CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021196Orig1s013

Trade Name:	Xyrem
Generic or Established:	Sodium Oxybate
Sponsor:	Jazz Pharmaceuticals
Approval Date:	December 17, 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

021196Orig1s013

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021196Orig1s013

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021196/S-013

SUPPLEMENT APPROVAL

Jazz Pharmaceuticals
Attention: Jennifer Ekelund
Executive Director, Regulatory Affairs
3481 Porter Drive
Palo Alto, CA 94304

Dear Ms. Ekelund:

We refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xyrem (Sodium Oxybate) 500 mg/ml oral solution.

Please refer to your Supplemental New Drug Application (sNDA) dated August 13, 2007, received August 15, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xyrem (Sodium Oxybate) 500 mg/ml oral solution.

We acknowledge receipt of your amendments dated February 3, 2011, April 24, 2012, and October 3, 2012.

This "Prior Approval" supplemental new drug application provides for compliance with the final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products."

We have completed our review of this supplemental application, as amended and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Medication Guide

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
12/17/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XYREM safely and effectively. See full prescribing information for XYREM.

Xyrem® (sodium oxybate) oral solution CIII
Initial U.S. Approval: 2002

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and MISUSE AND ABUSE.

See full prescribing information for complete boxed warning.

- **Respiratory depression can occur with Xyrem use (5.4)**
- **Xyrem is a Schedule III controlled substance and is the sodium salt of gamma hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma and death (5.2, 9.2)**
- **Because of the risks of CNS depression, abuse, and misuse, Xyrem is available only through a restricted distribution program called the Xyrem Success Program® using a centralized pharmacy. Prescribers and patients must enroll in the program. (5.3)**

----------RECENT MAJOR CHANGES----------

Contraindications, concomitant use with alcohol (4) ----------2/2012

----------INDICATIONS AND USAGE----------

Xyrem is a central nervous system depressant indicated for the treatment of:

- Cataplexy in narcolepsy (1.1).
- Excessive daytime sleepiness (EDS) in narcolepsy (1.2).

Xyrem may only be dispensed to patients enrolled in the Xyrem Success Program (1).

----------DOSAGE AND ADMINISTRATION----------

- Initiate dose at 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 (2.1)
- 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) (2.1).
- Recommended dose range: 6 g to 9 g per night orally (2.1).

Total Nightly Dose	Take at Bedtime	Take 2.5 to 4 Hours Later
4.5 g per night	2.25 g	2.25 g
6 g per night	3 g	3 g
7.5 g per night	3.75 g	3.75 g
9 g per night	4.5 g	4.5 g

- Take each dose while in bed and lie down after dosing (2.2).
- Allow 2 hours after eating before dosing (2.2).
- Prepare both doses prior to bedtime; dilute each dose with approximately ¼ cup of water in pharmacy-provided vials (2.2).
- Patients with Hepatic Impairment: starting dose is 2.25 g per night administered orally in two equal, divided doses of approximately 1.13 g at bedtime and approximately 1.13 g taken 2.5 to 4 hours later (2.3).

----------DOSAGE FORMS AND STRENGTHS----------

Oral solution, 0.5 g per mL (3)

----------CONTRAINDICATIONS----------

- Succinic semialdehyde dehydrogenase deficiency (4).
- In combination with sedative hypnotics or alcohol (4).

----------WARNINGS AND PRECAUTIONS----------

- CNS depression: Use caution when considering the concurrent use of Xyrem with other CNS depressants (5.1).
- Caution patients against hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after first initiating treatment until certain that Xyrem does not affect them adversely (5.1).
- Depression and suicidality: Monitor patients for emergent or increased depression and suicidality (5.4).
- Confusion/Anxiety: Monitor for impaired motor/cognitive function (5.5).
- Parasomnias: evaluate episodes of sleepwalking (5.7).
- High sodium content in Xyrem: Monitor patients with heart failure, hypertension, or impaired renal function (5.7).

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥ 5% and at least twice the incidence with placebo) were nausea, dizziness, vomiting, somnolence, enuresis, and tremor (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Jazz Pharmaceuticals at 1-800-520-5568, or FDA at 1-800-FDA-1088 or www.fda.gov/Medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm (8 1).
- Geriatric patients: Monitor for impaired motor and/or cognitive function when taking Xyrem (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and MISUSE AND ABUSE.

Xyrem (sodium oxybate) is a CNS depressant. In clinical trials at recommended doses obtundation and clinically significant respiratory depression occurred in Xyrem-treated patients. Almost all of the patients who received Xyrem during clinical trials in narcolepsy were receiving central nervous system stimulants [*see Warnings and Precautions (5.1)*].

Xyrem® (sodium oxybate) is the sodium salt of gamma hydroxybutyrate (GHB). Abuse of GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death [*see Warnings and Precautions (5.2)*].

