of children prior to age 15.¹¹ The diagnosis of narcolepsy is often delayed as the disorder is rare with low general awareness relative to other chronic diseases. While the median age of diagnosis has been reported as 33 years, the corresponding median age of symptom onset was 16 years.¹²

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Management of narcolepsy includes pharmacological and nonpharmacological approaches. Currently, Xyrem is the only approved drug for cataplexy.

FDA approved drugs used to treat EDS include modafinil and methylphenidate.

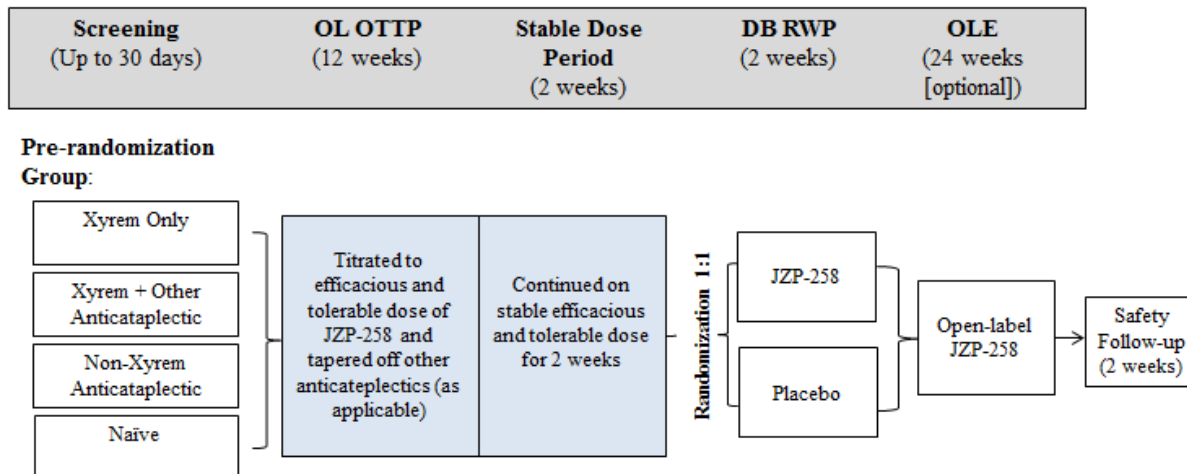
4 Benefit Assessment

The clinical benefit of Xywav was established in a pivotal Phase 3 study, study 15-006 (National Clinical Trial [NCT] 03030599), in adults with cataplexy and EDS in narcolepsy.¹³ Study 15-006 is a two-part randomized, double blind, placebo controlled, random withdrawal study, designed to evaluate the efficacy and safety of Xywav in adult patients with cataplexy and EDS in narcolepsy. Study 15-006 enrolled 201 subjects, with a median age of 38 years, and majority female (61%). At study entry, 52 subjects were being treated with Xyrem, 23 subjects with Xyrem plus other anti-cataplectic, 36 subjects with a non-Xyrem anti-cataplectic, and 90 subjects were treatment-naïve. All subjects started treatment with Xywav in a 12-week open label, optimized treatment and titration period (OTTP), followed by a 2-week stable dose period then a 2-week, double blind, placebo controlled, randomized withdrawal period. Figure 1 demonstrates the flow of study 15-006:

^e Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

^f Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

Figure 1 – Study 15-006 Design



The primary efficacy endpoint was the change in the average weekly number of cataplexy attacks from 2 weeks of the stable dose period to 2 weeks of the double blind, randomized withdrawal period. The key secondary efficacy endpoint was the change in the Epworth Sleepiness Scale (ESS) score from the end of the stable dose period to the end of the double blind, randomized withdrawal period.

Study 15-006 achieved the primary efficacy endpoint demonstrating clinical efficacy of Xywav for treatment of cataplexy and EDS in narcolepsy. Patients randomized to placebo during the double blind, randomized withdrawal period showed significant increase (worsening) in the average weekly number of cataplexy attacks compared with subjects randomized to continue treatment with Xywav (median of 2.35 on placebo versus 0.0 on Xywav; $p < 0.0001$). There was no change in the median average weekly number of cataplexy attacks in patients who remained on Xywav during the same period.

With regards to the secondary endpoint, subjects randomized to placebo during the double-blind randomized withdrawal period showed a significant increase (worsening) in the ESS score compared with subjects randomized to continue treatment with Xywav (median 2.0 on placebo versus 0.0 on Xywav, $p < 0.0001$). There was no change in the median ESS score in subjects remaining on Xywav treatment during the double randomized withdrawal period.

Overall, adult patients on stable doses of Xywav had fewer cataplexy attacks and experienced less worsening in the ESS than did patients withdrawn from Xywav and randomized to placebo.^{14,g} The effectiveness of oxybate in the treatment of cataplexy and excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy was established with Xyrem and not repeated in this study.¹⁵

5 Risk Assessment and Safe-Use Conditions

Sodium oxybate is a Schedule III controlled substance, as it is a salt of gamma hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse or misuse of illicit GHB is associated with CNS adverse reactions,

^g Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

including seizure, respiratory depression, decreased consciousness, coma, and death.^h Because of the risks of inappropriate prescribing, misuse and abuse sodium oxybate, currently marketed as Xyrem, is available only through a REMS.ⁱ Because Xywav references Xyrem as a basis for its approval, and shares the same active moiety, oxybate, the Agency determined Xywav will be subject to the same REMS requirements and should be incorporated into the currently approved Xyrem REMS.¹⁶

6 Expected Postmarket Use

Xywav is proposed to be prescribed and dispensed in the same manner as Xyrem for use in the outpatient setting. Prescribers of Xywav are likely to be specialist providers who are knowledgeable of the risks associated with Xyrem and therefore should be familiar with the Xywav and Xyrem REMS requirements.

7 Review of Proposed REMS

7.1 GENERAL

The Applicant submitted a full REMS proposal, including REMS document, REMS supporting document, and all REMS appended materials, that incorporates Xywav into the existing Xyrem REMS creating the new Xywav and Xyrem REMS.

7.2 REMS GOAL

The Applicant has updated the goals to include the addition of Xywav to the modified Xyrem REMS. The new goals will state:

The goal of the XYWAV and XYREM REMS is to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of XYWAV and XYREM by:

3. Informing prescribers, pharmacists, and patients of:
 - a. The risk of significant CNS and respiratory depression associated with XYWAV and XYREM
 - b. The contraindication of use of XYWAV and XYREM with sedative hypnotics and alcohol
 - c. The potential for abuse, misuse, and overdose associated with XYWAV and XYREM
 - d. The safe use, handling, and storage of XYWAV and XYREM
4. Ensuring that pharmacy controls exist prior to filling prescriptions for XYWAV and XYREM that:

^h Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

ⁱ Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

- a. Screen for concomitant use of sedative hypnotics and other potentially interacting agents
- b. Monitor for inappropriate prescribing, misuse, abuse, and diversion of XYWAV and XYREM
- c. Notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion

Reviewer's Comments: *We agree with the proposed goal for the Xywav and Xyrem REMS.*

7.3 REMS DOCUMENT

The Applicant submitted a REMS document based on the existing Xyrem REMS document and updated to be consistent with the Agency's draft *Format and Content of a REMS Document Guidance for Industry*¹⁷. The proposed REMS document has been revised to include Xywav in the current Xyrem REMS, and to include proposed Xywav specific REMS materials.

Reviewer Comment: We agree with the Applicant's proposed REMS document.

7.4 REMS REQUIREMENTS

7.4.1 REMS Participant Requirements and Materials

In order to include Xywav into the Xyrem REMS, the Applicant incorporated Xywav into existing materials or provided Xywav specific materials when needed. The Applicant also proposed a 'Takeback' Program whereby a patient may dispose of unused or expired drug using a Drug Enforcement Agency (DEA) compliant mailer obtained via the Certified Pharmacy. No other changes were made to the existing Xyrem ETASU. See below for specific REMS materials changes.

7.4.2 REMS Materials and Key Risk Messages

7.4.2.1 General

The key risk messages for the Xywav and Xyrem REMS remain the same as in the currently approved Xyrem REMS.

The Applicant proposes revising the existing Xyrem REMS materials for use in the Xywav and Xyrem REMS and adding three Xywav-specific REMS materials. The current Xyrem REMS materials that were revised include:

1. *Prescriber Enrollment Form*
2. *Patient Enrollment Form*
3. *Prescriber Brochure*
4. *Certified Pharmacy Training Program – Modules A and B*
5. *Modules A and B Knowledge Assessment*
6. *Xyrem Prescription Form*
7. *Xyrem Patient Quick Start Guide*
8. *Xyrem Brochure for Pediatric Patients and their Caregivers*
9. *Patient Counseling Checklist*
10. *Risk Management Report*

11. REMS Website

The new REMS materials specific to Xywav include:

1. *Xywav Patient Quick Start Guide*
2. *Xywav Brochure for Pediatric Patients and their Caregivers*
3. *Xywav Prescription Form*

7.4.2.2 Prescriber Enrollment Form Patient Enrollment Form Module A Knowledge Assessment Module B Knowledge Assessment Risk Management Report Xyrem Prescription Form

Editorial revisions to these materials have been proposed to incorporate Xywav into the REMS.

Reviewer Comment: We find the proposed Prescriber Enrollment Form, Patient Enrollment Form, Module A and Module B Knowledge Assessments, Risk Management Report and, Xyrem Prescription Form acceptable.

7.4.2.3 Prescriber Brochure Certified Pharmacy Training Program

Editorial revisions to these materials have been proposed to incorporate Xywav into the REMS. Additional language has been added to educate Prescribers and Pharmacy staff, respectively, on transitioning patients between the two drugs and detailing the drug-specific *Prescription Forms* and patient educational materials. The Applicant accepted the Agency's comment to remove promotional language (b) (4) and to align the content of the material with the draft PI.

Reviewer Comment: We find the proposed Prescriber Brochure and Certified Pharmacy Training Program acceptable.

7.4.2.4 Patient Counseling Checklist

Editorial revisions to this material have been proposed to incorporate Xywav into the REMS and to align the content of the material with the draft PI.

Reviewer Comment: We find the proposed Patient Counseling Checklist acceptable.

7.4.2.5 Xywav Prescription Form

This new material was proposed to incorporate Xywav into the REMS.

Reviewer Comment: We find the proposed Xywav Prescription Form acceptable.

7.4.2.6 Xyrem Patient Quick Start Guide Xyrem Brochure for Pediatric Patients and their Caregivers

Editorial revisions to these materials have been proposed to incorporate Xywav into the REMS. The Applicant accepted the Agency's comment to remove promotional language (b) (4) and to align the content of the material with the draft PI.

Reviewer Comment: We find the proposed Xyrem Patient Quick Start Guide and Xyrem Brochure for Pediatric Patients and their Caregivers acceptable.

7.4.2.7 Xywav Patient Quick Start Guide Xywav Brochure for Pediatric Patients and their Caregivers

These new materials were proposed to incorporate Xywav into the REMS. The Applicant accepted the Agency's comment to remove promotional language (b) (4) and to align the content of the material with the draft PI.

Reviewer Comment: We find the proposed Xywav Patient Quick Start Guide and Xywav Brochure for Pediatric Patients and their Caregivers acceptable.

7.5 REMS ASSESSMENT TIMETABLE

The timetable for submission of assessments of the REMS remains the same as that approved on February 27, 2015 in the Xyrem REMS.

8 Supporting Document

The Applicant made editorial revisions throughout the REMS Supporting Document (SD) to incorporate Xywav into the Xyrem REMS. Additionally, the attestations for the REMS stakeholders were updated to correlate with the new REMS document format.

Reviewer Comment: We agree with the Applicant's proposed REMS supporting document.

9 REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be included in the Xywav Approval letter and Xyrem REMS Modification Approval letter. The proposed REMS Assessment Plan (AP) is based off the most recent Xyrem REMS AP, and the following revisions were made to:

1. Align with the 2019 *Draft Guidance for Industry - REMS Assessment: Planning and Reporting*
2. To add metrics to clarify existing metrics in the current Xyrem REMS (in the areas of Program Implementation and Operations, Program Compliance, Safe Use, and Health Outcomes)
3. To add metrics related to the transition to a Shared REMS with Xywav and Xyrem

The revised REMS Assessment Plan is attached as Appendix A.

Reviewer Comment: We agree with the Applicant's proposed REMS Assessment Plan.

10 Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on May 15, 2020 to provide feedback on the full content of the proposed Xywav and Xyrem REMS. The OPDP review was completed by Rebecca Falter on June 26, 2020.¹⁸ At the time of the OPDP review, the prescribing information (PI) for Xywav was still under review in DN1 and the most recent draft PI available was dated June 22, 2020. OPDP recommendations are summarized below, under two general categories:

Removal of non-REMS information

OPDP noted the following statements in the REMS training and educational materials which may represent assurance of benefits of Xywav and be considered promotional in tone and recommends revising them in the REMS materials.

- Statements about time needed to titrate Xywav to reach an effective dose and how long it will take for a patient to see a change in symptoms related to the indication
 - *Reviewer Comment: We do not agree with removing this language from the REMS materials as this is an important patient counseling point to ensure that patients do not try to titrate their own dose.*
- Statements that Xywav and Xyrem “(b) (4)”
 - *Reviewer Comment: We agree with removing statements regarding (b) (4) (b) (4) for Xywav and Xyrem, as this is may be confusing to readers as they suggest a conflict with the Instructions for Use for Xyrem and Xywav, (b) (4) (b) (4).*
- Information about insurance coverage and the Certified Pharmacy’s role in billing for Xywav
 - *Reviewer Comment: Although we understand OPDP’s concern’s about including non-REMS information, we disagree. In this case, the reference to the pharmacist going over insurance information with the patient is currently included in the approved REMS for Xyrem.*
- Statements in the patient REMS materials that provide options for delivery of Xywav shipments to patients and their caregivers.
 - *Reviewer Comment: We do not agree with OPDP’s concerns about this delivery system as it is being managed by a pharmacy that has been trained and certified in the Xywav REMS program and it supports the restricted distribution of the products.*
- Statements in the patient educational materials that the REMS program provides (b) (4)
 - *Reviewer Comment: We agree with the removal of language within the materials that (b) (4) and have revised the REMS materials to remove such language.*

Align REMS materials with draft PI

- OPDP notes that the current Xywav PI is still being reviewed by DN1, and the REMS materials should be revised, as appropriate, to reflect all changes in the final approved PI for Xywav.
 - *Reviewer Comment: We agree the REMS materials should be revised to reflect all changes in the final approved PI for Xywav. At the time of this review, all REMS materials align with labeling.*

- OPDP noted statements in REMS educational materials that omit risk information listed in the PI and Medication Guide (MG), related to REMS-specific risks, and other Warnings and Precautions from the PI, related to abuse and misuse of GHB, central nervous system (CNS) depressants, respiratory depression, depression and suicidality.
 - *Reviewer Comment: We do not agree with the recommendation to include further detail on specific risks listed in the OPDP review, as the REMS includes the most relevant safety information from the PI and does not include all the risk information from the PI. The prescriber is encouraged in the REMS materials to read the PI prior to prescribing Xywav or Xyrem. Patient directed risk information is also adequately addressed in more detail in the Medication Guide for patients and their caregivers.*

The Division of Risk Management (DRM) appreciates and considered OPDP's recommendations and noted OPDP's concerns.¹⁹ DRM and OPDP subsequently discussed the recommendations provided in the consult to provide an understanding of each Division's perspective and why all the recommendations were not applied to the REMS.