Because of the risks of CNS depression, abuse, and misuse, Xyrem is available only through a restricted distribution program called the Xyrem Success Program®, using a centralized pharmacy. Prescribers and patients must enroll in the program. For further information go to www.XYREM.com or call 1-866-XYREM88® (1-866-997-3688). *[see Warnings and Precautions (5.3)].*

1 INDICATIONS AND USAGE

Limitations of Use

Xyrem may only be dispensed to patients enrolled in the Xyrem Success Program *[see Warnings and Precautions (5.3)]*.

1.1 Cataplexy in Narcolepsy

Xyrem (sodium oxybate) oral solution is indicated for the treatment of cataplexy in narcolepsy *[see Clinical Studies (14.1)]*.

1.2 Excessive Daytime Sleepiness in Narcolepsy

Xyrem (sodium oxybate) oral solution is indicated for the treatment of excessive daytime sleepiness (EDS) in narcolepsy *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe Xyrem must enroll in the Xyrem Success Program and must comply with the requirements to ensure safe use of Xyrem *[see Warnings and Precautions (5.3)]*.

2.1 Dosing Information

The recommended starting dose 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 (see Table 1). Increase the dose 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 g to 9 g per night orally. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

Table 1: Xyrem Dose Regimen (g = grams)

If A Patient's Total Nightly Dose is:	Take at Bedtime:	Take 2.5 to 4 Hours Later:
4.5 g per night	2.25 g	2.25 g
6 g per night	3 g	3 g
7.5 g per night	3.75 g	3.75 g
9 g per night	4.5 g	4.5 g

2.2 Important Administration Instructions

Take the first dose of Xyrem at least 2 hours after eating because food significantly reduces the bioavailability of sodium oxybate.

Prepare both doses of Xyrem prior to bedtime. Prior to ingestion, each dose of Xyrem should be diluted with approximately ¼ cup (approximately 60 mL) of water in the empty pharmacy vials provided. Patients should take Xyrem while in bed and lie down immediately after dosing as Xyrem may cause them to fall asleep abruptly without first feeling drowsy. Patients will often fall asleep within 5 minutes of taking Xyrem, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night. Rarely, patients may take up to 2 hours to fall asleep. Therefore, patients should remain in bed following ingestion of the first dose, and should not take the second dose until 2.5 to 4 hours later. Patients may need to set an alarm to awaken for the second dose.

2.3 Dose Modification in Patients with Hepatic Impairment

The recommended starting dose in patients with hepatic impairment is 2.25 g per night administered orally in two equal, divided doses: approximately 1.13 g at bedtime and approximately 1.13 g taken 2.5 to 4 hours later *[see Use in Specific Populations (8.6); Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Xyrem is a clear to slightly opalescent oral solution, in a concentration of 0.5 g per mL.

4 CONTRAINDICATIONS

Xyrem is contraindicated in patients being treated with sedative hypnotic agents.

Patients should not drink alcohol when using Xyrem.

Xyrem is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency. This is a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.

5 WARNINGS AND PRECAUTIONS

5.1 Central Nervous System Depression

Xyrem is a central nervous system (CNS) depressant. Alcohol and sedative hypnotics are contraindicated in patients who are using Xyrem. The concurrent use of Xyrem with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of these CNS depressants in combination with Xyrem is required, dose reduction or discontinuation of one or more CNS depressants (including Xyrem) should be considered. In addition, if short-term use of an opioid (e.g. post- or perioperative) is required, interruption of treatment with Xyrem should be considered.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that Xyrem does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking the second nightly dose of Xyrem. Patients should be queried about CNS depression-related events upon initiation of Xyrem therapy and periodically thereafter [*See Warnings and Precautions (5.3)*].

5.2 Abuse and Misuse

Xyrem is a Schedule III controlled substance. The active ingredient of Xyrem, sodium oxybate or gamma-hydroxybutyrate (GHB), is a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with the amnestic features of Xyrem, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim). Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g. increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy) [*see Warnings and Precautions (5.3); Drug Abuse and Dependence (9.2)*].

5.3 Xyrem Success Program

Because of the risks of central nervous system depression and abuse/misuse, Xyrem is available only through a restricted distribution program called the Xyrem Success Program.

Required components of the Xyrem Success Program are:

- Use of a centralized pharmacy
- Healthcare Providers who prescribe Xyrem must complete the enrollment forms and comply with the requirements.
- To receive Xyrem, patients must understand the risks and benefits of Xyrem.

Further information is available at www.XYREM.com or 1-866-XYREM88® (1-866-997-3688).

5.4 Respiratory Depression and Sleep-Disordered Breathing

Xyrem may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported *[see Overdosage (10)]*.

In a study assessing the respiratory-depressant effects of Xyrem at doses up to 9 g per night in 21 patients with narcolepsy, no dose-related changes in oxygen saturation were demonstrated

in the group as a whole. One of the four patients with preexisting, moderate-to-severe sleep apnea had significant worsening of the apnea/hypopnea index during treatment.