11 Discussion

The Clinical Reviewer recommends approval of Xywav on the basis of the efficacy and safety information currently available.¹⁰

Xywav is not a new molecular entity, both Xyrem and Xywav have the same active moiety and will have the same indication. Both products are central nervous system depressants, which can cause serious outcomes even at approved doses. The risk of respiratory depression is increased when these products are used with other central nervous system depressants, for this reason labeling contradicts the use of these products with alcohol and sedative-hypnotics.

Xywav and Xyrem are Schedule III controlled substances and are also associated with the risks of abuse and misuse. The Xyrem REMS is required to address the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion. Xywav shares the same risks as Xyrem and therefore this reviewer has determined that Xywav should be subject to the same REMS requirements. No new risks were identified in the review of the Xywav application.

DN1 and DRM agree a REMS that includes elements to assure safe use (ETASU) is necessary for Xywav to ensure that the benefits of the drug outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion. The REMS for Xywav and Xyrem will include the same goals and elements that were included in the Xyrem REMS. The REMS is comprised of elements to assure safe use (including that healthcare providers who prescribe Xywav and Xyrem are specially certified, that Xywav and Xyrem will be dispensed only by a central pharmacy that is specially certified, and that Xywav and Xyrem will be dispensed and shipped only to patients who are enrolled in the Xywav and Xyrem REMS with documentation of safe use conditions), an implementation system, and a timetable for submission of assessments of the REMS.

In reaching this determination regarding the need for a REMS with ETASU for Xywav, DN1 has documented this in their REMS Memorandum.¹⁰

The Applicant has incorporated all Agency feedback provided on the REMS Document, REMS supporting document, and appended materials. This REMS proposal if approved will require a modification to the existing Xyrem (NDA 021196) REMS as the two NDAs will share a REMS document, REMS Supporting Document, and appended REMS materials.

12 Conclusions and Recommendations

DRM finds the proposed Xywav and Xyrem REMS which was submitted to each application on July 20, 2020 acceptable for approval and is appended to this review.

The timetable for submission of assessments of the REMS remains the same as that approved for the Xyrem REMS on February 27, 2015.

The REMS Assessment Plan, as summarized in the REMS Supporting Document, has been revised to include metrics for the Xywav and Xyrem REMS (See Appendix A). The plan and should be included in the approval letter for Xywav and the Xyrem REMS Modification Approval letter.

13 Appendix

A. Xywav and Xyrem REMS Assessment Plan

The XYWAV and XYREM REMS Assessment Plan will include, but is not limited to, the following information:

Program Implementation and Operations

1. REMS Program Implementation (1st assessment after approval only)
 - a. Date of first commercial distribution of XYWAV
 - b. Date when the XYWAV and XYREM REMS website became live and fully operational
 - c. Date when the REMS Call Center was operationalized to include both XYWAV and XYREM
2. REMS Enrollment Statistics (per reporting period and cumulatively)
 - a. Patients:
 - i. Number and percentage of newly enrolled patients stratified by age, geographic region (defined by US Census), and gender
 - ii. Number and percentage of active patients enrolled (patients who received at least one shipment of XYWAV or XYREM during the reporting period) stratified by age, geographic region (defined by US Census), and gender
 - iii. Number and percentage of patients who have discontinued XYWAV or XYREM after receiving at least one shipment of XYWAV or XYREM. Include demographics of discontinued patients and reasons for discontinuation.
 - iv. Number and percentage of patients who transitioned from XYREM to XYWAV
 - v. Number and percentage of patients who transitioned from XYWAV to XYREM

- b. Healthcare Providers:
 - i. Number and percentage of newly certified healthcare providers stratified by professional designation (i.e. MD, DO, PA, NP), medical specialty, and geographic region (defined by US Census)
 - ii. Number and percentage of active certified healthcare providers (healthcare providers who have written at least one prescription for XYWAV or XYREM during the reporting period) stratified by professional designation (i.e. MD, DO, PA, NP), medical specialty, and geographic region (defined by US Census)
 - iii. Number of patients by current enrolled prescriber.
- c. Certified Pharmacy
 - i. If the Certified Pharmacy was decertified during the reporting period and reasons for decertification.
- 3. Utilization Data (per reporting period and cumulatively)
 - a. Number and percentage of XYREM prescriptions (new and refills) dispensed
 - b. Number and percentage of XYWAV prescriptions (new and refills) dispensed
 - c. Number and percentage of XYREM bottles and shipments sent
 - d. Number and percentage of XYWAV bottles and shipments sent
- 4. REMS Program Operation and Performance Data (per reporting period and cumulatively)
 - a. REMS Program Central Database Report
 - i. Number and percentage of contacts by stakeholder type (e.g. patients, healthcare providers, pharmacy, other)
 - ii. Summary of reasons for contacts (e.g., enrollment questions) by reporter (authorized representative, patient, healthcare provider, other)
 - iii. Call center report with number of calls received and a summary of reasons for calls by stakeholder type
 - iv. Summary of frequently asked questions by stakeholder type and topic
 - v. Summary of any REMS-related problems identified and a description of any corrective actions taken
 - vi. If the summary reason for the calls indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues
 - vii. Summary of program or system problems and a description of any corrective actions taken.
- 5. REMS Program Compliance (per reporting period and cumulatively)
 - a. Audits: Summary of audit activities including but not limited to:
 - i. A copy of the audit plan for each audited stakeholder.
 - ii. The number of audits expected, and the number of audits performed

- iii. The number and type of deficiencies noted
 - iv. For those with deficiencies noted, report the status of corrective and preventative action (CAPA) proposed to address the deficiencies. The status to include completion status.
 - v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
 - vi. Provide details on deviations for the CAPA proposed, including timelines, and mitigating steps to address the deviations
 - vii. Confirm documentation of completion of training for relevant staff
 - viii. Review of accumulative findings to identify any trends of potential repeat issues, and steps to be taken to address these findings
 - ix. A summary report of the processes and procedures that are implemented to be in compliance with the REMS requirements
- b. A summary report of non-compliance, associated corrective and preventive actions (CAPA) plans, and the status of CAPA plans including but not limited to:
 - i. A copy of the Non-Compliance Plan which addresses the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
 - ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:
 - 1. The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
 - 2. The source of the noncompliance data
 - 3. The results of root cause analysis
 - 4. What action(s) were taken in response
- c. Healthcare Providers
 - i. Number and percentage of certified prescribers who were disenrolled during the reporting period and reasons for disenrollment. Include if any prescribers were re-certified.
 - ii. Number of disenrolled prescribers who were associated with a XYWAV and XYREM prescription and number of disenrolled prescribers associated with a XYWAV and XYREM shipment
 - iii. Number and percentage of XYWAV prescriptions filled from a prescriber who was not enrolled.
 - iv. Number and percentage of XYREM prescriptions filled from a prescriber who was not enrolled.
- d. Certified Pharmacy