In a study assessing the effects of Xyrem 9 g per night in 50 patients with obstructive sleep apnea, Xyrem did not increase the severity of sleep-disordered breathing and did not adversely affect the average duration and severity of oxygen desaturation overall. However, there was a significant increase in the number of central apneas in patients taking Xyrem, and clinically significant oxygen desaturation ($\leq$ 55%) was measured in three patients (6%) after Xyrem administration, with one patient withdrawing from the study and two continuing after single brief instances of desaturation. Prescribers should be aware that increased central apneas and clinically relevant desaturation events have been observed with Xyrem administration.

In clinical trials in 128 patients with narcolepsy, two subjects had profound CNS depression, which resolved after supportive respiratory intervention. Two other patients discontinued sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea. In two controlled trials assessing polysomnographic (PSG) measures in patients with narcolepsy, 40 of 477 patients were included with a baseline apnea/hypopnea index of 16 to 67 events per hour, indicative of mild to severe sleep-disordered breathing. None of the 40 patients had a clinically significant worsening of respiratory function as measured by apnea/hypopnea index and pulse oximetry at doses of 4.5 g to 9 g per night.

Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients and in postmenopausal women not on hormone replacement therapy as well as among patients with narcolepsy.

5.5 Depression and Suicidality

In clinical trials in patients with narcolepsy (n=781), there were two suicides and two attempted suicides in Xyrem-treated patients, including three patients with a previous history of depressive psychiatric disorder. Of the two suicides, one patient used Xyrem in conjunction with other drugs. Xyrem was not involved in the second suicide. Adverse reactions of depression were reported by 7% of 781 Xyrem-treated patients, with four patients (< 1%) discontinuing because of depression. In most cases, no change in Xyrem treatment was required.

In a controlled trial, with patients randomized to fixed doses of 3 g, 6 g, or 9 g per night Xyrem or placebo, there was a single event of depression at the 3 g per night dose. In another controlled trial, with patients titrated from an initial 4.5 g per night starting dose, the incidences of depression were 1 (1.7%), 1 (1.5%), 2 (3.2%), and 2 (3.6%) for the placebo, 4.5 g, 6 g, and 9 g per night doses, respectively.

The emergence of depression in patients treated with Xyrem requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking Xyrem.

5.6 Other Behavioral or Psychiatric Adverse Reactions

During clinical trials in narcolepsy, 3% of 781 patients treated with Xyrem experienced confusion, with incidence generally increasing with dose.

Less than 1% of patients discontinued the drug because of confusion. Confusion was reported at all recommended doses from 6 g to 9 g per night. In a controlled trial where patients were randomized to fixed total daily doses of 3 g, 6 g, or 9 g per night or placebo, a dose-response relationship for confusion was demonstrated, with 17% of patients at 9 g per night experiencing confusion. In all cases in that controlled trial, the confusion resolved soon after termination of treatment. In Trial 3 where sodium oxybate was titrated from an initial 4.5 g per night dose, there was a single event of confusion in one patient at the 9 g per night dose. In the majority of

cases in all clinical trials in narcolepsy, confusion resolved either soon after termination of dosing or with continued treatment. However, patients treated with Xyrem who become confused should be evaluated fully, and appropriate intervention considered on an individual basis.

Anxiety occurred in 5.8% of the 874 patients receiving Xyrem in clinical trials in another population. The emergence of or increase in anxiety in patients taking Xyrem should be carefully monitored.

Other neuropsychiatric reactions reported in Xyrem clinical trials included hallucinations, paranoia, psychosis, and agitation. The emergence of thought disorders and/or behavior abnormalities requires careful and immediate evaluation.

5.7 Parasomnias

Sleepwalking, defined as confused behavior occurring at night and at times associated with wandering, was reported in 6% of 781 patients with narcolepsy treated with Xyrem in controlled and long-term open-label studies, with < 1% of patients discontinuing due to sleepwalking. Rates of sleepwalking were similar for patients taking placebo and patients taking Xyrem in controlled trials It is unclear if some or all of the reported sleepwalking episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Five instances of significant injury or potential injury were associated with sleepwalking during a clinical trial of Xyrem in patients with narcolepsy.

Parasomnias including sleepwalking have been reported in postmarketing experience with Xyrem. Therefore, episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

5.8 Use in Patients Sensitive to High Sodium Intake

Xyrem has a high salt content. In patients sensitive to salt intake (e.g., those with heart failure, hypertension, or renal impairment) consider the amount of daily sodium intake in each dose of Xyrem. Table 2 provides the approximate sodium content per Xyrem dose.

Table 2

Approximate Sodium Content per Total Nightly Dose of Xyrem (g = grams)

Xyrem Dose	Sodium Content/Total Nightly Exposure
3 g per night	550 mg
4.5 g per night	820 mg
6 g per night	1100 mg
7.5 g per night	1400 mg
9 g per night	1640 mg

6 ADVERSE REACTIONS

The following adverse reactions appear in other sections of the labeling:

- CNS depression [*see Warnings and Precautions (5.1)*]
- Abuse and Misuse [*see Warnings and Precautions (5.2)*]

- Respiratory Depression and Sleep-disordered Breathing [*see Warnings and Precautions (5.4)*]
- Depression and Suicidality [*see Warnings and Precautions (5.5)*]
- Other Behavioral or Psychiatric Adverse Reactions [*see Warnings and Precautions (5.6)*]
- Parasomnias [*see Warnings and Precautions (5.7)*]
- Use in Patients Sensitive to High Sodium Intake [*see Warnings and Precautions (5.8)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Xyrem was studied in three placebo-controlled clinical trials (Trials N1, N3, and N4, described in Sections 14.1 and 14.2) in 611 patients with narcolepsy (398 subjects treated with Xyrem, and 213 with placebo). A total of 781 patients with narcolepsy were treated with Xyrem in controlled and uncontrolled clinical trials.

Section 6.1 and Table 3 presents adverse reactions from three pooled, controlled trials (N1, N3, N4,) in patients with narcolepsy.

Adverse Reactions Leading to Treatment Discontinuation

Of the 398 Xyrem-treated patients with narcolepsy, 10.3% of patients discontinued because of adverse reactions compared with 2.8% of patients receiving placebo. The most common adverse reaction leading to discontinuation was nausea (2.8%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.

Commonly Observed Adverse Reactions in Controlled Clinical Trials:

The most common adverse reactions (incidence ≥ 5% and twice the rate seen with placebo) in Xyrem-treated patients were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.

Adverse Reactions Occurring at an Incidence of 2% or greater:

Table 3 lists adverse reactions that occurred at a frequency of 2% or more in any treatment group for three controlled trials and were more frequent in any Xyrem treatment group than with placebo. Adverse reactions are summarized by dose at onset. Nearly all patients in these studies initiated treatment at 4.5 g per night. In patients who remained on treatment, adverse reactions tended to occur early and to diminish over time.

Table 3
Adverse Reactions Occurring in ≥2% of Patients and More Frequently with Xyrem than Placebo in Three Controlled Trials (N1, N3, N4) by Body System and Dose at Onset

System Organ Class /MedDRA Preferred Term	Placebo (n=213) %	Xyrem 4.5g (n=185) %	Xyrem 6g (n=258) %	Xyrem 9g (n=178) %
ANY ADVERSE REACTION	62	45	55	70
GASTROINTESTINAL DISORDERS				
Nausea	3	8	13	20
Vomiting	1	2	4	11
Diarrhea	2	4	3	4
Abdominal pain upper	2	3	1	2
Dry mouth	2	1	2	1
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS				
Pain	1	1	<1	3
Feeling drunk	1	0	<1	3
Edema peripheral	1	3	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Pain in extremity	1	3	1	1
Cataplexy	1	1	1	2
Muscle spasms	2	2	<1	2
NERVOUS SYSTEM DISORDERS				
Dizziness	4	9	11	15
Somnolence	4	1	3	8
Tremor	0	0	2	5
Paresthesia	1	2	1	3
Disturbance in attention	0	1	0	4
Sleep paralysis	1	0	1	3
PSYCHIATRIC DISORDERS				
Disorientation	1	1	2	3
Anxiety	1	1	1	2
Irritability	1	0	<1	3
Sleep walking	0	0	0	3
RENAL AND URINARY DISORDERS				
Enuresis	1	3	3	7
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Hyperhidrosis	0	1	1	3

Dose-Response Information

In clinical trials in narcolepsy, a dose-response relationship was observed for nausea, vomiting, paresthesia, disorientation, irritability, disturbance in attention, feeling drunk, sleepwalking, and enuresis. The incidence of all these reactions was notably higher at 9 g per night.

In controlled trials in narcolepsy, discontinuations of treatment due to adverse reactions were greater at higher doses of Xyrem.

6.2 Postmarketing Experience

The following additional adverse reactions that have a likely causal relationship to Xyrem exposure have been identified during postmarketing use of Xyrem. These adverse reactions include: arthralgia, decreased appetite, fall, fluid retention, hangover, headache, hypersensitivity, hypertension, memory impairment, panic attack, vision blurred, and weight decreased. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency.

7 DRUG INTERACTIONS

Xyrem should not be used in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of Xyrem.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Xyrem should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Oral administration of sodium oxybate to pregnant rats (150, 350, or 1,000 mg/kg/day) or rabbits (300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity. The highest doses tested in rats and rabbits were approximately 1 and 3 times, respectively, the maximum recommended human dose (MRHD) of 9 g per night on a body surface area (mg/m^2) basis.

Oral administration of sodium oxybate (150, 350, or 1,000 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and body weight gain at the highest dose tested. The no-effect dose for pre- and post-natal developmental toxicity in rats is less than the MRHD on a mg/m^2 basis.

8.2 Labor and Delivery

Xyrem has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate, newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid, but umbilical vein levels of sodium oxybate were no more than 25% of the maternal concentration. No sodium oxybate was detected in the infant's blood 30 minutes after delivery. Elimination curves of sodium oxybate between a 2-day-old infant and a 15-year-old patient were similar. Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown.