- i. Number and percentage of XYWAV prescriptions dispensed for more than a 30 days' supply (first fill) or more than a 90 days' supply (refills) and reasons
 - ii. Number and percentage of XYREM prescriptions dispensed for more than a 30 days' supply (first fill) or more than a 90 days' supply (refills) and reasons
 - iii. Number and percentage of XYWAV shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and Risk Management Reports (RMRs) completed
 - iv. Number and percentage of XYREM shipments lost in delivery (and unrecovered) with number of DEA 106 Forms and Risk Management Reports (RMRs) completed
 - v. Number and percentage of initial XYWAV shipments sent to patients without completion of the XYWAV and XYREM REMS Patient Counseling Checklist.
 - vi. Number and percentage of initial XYREM shipments sent to patients without completion of the XYWAV and XYREM REMS Patient Counseling Checklist.
- e. Patients
 - i. Number and percentage of patients who were disenrolled from the program and reasons for disenrollment
 - ii. Number and percentage of patients associated with more than one prescriber during their therapy
 - iii. Number and percentage of patients prescribed a daily dose of XYWAV of >9 g
 - iv. Number and percentage of patients prescribed a daily dose of XYREM of >9 g
 - v. Number and percentage of patients with overlapping prescriptions (more than one active prescription shipped)
 - vi. Number and percentage of patients with concurrent XYWAV and XYREM prescriptions
 - vii. Number of duplicate patients detected by the Certified Pharmacy
 - viii. Number and percentage of duplicate patients who were shipped XYWAV or XYREM under more than one name or identifier
 - ix. Number and percentage of patients who were shipped XYWAV or XYREM after being disenrolled
 - x. Number and percentage of patients who requested an early refill of XYWAV and reason for the request
 - 1) Number and percentage of requests approved
 - 2) Number and percentage of requests denied by the prescriber
 - 3) Number and percentage of requests denied by the Certified Pharmacy
 - 4) Number and percentage of patients with multiple requests for early refills.

- xi. Number and percentage of patients who requested an early refill of XYREM and reason for request
 - 1) Number and percentage of requests approved
 - 2) Number and percentage of requests denied by the prescriber
 - 3) Number and percentage of requests denied by the Certified Pharmacy
 - 4) Number and percentage of patients with multiple requests for early refills.

Safe Use Behaviors

- 6. Pharmacy Notifications (per reporting period and cumulatively, for both XYWAV and XYREM)
 - i. A summary of the notifications by pharmacies to prescribers for both XYWAV and XYREM. For each of the following situations, include the number and percentage of notifications, number of unique patients, the outcome of the pharmacy notification (e.g. counseled patient, discussed with prescriber and prescriber's designee) and outcome of XYWAV and XYREM prescription disposition (e.g. prescriber approved shipment, prescriber requested shipment hold, prescriber denied shipment, pharmacy approved shipment):
 - 1) Use with sedative-hypnotics indicated for sleep (e.g. zolpidem, eszopiclone, zaleplon, ramelteon)
 - 2) Use with other concomitant CNS-depressant medications (opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptics, sedating antihistamines, general anesthetics, muscle relaxants, opioid analgesics, or illicit CNS depressants)
 - 3) Patient report of alcohol use
 - 4) Patient report of diagnosis of sleep apnea
 - 5) Patient report of diagnosis of asthma, COPD, or other conditions affecting breathing
 - 6) Suspected abuse, misuse, or diversion
 - 7) Alerts regarding potential abuse, misuse, or diversion on the patient profiles
 - 8) Prescription error
 - 9) Early refill requests
- 7. Risk Management Reports (RMRs) (per reporting period and cumulatively, for both XYWAV and XYREM)
 - i. Number and percentage of RMRs submitted
 - ii. Number and percentage of unique patients with a RMR
 - iii. Number and percentage of unique patients with multiple RMRs
 - iv. Number and percentage of alerts generated from RMRs
 - v. Number and percentage of RMRs generated from early refill requests

- vi. Number and percentage of RMRs generated for other reasons (list reasons)
- vii. Number and percentage of prescriber-related RMRs
- viii. Number and percentage of RMRs that included an adverse event
- 8. REMS Program Patient Counseling Checklist (per reporting period and cumulatively, for both XYWAV and XYREM)
 - i. Summary table for both XYWAV and XYREM from REMS Program Patient Counseling Checklists of the number and percentage of patients taking the following concomitant medications and who subsequently received at least one shipment of drug:
 - 1) Sedative hypnotics indicated for sleep (e.g. zolpidem, eszopiclone, zaleplon, ramelteon)
 - 2) Alcohol
 - 3) Other potentially interacting agents:
 - Benzodiazepines
 - Sedating antidepressants or antipsychotics, and sedating anti-epileptics, and sedating antihistamines
 - General anesthetics
 - Muscle relaxants
 - Opioid analgesics
 - Divaproex sodium or other valproate drug (e.g., valproic acid)
 - Illicit CNS depressants (e.g., heroin or gamma-hydroxybutyrate [GHB])
 - ii. Summary tables for both XYWAV and XYREM from REMS Program Patient Counseling Checklists of the number and percentage of patients who have been diagnosed with the following conditions and who subsequently received at least one shipment of drug:
 - 1) Sleep apnea
 - 2) Asthma, COPD, or other conditions affecting the respiratory system.

Health Outcomes and/or Surrogates of Health Outcomes

- 9. Pharmacovigilance/surveillance (per reporting period)
 - a. Separate summary tables for XYWAV and XYREM of the number of reports of serious adverse events. The summary tables will include the following data fields (CIOMS II line listings): date, report ID, report type, notifier, age, gender, start and stop date, dose, frequency, onset date, system organ class, outcome, and causality. All tables should include an overall narrative summary of the adverse events and data fields reported.
 - i. All cases of death
 - 1) Number, percentage, and type of RMRs, notifications, and alerts associated with any reported deaths.

- ii. All outcomes of death, emergency department visits (when admitted to hospital), or hospitalizations resulting from or associated with the following:
 - 1) Use with concurrent sedative hypnotics and alcohol. Provide a breakdown of concomitant sedative hypnotics usage (ex. zolpidem=6%, eszopiclone=3%)
 - 2) Intentional misuse
 - 3) Abuse
 - 4) Overdose
 - 5) Medication error
- iii. Cases of sexual abuse
- iv. Proportion of discontinued patients who were associated with a report of a serious adverse event, including death

Knowledge

10. Knowledge, Attitude, and Behavior (KAB) Surveys of Patients, Caregivers, and Healthcare Providers (to be submitted annually)

- a. Assessment of patients'/caregivers' and healthcare providers' understanding of the following:
 - i. The risk of significant CNS and respiratory depression associated with XYWAV and XYREM even at recommended doses
 - ii. The contraindicated uses of XYWAV and XYREM
 - iii. The potential for abuse, misuse, and overdose associated with XYWAV and XYREM
 - iv. The safe use, handling, and storage of XYWAV and XYREM
 - v. The XYWAV and XYREM REMS Program requirements.

11. Knowledge, Attitude, and Behavior (KAB) Surveys of Pharmacists (Beginning with the 5-year assessment and annually thereafter)

- a. Assessment of pharmacists' understanding of the following:
 - i. The risk of significant CNS and respiratory depression associated with XYWAV and XYREM even at recommended doses
 - ii. The contraindicated uses of XYWAV and XYREM
 - iii. The potential for abuse, misuse, and overdose associated with XYWAV and XYREM
 - iv. The safe use, handling, and storage of XYWAV and XYREM

v. The XYWAV and XYREM REMS Program requirements.

12. Certified Pharmacy knowledge assessments (per reporting period and cumulatively)

- a. Number of pharmacy staff who completed post-training knowledge assessments including method of completion and the number of attempts needed to complete.
 - i. Provide a breakdown of scores within Module A and B
- b. Summary of the most frequently missed post-training knowledge assessment questions
- c. Summary of potential comprehension or perception issues identified with the post-training knowledge assessment by module
- d. Number of pharmacy staff who did not pass the knowledge assessments.
- e. Summary of potential comprehension or perception issues identified with the post-training knowledge assessment by module
- f. Number of pharmacy staff who did not pass the knowledge assessments.