8.3 Nursing Mothers

It is not known whether sodium oxybate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Xyrem is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of Xyrem in patients with narcolepsy did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects. In controlled trials in another population, 39 (5%) of 874 patients were 65 years or older. Discontinuations of treatment due to adverse reactions were increased in the elderly compared to younger adults (20.5% v. 18.9%). Frequency of headaches was markedly increased in the elderly (38.5% v. 18.9%). The most common adverse reactions were similar in both age categories. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

The starting dose of Xyrem should be reduced by one-half in patients with liver impairment *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Xyrem is a Schedule III controlled substance under the Federal Controlled Substances Act. Non-medical use of Xyrem could lead to penalties assessed under the higher Schedule I controls.

9.2 Abuse

Xyrem (sodium oxybate), the sodium salt of GHB, produces dose-dependent central nervous system effects, including hypnotic and positive subjective reinforcing effects. The onset of effect is rapid, enhancing its potential for abuse or misuse.

The rapid onset of sedation, coupled with the amnestic features of Xyrem, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).

Illicit GHB is abused in social settings primarily by young adults. Some of the doses estimated to be abused are in a similar dosage range to that used for treatment of patients with cataplexy. GHB has some commonalties with ethanol over a limited dose range, and some cross tolerance with ethanol has been reported as well. Cases of severe dependence and craving for GHB have been reported when the drug is taken around the clock. Patterns of abuse indicative of dependence include: 1) the use of increasingly large doses, 2) increased frequency of use, and 3) continued use despite adverse consequences.

Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g. increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy). Dispose of Xyrem according to state and federal regulations. It is safe to dispose of Xyrem down the sanitary sewer.

9.3 Dependence

There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the therapeutic dose range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor,

sweating, muscle cramps, tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal, visual hallucinations, agitation, and delirium. These symptoms generally abated in 3 to 14 days. In cases of severe withdrawal, hospitalization may be required. The discontinuation effects of Xyrem have not been systematically evaluated in controlled clinical trials. In the clinical trial experience with Xyrem in narcolepsy/cataplexy patients at therapeutic doses, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time.

Tolerance

Tolerance to Xyrem has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended Xyrem dosage regimen. Clinical studies of sodium oxybate in the treatment of alcohol withdrawal suggest a potential cross-tolerance with alcohol. The safety and effectiveness of Xyrem in the treatment of alcohol withdrawal have not been established.

10 OVERDOSAGE

10.1 Human Experience

Information regarding overdose with Xyrem is derived largely from reports in the medical literature that describe symptoms and signs in individuals who have ingested GHB illicitly. In these circumstances the co-ingestion of other drugs and alcohol was common, and may have influenced the presentation and severity of clinical manifestations of overdose.

In clinical trials two cases of overdose with Xyrem were reported. In the first case, an estimated dose of 150 g, more than 15 times the maximum recommended dose, caused a patient to be unresponsive with brief periods of apnea and to be incontinent of urine and feces. This individual recovered without sequelae. In the second case, death was reported following a multiple drug overdose consisting of Xyrem and numerous other drugs.

10.2 Signs and Symptoms

Information about signs and symptoms associated with overdosage with Xyrem derives from reports of its illicit use. Patient presentation following overdose is influenced by the dose ingested, the time since ingestion, the co-ingestion of other drugs and alcohol, and the fed or fasted state. Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even when obtunded), diaphoresis, headache, and impaired psychomotor skills have been observed. No typical pupillary changes have been described to assist in diagnosis; pupillary reactivity to light is maintained. Blurred vision has been reported. An increasing depth of coma has been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported. Respiration may be unaffected or compromised in rate and depth. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact.

10.3 Recommended Treatment of Overdose

General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid-

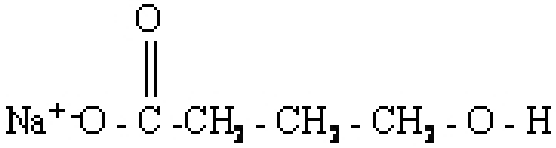
sequence induction (without the use of sedative) should be considered. Vital signs and consciousness should be closely monitored. The bradycardia reported with GHB overdose has been responsive to atropine intravenous administration. No reversal of the central depressant effects of Xyrem can be expected from naloxone or flumazenil administration. The use of hemodialysis and other forms of extracorporeal drug removal have not been studied in GHB overdose. However, due to the rapid metabolism of sodium oxybate, these measures are not warranted.

10.4 Poison Control Center

As with the management of all cases of drug overdosage, the possibility of multiple drug ingestion should be considered. The healthcare provider is encouraged to collect urine and blood samples for routine toxicologic screening, and to consult with a regional poison control center (1-800-222-1222) for current treatment recommendations.