13. The requirements for assessments of an approved REMS under section 505-1 (g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

B. Appended REMS Materials

Enrollment Forms:

Prescriber:

1. Prescriber Enrollment Form

Patient:

2. Patient Enrollment Form

Training and Educational Materials

Prescriber:

3. Prescriber Brochure

Patient:

4. Xyrem Patient Quick Start Guide
5. Xywav Patient Quick Start Guide
6. Xyrem Brochure for Pediatric Patients and their Caregivers
7. Xywav Brochure for Pediatric Patients and their Caregivers

Pharmacy

8. Certified Pharmacy Training Program
9. Pharmacy Knowledge Assessment – Module A
10. Pharmacy Knowledge Assessment – Module B

Patient Care Forms

11. Xyrem Prescription Form
12. Xywav Prescription Form
13. Patient Counseling Checklist

14. Risk Management Report

Other Materials

15. REMS website

14 References

- ¹ Jazz. New Drug Application 212690 for Xywav, January 21, 2020.
- ² Jazz. Proposed Risk Evaluation and Mitigation Strategy Modification for Xyrem, NDA 021196/S-34, July 16, 2020.
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- ⁴ Kishore, V. Division of Neurology 1. Meeting Preliminary Comments RE: May 20, 2015 Type B Meeting Request for IND 049461, September 18, 2015.
- ⁵ Yves Dauvilliers et al. Narcolepsy with cataplexy. *Lancet* 2007; 369: 499-511.
- ⁶ Longstreth et al. The Epidemiology of Narcolepsy; *Sleep*, 2007; Vol. 30, No, 1: 13-26.
- ⁷ Sansa et al. Obstructive sleep apnea in narcolepsy. *Sleep Medicine*, 2010; 11(1):93-95.
- ⁸ Ohayon MM. Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population. *Sleep Medicine*, 2013; 14(6): 488-492.
- ⁹ Jennum P, Pickering L, Thorstensen EW, et al. Morbidity of childhood onset narcolepsy: a controlled national study. *Sleep Med* 2017; 29:13-7.
- ¹⁰ Challamel MJ, Mazzola ME, Nevisimalova S, et al. Narcolepsy in children. *Sleep* 1994; 17s:17.
- ¹¹ Toss RE and Daly DD. Narcolepsy in Children. *Pediatrics* 1960; 25:1025-33.
- ¹² Thorpy MG and Cronin S. Age of onset and time to diagnosis of narcolepsy. *Neurology* 1999; 52 (Suppl 2):A110.
- ¹³ Jazz. Summary of Clinical Efficacy for Xywav NDA 212690, January 21, 2020.
- ¹⁴ Yasuda, S. Division of Neurology 1. Draft REMS Memorandum for Xywav NDA 212690, June 19, 2020.
- ¹⁵ Mani, R. Division of Neurology Products. Review and Evaluation of Clinical Data for Xyrem NDA 021196/S-030, October 26, 2018.
- ¹⁶ Kishore, V. Division of Neurology 1. Meeting Minutes for Pre-NDA Type C Meeting for IND 049641, October 30, 2019
- ¹⁷ U.S. Food and Drug Administration. Draft Format and Content of a REMS Document Guidance for Industry, October 2017.
- ¹⁸ Falter, R. Office of Prescription Drug Promotion. Comments on draft REMS Materials for Xywav, NDA 212690. June 26, 2020.
- ¹⁹ Blair, J. Division of Risk Management. DRM Response to OPDP Consult for Xywav NDA 212690. July 20, 2020.

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SHELLY L HARRIS
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JACQUELINE E SHEPPARD
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Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEUROSCIENCE
DIVISION OF NEUROLOGY 1**

NDA/BLA #s: 212690
Products: Xywav (calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate [gamma-hydroxybutyrate]), oral solution
APPLICANT: Jazz Pharmaceuticals, Inc.
FROM: Eric Bastings, MD
DATE: July 21, 2020

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use (ETASU) is necessary for Xywav (calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate [gamma-hydroxybutyrate]) to ensure that the benefits of the drug outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion. This REMS is a REMS with Xyrem (sodium

oxybate) oral solution (NDA 021196) (Jazz Pharmaceuticals, Inc), which contains the same active ingredient as Xywav (calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate [gamma-hydroxybutyrate]) oral solution (NDA 212690). The REMS for Xyrem (sodium oxybate) was originally approved on February 27, 2015. The REMS will be known as the Xywav and Xyrem REMS. In reaching this determination regarding the need for a REMS with ETASU for Xywav, we considered the following:

- A. Xywav will be indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. The prevalence of narcolepsy with cataplexy has been estimated to be between 25 and 50 per 100,000 people and the incidence of narcolepsy with cataplexy has been estimated to be 0.74 per 100,000 person years.¹
- B. Narcolepsy is a clinical syndrome of daytime sleepiness with cataplexy, hypnagogic hallucinations, and sleep paralysis. It is the second most common cause of disabling daytime sleepiness after obstructive sleep apnea.^{2,3} Cataplexy is a chronic and life-long disorder that is disabling and may lead to serious injury. Excessive daytime sleepiness can impair performance over time, as measured by response latency, response variability, speed, accuracy, hand-eye coordination, decision-making, and memory. Of particular importance are the adverse consequences of such effects on driving and the increased risk of potentially fatal motor vehicle accidents.
- C. Adult patients on stable doses of Xywav had fewer cataplexy attacks and experienced less worsening in the Epworth Sleepiness Scale than did patients withdrawn from Xywav and randomized to placebo. The effectiveness of oxybate in the treatment of cataplexy and excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy was established with Xyrem.
- D. Xywav will be used on a chronic basis in patients with narcolepsy.
- E. The active moiety of Xywav, oxybate (also known as gamma-hydroxybutyrate or GHB), is associated with the risks of central nervous system depression, respiratory depression, abuse, and misuse. Xywav is a central nervous system depressant, which may cause serious outcomes even at approved doses. Because of its effects on the central nervous system, Xywav may impair respiratory drive, especially in patients with compromised respiratory function. In clinical trials with Xyrem (sodium oxybate), clinically significant respiratory depression occurred in Xyrem-treated patients even at doses currently

¹ The epidemiology of narcolepsy. Longstreth WT Jr, Koepsell TD, Ton TG, Hendrickson AF, van Belle G. Sleep. 2007;30(1):13.

² Narcolepsy and excessive daytime sleepiness. Zeman A, Britton T, Douglas N, Hansen A, Hicks J, Howard R, Meredith A, Smith I, Stores G, Wilson S, Zaiwalla Z. BMJ. 2004;329(7468):724.

³ The neurobiology, diagnosis, and treatment of narcolepsy. Scammell TE. Ann Neurol. 2003;53(2):154.

recommended in labeling. When used with other central nervous system depressants, however, the risk of adverse outcomes including respiratory depression, hypotension, profound sedation, syncope, and death increases. For this reason, the use of Xywav with alcohol and sedative-hypnotics is contraindicated.

Xyrem, which is a Schedule III controlled substance, is also associated with the risks of abuse and misuse. GHB, the active ingredient of Xyrem and of Xywav, is a Schedule I controlled substance. Abuse of GHB either alone or in combination with other CNS depressants is associated with adverse reactions including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with amnesia, particularly when combined with alcohol, has proven to be dangerous for voluntary and involuntary users (e.g., assault victims).

Misuse and inappropriate prescribing of Xyrem itself have also been demonstrated to occur, which has the potential to cause serious outcomes primarily related to the risks of central nervous system and respiratory depression.

F. Xywav is not a new molecular entity.

The elements of the REMS will be: elements to assure safe use (including that healthcare providers who prescribe Xywav are specially certified, that Xywav will be dispensed only by a pharmacy that is specially certified, and that Xywav will be dispensed and shipped only to patients who are enrolled in the Xywav REMS Program with documentation of safe use conditions), an implementation system, and a timetable for submission of assessments of the REMS.

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/s/

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type/Numbers NDA 021196
NDA 212690

PDUFA Goal Date July 21, 2020

OSE RCM # 2020-124

Reviewer Names Yasmeen Abou-Sayed, PharmD
Shelly Harris, ScD, MPH
Joan Blair, RN, M.P.H

Acting Team Leader Jacqueline Sheppard, PharmD

Division Director Cynthia LaCivita, PharmD

Review Completion Date July 17, 2020

Subject Evaluation of REMS submission

Established Name sodium oxybate (Xyrem); calcium, magnesium, potassium, and sodium oxybates (Xywav)

Trade Name Xyrem (021196), Xywav (212690)

Name of Applicant Jazz Pharmaceuticals, Inc.

Therapeutic Class Central Nervous System (CNS) depressant

Formulation 0.5 g/ml sodium oxybate (Xyrem); 0.5 g/mL total salts (equivalent to 0.413 g/ml of oxybate) oral solution (Xywav)

Dosing Regimen For Adult Patients:

- Initiate dosage at 4.5 grams (g) per night orally, divide into two doses
- 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 g to 9 g per night orally

For Pediatric Patients:

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	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

Introduction

The following comments and attached redlined appended materials are based upon the Agency's review of the proposed risk evaluation and mitigation strategy (REMS) for Xywav (calcium, magnesium, potassium, and sodium oxybates) submitted by Jazz Pharmaceuticals, Inc (Jazz) on January 21, 2020, and amended on July 7, 2020, July 13, 2020, and July 16, 2020, and the proposed REMS modification for Xyrem submitted by Jazz on July 16, 2020. Jazz submitted a New Drug Application (NDA) 212690 under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, for Xywav with the proposed indication for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. The reference listed drug Xyrem (sodium oxybate) is approved with a REMS with elements to assure safe use (ETASU) to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing misuse, abuse, and diversion of Xyrem. The Xyrem REMS is being modified under a prior approval supplement (PAS) 34 to NDA 021196 to align with the proposed REMS submitted to Xywav NDA 212690. The applicant's proposed REMS consists of ETASU, an implementation system, and a timetable for submission of assessments to ensure the benefits of Xywav outweigh the risks.

To facilitate further review, we are asking the Applicant to revise the REMS proposal and modification based on the following comments and redlined materials and submit the revised REMS materials to the application by 9 am EST, July 20, 2020. All content in the materials must align with the final REMS Document and final labels - and include content that is consistent across all REMS materials and website.

1.1 REGULATORY HISTORY

The following is a summary of the regulatory history for Xywav NDA 212690 and Xyrem NDA 021196 relevant to this review:

- 7/16/2020: The Agency provided feedback on the Applicant's 7/16/2020 submission to NDA 212690, including revisions to the REMS document, an updated REMS Assessment Plan, and request for further REMS Website Screenshots revisions
- 7/16/2020: The Applicant submitted a REMS amendment to NDA 212690 consisting of a full REMS Document, REMS supporting document, and appended REMS Materials, and a corresponding REMS modification under PAS-34 to NDA 021196 to align the Xyrem REMS with the Xywav REMS proposal

2 Comments for the Applicant

The Agency has reviewed the proposed Xywav and Xyrem REMS submitted on July 16, 2020 to NDAs 021196 and 212690 and has the following comments. The review of materials is still on-going and there may be need for further revisions.

2.1 Question for Jazz

Provide a date on which you intend to commence commercial marketing of Xywav.

2.2 REMS Supporting Document

The Agency has provided revisions to your proposed edits to the REMS Assessment Plan within the REMS supporting document – see the attached redlined document.

2.3 REMS Materials

2.3.1 General

Editorial revisions have been made to the following materials, see attached redline documents for detail:

- *Pharmacy Knowledge Assessment: Module A*
- *Patient Enrollment Form*

These comments apply to the materials below:

- *Xyrem Patient Quick Start Guide*
- *Xywav Patient Quick Start Guide*
- *Xyrem Brochure for Pediatric Patients and their Caregivers*
- *Xywav Brochure for Pediatric Patients and their Caregivers*
- *Prescriber Brochure*
- *Certified Pharmacy Training Program*

Amend the text referencing the ‘Takeback Program’ in the REMS materials to eliminate language related to (b) (4) as it is promotional in nature.

Remove language comparing the (b) (4) of Xyrem and Xywav from the REMS materials, to align with the Prescribing Information for both products.

See attached redlined documents for detail.

2.3.2 Prescriber Brochure

On pages 8 and 9 of the Prescriber Brochure, provide your rationale for changing the mode of electronic prescribing of Xyrem and Xywav, from using approved software, to direct submission via the REMS website. See attached redlined document.

Resubmission Instructions:

Provide responses to the question posed above, and submit the full revised REMS, including the REMS Document, REMS supporting document, and all appended REMS materials to your application by 9 am

EST, July 20, 2020. All content in the materials must align with the final REMS Document and final label - and include content that is consistent across all the REMS materials and website.

Accept the track changes with which you agree in the MS Word newly redlined documents and only indicate any new ones you propose as redlined changes in your next submission. Ensure that all MS Word versions include a setting for which the author of comments and revisions can be identified (not anonymous).

The next submission to the Gateway should include Clean MS Word, Tracked MS Word, and pdf formatted versions of the full Xywav and Xyrem REMS, including the REMS Document, REMS supporting document, and all appended REMS materials. Ensure that all word documents align with the final PDF versions submitted.

3 Appendix

Pharmacy Knowledge Assessment: Module A

Patient Enrollment Form

Xyrem Patient Quick Start Guide

Xywav Patient Quick Start Guide

Xyrem Brochure for Pediatric Patients and their Caregivers

Xywav Brochure for Pediatric Patients and their Caregivers

Prescriber Brochure

Certified Pharmacy Training Program

REMS Assessment Plan

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	212690
PDUFA Goal Date	July 21, 2020
OSE RCM #	2020-124
Reviewer Names	Yasmeen Abou-Sayed, PharmD Shelly Harris, ScD, MPH Joan Blair, RN, M.P.H
Acting Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	July 15, 2020
Subject	Evaluation of REMS submission
Established Name	calcium, magnesium, potassium, and sodium oxybates
Trade Name	Xywav
Name of Applicant	Jazz Pharmaceuticals, Inc.
Therapeutic Class	Central Nervous System (CNS) depressant
Formulation	0.5 g/mL total salts (equivalent to 0.413 g/ml of oxybate) oral solution
Dosing Regimen	For Adult Patients: - Initiate dosage at 4.5 grams (g) per night orally, divide into two doses - 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 g to 9 g per night orally

For Pediatric Patients:

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	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
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Introduction

The following comments and attached redlined appended materials are based upon the Agency's review of the proposed risk evaluation and mitigation strategy (REMS) for Xywav (calcium, magnesium, potassium, and sodium oxybates) submitted by Jazz Pharmaceuticals, Inc (Jazz) on January 21, 2020, and amended on July 7, 2020 and July 13, 2020. Jazz submitted a New Drug Application (NDA) 212690 under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, for Xywav with the proposed indication for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. The reference listed drug Xyrem (sodium oxybate) is approved with a REMS with elements to assure safe use (ETASU) to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing misuse, abuse, and diversion of Xyrem. The applicant's proposed REMS consists of ETASU, an implementation system, and a timetable for submission of assessments to ensure the benefits of Xywav outweigh the risks.

To facilitate further review, we are asking the Applicant to revise the REMS proposal based on the following comments and redlined materials and submit the revised REMS materials to the application by July 16, 2020. All content in the materials must align with the final REMS Document and final label - and include content that is consistent across all REMS materials and website.

1.1 REGULATORY HISTORY

The following is a summary of the regulatory history for Xywav NDA 212690 relevant to this review:

- 7/9/2020: The Agency provided feedback on the Applicant's 7/7/2020 submission, including revisions to the REMS document, an updated REMS Assessment Plan, and request for further REMS Website Screenshots revisions.
- 7/13/2020: The Applicant submitted a REMS amendment consisting of a redlined REMS Document, REMS Assessment Plan, and *REMS Website Screenshots*.