11 DESCRIPTION

Sodium oxybate, a CNS depressant, is the active ingredient in Xyrem. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is $C_4H_7NaO_3$, and the molecular weight is 126.09 g/mole. The chemical structure is:



Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions. Each mL of Xyrem contains 0.5 g of sodium oxybate in USP Purified Water, neutralized to pH 7.5 with malic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Xyrem is a CNS depressant. The mechanism of action of Xyrem in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of gamma hydroxybutyrate, an endogenous compound and metabolite of the neurotransmitter GABA. It is hypothesized that the therapeutic effects of Xyrem on cataplexy and excessive daytime sleepiness are mediated through $GABA_B$ actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.

12.3 Pharmacokinetics

Pharmacokinetics of sodium oxybate are nonlinear and are similar following single or repeat dosing.

Absorption

Following oral administration, sodium oxybate is absorbed rapidly across the clinical dose range, with an absolute bioavailability of about 88%. The average peak plasma concentrations (C_{max}) following administration of each of the two 2.25 g doses given under fasting conditions 4 hours apart were similar. The average time to peak plasma concentration (T_{max}) ranged from 0.5 to 1.25 hours. Following oral administration, the plasma levels of sodium oxybate increased

more than dose-proportionally, with blood levels increasing 3.7-fold as total daily dose is doubled from 4.5 g to 9 g. Single doses greater than 4.5 g have not been studied. Administration of Xyrem immediately after a high-fat meal resulted in delayed absorption (average T_{max} increased from 0.75 hr to 2 hr) and a reduction in C_{max} by a mean of 59% and of systemic exposure (AUC) by 37%.

Distribution

Sodium oxybate is a hydrophilic compound with an apparent volume of distribution averaging 190 mL/kg to 384 mL/kg. At sodium oxybate concentrations ranging from 3 mcg/mL to 300 mcg/mL, less than 1% is bound to plasma proteins.

Metabolism

Animal studies indicate that metabolism is the major elimination pathway for sodium oxybate, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by beta-oxidation. The primary pathway involves a cytosolic $NADP^+$-linked enzyme, GHB dehydrogenase, that catalyzes the conversion of sodium oxybate to succinic semialdehyde, which is then biotransformed to succinic acid by the enzyme succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle where it is metabolized to carbon dioxide and water. A second mitochondrial oxidoreductase enzyme, a transhydrogenase, also catalyzes the conversion to succinic semialdehyde in the presence of α-ketoglutarate. An alternate pathway of biotransformation involves β-oxidation via 3,4-dihydroxybutyrate to carbon dioxide and water. No active metabolites have been identified.

Elimination

The clearance of sodium oxybate is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible. Sodium oxybate has an elimination half-life of 0.5 to 1 hour.

Specific Populations

Geriatric

There is limited experience with Xyrem in the elderly. Results from a pharmacokinetic study (n=20) in another studied population indicate that the pharmacokinetic characteristics of sodium oxybate are consistent among younger (age 48 to 64 years) and older (age 65 to 75 years) adults.

Pediatric

The pharmacokinetics of sodium oxybate in patients younger than 18 years of age have not been studied.

Gender

In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of sodium oxybate oral solution following a single oral dose of 4.5 g.

Race

There are insufficient data to evaluate any pharmacokinetic differences among races.

Renal Impairment

No pharmacokinetic study in patients with renal impairment has been conducted.

Hepatic Impairment

The pharmacokinetics of Xyrem in 16 cirrhotic patients, half without ascites (Child's Class A) and half with ascites (Child's Class C), were compared to the kinetics in 8 subjects with normal hepatic function after a single oral dose of 25 mg/kg. AUC values were double in the cirrhotic patients, with apparent oral clearance reduced from 9.1 mL/min/kg in healthy adults to 4.5 and 4.1 mL/min/kg in Class A and Class C patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control patients (mean $t_{1/2}$ of 59 and 32 minutes, respectively, versus 22 minutes). The starting dose of Xyrem should be reduced by one-half in patients with liver impairment *[see Dosage and Administration (2.3); Use in Specific Populations (8.6)]*.

Drug Interactions Studies

Studies *in vitro* with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A up to the concentration of 3 mM (378 mcg/mL), a level considerably higher than levels achieved with therapeutic doses.

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, and modafinil. Also, there were no pharmacokinetic interactions with the alcohol dehydrogenase inhibitor fomepizole. However, pharmacodynamic interactions with these drugs cannot be ruled out. Alteration of gastric pH with omeprazole produced no significant change in the oxybate kinetics *[see Drug Interactions (7)]*. In addition, drug interaction studies in healthy adults demonstrated no pharmacokinetic or clinically significant pharmacodynamic interactions between sodium oxybate and the SNRI duloxetine HCl.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Administration of sodium oxybate to rats at oral doses of up to 1,000 mg/kg/day for 83 (males) or 104 (females) weeks resulted in no increase in tumors. Plasma exposure (AUC) at the highest dose tested was 2 times that in humans at the maximum recommend human dose (MRHD) of 9 g per night.

The results of 2-year carcinogenicity studies in mouse and rat with gamma-butyrolactone, a compound that is metabolized to sodium oxybate *in vivo,* showed no clear evidence of carcinogenic activity. The plasma AUCs of sodium oxybate achieved at the highest doses tested in these studies were less than that in humans at the MRHD.