2 Comments for the Applicant

The Agency has reviewed the proposed Xywav and Xyrem REMS document, REMS assessment plan, and Website screenshots (including pop-up and FAQ's) submitted on July 13, 2020 and has the following comments. The review of materials is still on-going and there may be need for further revisions.

2.1 REMS DOCUMENT

The proposed edits to the REMS Document are acceptable.

2.2 REMS ASSESSMENT PLAN

The Agency has provided revisions to your proposed edits to the REMS Assessment Plan – see the attached redlined document.

2.3 XYWAV AND XYREM REMS WEBSITE

2.3.1 Website Screenshots

-  (b) (4)
- Page 6 – Under the Patient Enrollment graphic, replace the  (b) (4) with the correctly named *Patient Enrollment Form*.
- Page 10 – The Agency would like to clarify if the links to the *Prescriber Enrollment Form*, *Patient Enrollment Form*, and *Prescription Forms* are fillable PDF versions of the correlating REMS materials under review, which are then meant to be electronically signed (via DocuSign as referenced within the *Website Screenshots*) and submitted to the REMS.

2.3.1.1 FAQ's

The Agency finds the content of the FAQ's is acceptable.

2.3.1.2 Pop-up Window

Insert a hyphen between 'user' and 'friendly'. The Agency finds the remaining content of the pop-up window acceptable.

Resubmission Instructions:

Submit the full revised REMS, including the REMS Document, REMS supporting document, and all appended REMS materials to your application by 2 pm, July 16, 2020. All content in the materials must align with the final REMS Document and final label - and include content that is consistent across all the REMS materials and website.

Accept the track changes with which you agree in the MS Word newly redlined documents and only indicate any new ones you propose as redlined changes in your next submission. Ensure that all MS Word versions include a setting for which the author of comments and revisions can be identified (not anonymous).

The next submission to the Gateway should include Clean MS Word, Tracked MS Word, and pdf formatted versions of the full Xywav and Xyrem REMS, including the REMS Document, REMS supporting document, and all appended REMS materials.

3 Appendix

REMS Website Screenshots

REMS Assessment Plan

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	212690
PDUFA Goal Date	July 21, 2020
OSE RCM #	2020-124
Reviewer Names	Yasmeen Abou-Sayed, PharmD Shelly Harris, ScD, MPH Joan Blair, RN, M.P.H
Acting Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	July 9, 2020
Subject	Evaluation of REMS submission
Established Name	calcium, magnesium, potassium, and sodium oxybates
Trade Name	Xywav
Name of Applicant	Jazz Pharmaceuticals, Inc.
Therapeutic Class	Central Nervous System (CNS) depressant
Formulation	0.5 g/mL total salts (equivalent to 0.413 g/ml of oxybate) oral solution
Dosing Regimen	For Adult Patients: • Initiate dosage at 4.5 grams (g) per night orally, divide into two doses • 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 g to 9 g per night orally

For Pediatric Patients:

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	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
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Introduction

The following comments and attached redlined appended materials are based upon the Agency's review of the proposed risk evaluation and mitigation strategy (REMS) for Xywav (calcium, magnesium, potassium, and sodium oxybates) submitted by Jazz Pharmaceuticals, Inc (Jazz) on January 21, 2020, and amended on July 7, 2020. Jazz Pharmaceuticals, Inc. (Jazz) submitted a New Drug Application (NDA) 212690 under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, for Xywav with the proposed indication for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. The reference listed drug Xyrem (sodium oxybate) is approved with a REMS with elements to assure safe use (ETASU) to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing misuse, abuse, and diversion of Xyrem. The applicant's proposed REMS consists of ETASU, an implementation system, and a timetable for submission of assessments to ensure the benefits of Xywav outweigh the risks.

To facilitate further review, we are asking the Applicant to revise the REMS proposal based on the following comments and redlined materials and submit the revised REMS materials to the application by July 13, 2020. All content in the materials must align with the final REMS Document and final label - and include content that is consistent across all REMS materials and website.

1.1 REGULATORY HISTORY

The following is a summary of the regulatory history for Xywav NDA 212690 relevant to this review:

- 6/30/2020: The Agency issued interim comments to the Applicant providing comments and redlined materials on the REMS supporting document and appended materials.
- 7/2/2020: The Agency issued interim comments to the Applicant providing edits and a redlined version of the REMS Document.
- 7/6/2020: The Applicant sent in two email communications to clarify Agency comments from the 6/30/2020 communication regarding the placement of product names on joint and single product materials, clarification of the Agency comment on the *Xyrem and Xywav REMS Prescriber Brochure*, and to request guidance on submitting only a portion of the amended REMS materials due to ongoing labeling negotiations.
- 7/6/2020: The Agency provided feedback on the Applicant's email communications from 7/6/2020, clarifying comments on the placement of product names on joint and single product materials, the *Xyrem and Xywav REMS Prescriber Brochure*, and providing feedback that the Applicant should submit the REMS Document, REMS supporting document, and REMS Website screenshots only in the forthcoming REMS amendment.
- 7/7/2020: The Applicant submitted a REMS amendment consisting of a redlined REMS document, REMS supporting document, and REMS Website screenshots.

2 Comments for the Applicant

The Agency has reviewed the proposed Xywav and Xyrem REMS document, supporting document, and Website screenshots submitted on July 7, 2020 and has made comments and revisions to the clean versions of the materials. The review of materials is still on-going and there may be need for further revisions.

2.1 REMS DOCUMENT

The Agency made revisions to correct grammatical errors in the REMS document. We also request clarification on the difference between the training and certification requirements listed for pharmacists – see the redlined REMS Document for further detail.

2.2 XYWAV AND XYREM REMS WEBSITE

Submit revised website screenshots that include the following:

- Additional screenshots that show all aspects of the functionality of online enrollment for both patients and prescribers. This includes the online versions of the patient enrollment form and the prescriber enrollment forms, including all necessary fields, plus any text shown on the website screens to direct patients and prescribers on how to enroll online and their next steps in doing so. The Agency needs to ensure website functionality aligns with the operational aspects of the REMS.
- Remove all references to the (b) (4), as this is not a REMS material and this content is included in the PI.
- Remove the word (b) (4) before Prescribing Information to align with updated labeling guidelines.
- Remove (b) (4) on the first page of the website and content related to the REMS goal on the last screenshot page. These are non-REMS items and are not necessary on a REMS website.
- Submit an MS Word version of the website FAQs for the Agency's review.
- Consider adding a pop-up window that explains the new Xywav and Xyrem REMS in light of the previous Xyrem REMS. This pop-up window should also be included on the Xyrem REMS website as well, so stakeholders are directed to the new Xywav and Xyrem REMS website.

2.3 REMS SUPPORTING DOCUMENT

Revisions have been made to the REMS Assessment Plan and are detailed in the attached redlined document. The assessment plan has been revised to:

1. Align with the 2019 Draft Guidance for Industry - *REMS Assessment: Planning and Reporting*
2. To add metrics to clarify existing metrics in the current Xyrem REMS (in the areas of Program Implementation and Operations, Program Compliance, Safe Use, and Health Outcomes)
3. To add metrics related to the transition to a Shared REMS with Xywav and Xyrem

Substantive changes/additions are underlined, see Appendix.

Resubmission Instructions:

Submit the following revised REMS materials to your application by COB, July 13, 2020. All content in the materials must align with the final REMS Document and final label - and include content that is consistent across all the REMS materials and website.

Accept the track changes with which you agree in the MS Word newly redlined documents and only indicate any new ones you propose as redlined changes in your next submission. Ensure that all MS Word versions include a setting for which the author of comments and revisions can be identified (not anonymous).

The next submission to the Gateway should include Clean MS Word, Tracked MS Word, and pdf formatted versions of the following 3 documents:

- REMS Document
- REMS Assessment Plan
- *Xywav and Xyrem REMS Website Screenshots*

3 Appendix

Xywav and Xyrem REMS Document

Xywav and Xyrem REMS Assessment Plan

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	212690
PDUFA Goal Date	July 21, 2020
OSE RCM #	2020-124
Reviewer Names	Yasmeen Abou-Sayed, PharmD Joan Blair, RN, M.P.H
Acting Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	June 30, 2020
Subject	Evaluation of REMS submission
Established Name	calcium, magnesium, potassium, and sodium oxybates
Trade Name	Xywav
Name of Applicant	Jazz Pharmaceuticals, Inc.
Therapeutic Class	Central Nervous System (CNS) depressant
Formulation	0.5 g/mL total salts (equivalent to 0.413 g/ml of oxybate) oral solution
Dosing Regimen	For Adult Patients: - Initiate dosage at 4.5 grams (g) per night orally, divide into two doses - 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 g to 9 g per night orally

For Pediatric Patients:

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	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

Introduction

The following comments and attached redlined appended materials are based upon the Agency's review of the proposed risk evaluation and mitigation strategy (REMS) for Xywav (calcium, magnesium, potassium, and sodium oxybates) submitted by Jazz Pharmaceuticals, Inc (Jazz) on January 21, 2020. Jazz Pharmaceuticals, Inc. (Jazz) submitted a New Drug Application (NDA) 212690 under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, for Xywav with the proposed indication for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy. The reference listed drug Xyrem (sodium oxybate) is approved with a REMS with elements to assure safe use (ETASU) to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing misuse, abuse, and diversion of Xyrem. The applicant's proposed REMS consists of ETASU, an implementation system, and a timetable for submission of assessments to ensure the benefits of Xywav outweigh the risks.

To facilitate further review, we are asking the Applicant to revise the REMS proposal based on the following comments and redlined materials and submit the revised REMS materials to the application by July 8, 2020. All content in the materials must align with the final REMS Document and final label - and include content that is consistent across all REMS materials and website.

1.1 REGULATORY HISTORY

The following is a summary of the regulatory history for Xywav NDA 212690 relevant to this review:

- 10/2/2019: Applicant was informed at pre-NDA meeting that a REMS for Xywav was needed to ensure the benefits of Xywav outweigh the risks and the REMS for Xywav should be incorporated into the currently approved Xyrem REMS and included in the initial NDA submission.
- 1/21/2020: NDA 212690 submission for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy received
- 6/19/2020: Information Request (IR) to clarify the Applicant's rationale for the creation of new Xywav specific REMS materials, and the addition of the option for patients to dispose of unused or expired drug via the pharmacy.
- 6/23/2020: Jazz submitted a response to the Agency's IR, providing their rationale for the creation of new Xywav specific REMS materials, and an explanation of the proposed option for patients to contact the certified pharmacy to dispose of unused or expired drug.

2 Comments for the Applicant

The Agency has reviewed the proposed Xywav and Xyrem REMS materials submitted on January 21, 2020 and has made comments and revisions to the clean MS Word versions of the materials in addition to the general comments listed below. The review of materials is still on-going and there may be need for further revisions.

2.1 GENERAL COMMENTS

1. The Division of Medication Error Prevention and Analysis (DMEPA) found the proprietary name 'Xywav' to be conditionally acceptable. Update all references to 'TRADENAME' throughout the REMS document, all appended materials, and supporting document to 'Xywav'.
2. Include both the Xyrem and the Xywav product logos on all REMS materials that discuss both products. Include the word "REMS" in the titles of all REMS materials, both on the materials themselves and any listing of the specific titles of those materials. Deleting the word "(b) (4)" in each title is acceptable. For example, the patient enrollment form should be referenced as *Xyrem and Xywav REMS Patient Enrollment Form*.
3. Align all materials with the final labeling for Xyrem and Xywav.
4. Include the role of the reverse distributor in the proposed "Takeback" program for patient return of unused or expired drug throughout the applicable materials. These include all Pharmacy Specific Materials and Brochures for Patients and Providers.

2.2 REMS DOCUMENT

The REMS Document continues to go through Agency review and clearance. Comments will be provided in the near future. .

2.3 REMS APPENDED MATERIALS

Revisions to the REMS appended materials are needed. All REMS materials must align with the final labeling and REMS document and may continue to need further revisions. We have provided edits in tracked changes as well as additional comments that should be addressed in your materials. See attached redlined documents and additional comments below.

Xyrem and Xywav REMS Patient Enrollment Form

As separate materials have been proposed for Xyrem and Xywav Patient and Caregiver Brochures, add a statement to the Patient Enrollment form clarifying that the single combined form is to be used when enrolling patients regardless of product choice.

Xyrem and Xywav REMS Prescriber Brochure

The removal of the generic name of Xyrem in the introduction to the Prescriber Brochure is not acceptable. Retain the established names of both products in the Prescriber Brochure.

Xywav REMS Brochure for Pediatric Patients and Their Caregivers

Add a Figure 4 to page 15, corresponding with Figure 4 in the Xyrem version of this brochure. The content of the figure should reflect the dosing considerations for Xywav but convey the same educational content for the pediatric patient and their caregiver.

Xywav and Xyrem REMS Website

The screenshots submitted on January 21, 2020, do not reflect the addition of Xywav to the Xyrem REMS. Submit revised website screenshots that include all REMS materials and their new titles as well as align content with revisions in the REMS materials, REMS Document, and the final label. The submitted website screenshots should show all content and functionality of the REMS website, including prescriber and patient enrollment. The REMS website should not be the sole source of REMS materials.

Provide a link to the Xywav and Xyrem REMS on both product websites. The Xywav and Xyrem REMS website URL should link directly to REMS-only information and materials, other than the PI and Medication Guide.

2.4 REMS SUPPORTING DOCUMENT

Provide detail describing the operational aspects of the proposed 'Takeback' program for patient return of unused or expired drug within the REMS Supporting Document (SD). Comments on the SD and Assessment Plan will be provided in the near future.

Resubmission Instructions:

Submit the following revised REMS materials to your application by COB, July 8, 2020. All content in the materials must align with the final REMS Document and final label - and include content that is consistent across all the REMS materials and website.

Accept the track changes with which you agree in the MS Word newly redlined documents and only indicate any new ones you propose as redlined changes in your next submission. Ensure that all MS Word versions include a setting for which the author of comments and revisions can be identified (not anonymous).

The next submission to the Gateway should include Clean MS Word, Tracked MS Word, and pdf formatted versions of the following 16 documents:

- ***REMS Document***
- ***REMS Supporting Document***
- ***Xyrem and Xywav REMS Pharmacy Knowledge Assessment - Module A***
- ***Xyrem and Xywav REMS Pharmacy Knowledge Assessment - Module B***
- ***Xyrem and Xywav REMS Patient Enrollment Form***
- ***Xyrem and Xywav REMS Certified Pharmacy Training***
- ***Xyrem and Xywav REMS Patient Counseling Checklist***
- ***Xyrem and Xywav REMS Prescriber Brochure***
- ***Xyrem and Xywav REMS Prescriber Enrollment Form***
- ***Xyrem and Xywav REMS Risk Management Report***
- ***Xyrem and Xywav Website Screenshots***
- ***Xywav REMS Prescription Form***
- ***Xyrem REMS Prescription Form***
- ***Xywav REMS Brochure for Pediatric Patients and Their Caregivers***
- ***Xyrem REMS Brochure for Pediatric Patients and Their Caregivers***
- ***Xyrem REMS Patient Quick Start Guide***
- ***Xywav REMS Patient Quick Start Guide***

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