Mutagenesis

Sodium oxybate was negative in the *in vitro* bacterial gene mutation assay, an *in vitro* chromosomal aberration assay in mammalian cells, and in an *in vivo* rat micronucleus assay.

Impairment of Fertility

Oral administration of sodium oxybate (150, 350, or 1,000 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females through early gestation resulted in

no adverse effects on fertility. The highest dose tested is approximately equal to the MRHD on a mg/m^2 basis.

14 CLINICAL STUDIES

14.1 *Cataplexy in Narcolepsy*

The effectiveness of Xyrem in the treatment of cataplexy was established in two randomized, double-blind, placebo-controlled, multicenter, parallel-group trials (Trials N1 and N2) in patients with narcolepsy (see Table 4). In Trials N1 and N2, 85% and 80% of patients, respectively, were also being treated with CNS stimulants. The high percentages of concomitant stimulant use make it impossible to assess the efficacy and safety of Xyrem independent of stimulant use. In each trial, the treatment period was 4 weeks and the total nightly Xyrem doses ranged from 3 g to 9 g, with the total nightly dose administered as two equal doses. The first dose each night was taken at bedtime and the second dose was taken 2.5 to 4 hours later. There were no restrictions on the time between food consumption and dosing.

Trial N1 enrolled 136 narcoleptic patients with moderate to severe cataplexy (median of 21 cataplexy attacks per week) at baseline. Prior to randomization, medications with possible effects on cataplexy were withdrawn, but stimulants were continued at stable doses. Patients were randomized to receive placebo, Xyrem 3 g per night, Xyrem 6 g per night, or Xyrem 9 g per night.

Trial N2 was a randomized withdrawal trial with 55 narcoleptic patients who had been taking open-label Xyrem for 7 to 44 months prior to study entry. To be included, patients were required to have a history of at least 5 cataplexy attacks per week prior to any treatment for cataplexy. Patients were randomized to continued treatment with Xyrem at their stable dose (ranging from 3 g to 9 g per night) or to placebo for 4 weeks. Trial N2 was designed specifically to evaluate the continued efficacy of sodium oxybate after long-term use

The primary efficacy measure in Trials N1 and N2 was the frequency of cataplexy attacks.

Table 4
Median Number of Cataplexy Attacks in Trials N1 and N2

Trial/Dosage Group	Baseline	Median Change from Baseline	Comparison to Placebo (p-value)
Trial N1 (Prospective, Randomized, Parallel Group Trial)			
		(median attacks/week)	
Placebo (n=33)	20.5	-4	–
Xyrem 6 g per night (n=31)	23.0	-10	0.0451
Xyrem 9 g per night (n=33)	23.5	-16	0.0016
Trial N2 (Randomized Withdrawal Trial)			
		(median attacks/2 weeks)	
Placebo (n=29)	4.0	21	–
Xyrem (n=26)	1.9	0	< 0.001

In Trial N1, both the 6 g and 9 g per night Xyrem doses resulted in statistically significant reductions in the frequency of cataplexy attacks. The 3 g per night dose had little effect. In Trial N2, patients randomized to placebo after discontinuing long-term open-label Xyrem therapy

experienced a significant increase in cataplexy attacks ($p < 0.001$), providing evidence of long-term efficacy of Xyrem. In Trial N2, the response was numerically similar for patients treated with doses of 6 g to 9 g per night, but there was no effect seen in patients treated with doses less than 6 g per night, suggesting little effect at these doses.

14.2 Excessive Daytime Sleepiness in Narcolepsy

The effectiveness of Xyrem in the treatment of excessive daytime sleepiness in patients with narcolepsy was established in two randomized, double-blind, placebo-controlled trials (Trials N3 and N4) (see Tables 7 to 9). Seventy-eight percent of patients in Trial N3 were also being treated with CNS stimulants.

Trial N3 was a multicenter randomized, double-blind, placebo-controlled, parallel-group trial that evaluated 228 patients with moderate to severe symptoms at entry into the study including a median Epworth Sleepiness Scale (see below) score of 18, and a Maintenance of Wakefulness Test (see below) score of 8.3 minutes. Patients were randomized to one of 4 treatment groups: placebo, Xyrem 4.5 g per night, Xyrem 6 g per night, or Xyrem 9 g per night. The period of double-blind treatment in this trial was 8 weeks. Antidepressants were withdrawn prior to randomization; stimulants were continued at stable doses.

The primary efficacy measures in Trial N3 were the Epworth Sleepiness Scale and the Clinical Global Impression of Change. The Epworth Sleepiness Scale is intended to evaluate the extent of sleepiness in everyday situations by asking the patient a series of questions. In these questions, patients were asked to rate their chances of dozing during each of 8 activities on a scale from 0-3 (0=never; 1=slight; 2=moderate; 3=high). Higher total scores indicate a greater tendency to sleepiness. The Clinical Global Impression of Change is evaluated on a 7-point scale, centered at *No Change*, and ranging from *Very Much Worse* to *Very Much Improved*. In Trial N3, patients were rated by evaluators who based their assessments on the severity of narcolepsy at baseline.

In Trial N3, statistically significant improvements were seen on the Epworth Sleepiness Scale score at Week 8 and on the Clinical Global Impression of Change score at Week 8 with the 6 g and 9 g per night doses of Xyrem compared to the placebo group.

Table 5
Change from Baseline in Daytime Sleepiness Score (Epworth Sleepiness Scale) at Week 8 in Trial N3 (Range 0-24)

Treatment Group	Baseline	Week 8	Median Change from Baseline at Week 8	p-value
Placebo (n=59)	17.5	17.0	-0.5	-
Xyrem 6 g per night (n=58)	19.0	16.0	-2.0	< 0.001
Xyrem 9 g per night (n=47)	19.0	12.0	-5.0	< 0.001

Table 6
Proportion of patients with a very much or much improved Clinical Global Impression of Change in Daytime and Nighttime Symptoms in Trial N3

Treatment Group	Percentages of Responders (Very Much Improved or Much Improved)	Change from Baseline Significance Compared to Placebo (p-value)
Placebo (59)	22%	-
Xyrem 6 g per night (n=58)	52%	< 0.001
Xyrem 9 g per night (n=47)	64%	< 0.001

Trial N4 was a multicenter randomized, double-blind, placebo-controlled, parallel-group trial that evaluated 222 patients with moderate to severe symptoms at entry into the study including a median Epworth Sleepiness Scale score of 15, and a Maintenance of Wakefulness Test (see below) score of 10.3 minutes. At entry, patients had to be taking modafinil at stable doses of 200 mg, 400 mg, or 600 mg daily for at least 1 month prior to randomization. The patients enrolled in the study were randomized to one of 4 treatment groups: placebo, Xyrem, modafinil, or Xyrem plus modafinil. Xyrem was administered in a dose of 6 g per night for 4 weeks, followed by 9 g per night for 4 weeks. Modafinil was continued in the modafinil alone and the Xyrem plus modafinil treatment groups at the patient's prior dose. Trial N4 was not designed to compare the effects of Xyrem to modafinil because patients receiving modafinil were not titrated to a maximal dose. Patients randomized to placebo or to Xyrem treatment were withdrawn from their stable dose of modafinil. Patients taking antidepressants could continue these medications at stable doses.

The primary efficacy measure in Trial N4 was the Maintenance of Wakefulness Test. The Maintenance of Wakefulness Test measures latency to sleep onset (in minutes) averaged over 4 sessions at 2-hour intervals following nocturnal polysomnography. For each test session, the subject was asked to remain awake without using extraordinary measures. Each test session is terminated after 20 minutes if no sleep occurs, or after 10 minutes, if sleep occurs. The overall score is the mean sleep latency for the 4 sessions.

In Trial N4, a statistically significant improvement in the change in the Maintenance of Wakefulness Test score from baseline at Week 8 was seen in the Xyrem and Xyrem plus modafinil groups compared to the placebo group.

This trial was not designed to compare the effects of Xyrem to modafinil, because patients receiving modafinil were not titrated to a maximally effective dose.

Table 7
Change in Baseline in the Maintenance of Wakefulness Test Score (in minutes) at Week 8 in Trial N4

Treatment Group	Baseline	Week 8	Mean Change from Baseline at Week 8	p-value
Placebo (modafinil withdrawn) (n=55)	9.7	6.9	-2.7	-
Xyrem (modafinil withdrawn) (n=50)	11.3	12.0	0.6	<0.001
Xyrem plus modafinil (n=54)	10.4	13.2	2.7	<0.001

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Xyrem is a clear to slightly opalescent oral solution. Each prescription includes a carton containing one bottle of Xyrem, a press-in-bottle-adaptor, an oral measuring device (plastic syringe), and a Medication Guide. The pharmacy provides two empty vials with child-resistant caps with each Xyrem shipment.

Each amber bottle contains Xyrem oral solution at a concentration of 0.5 g per mL and has a child-resistant cap.

Carton containing one 180 mL bottle NDC 68727-100-01

16.2 Storage

Keep out of reach of children.

Xyrem should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

Dispense in tight containers.

16.3 Handling and Disposal

Xyrem is a Schedule III drug under the Controlled Substances Act. Xyrem should be handled according to state and federal regulations. It is safe to dispose of Xyrem down the sanitary sewer.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Xyrem Success Program

- Inform patients that Xyrem is available only through a restricted distribution program called the Xyrem Success Program.
- The contents of the Xyrem Medication Guide and educational materials are reviewed with every patient before initiating treatment with Xyrem.

- Patients must read and understand the materials in the Xyrem Success Program prior to initiating treatment. Inform the patient that they should be seen by the prescriber frequently to review dose titration, symptom response, and adverse reactions; a follow-up of every three months is recommended.
- Discuss safe and proper use of Xyrem and dosing information with patients prior to the initiation of treatment. Instruct patients to store Xyrem bottles and Xyrem doses in a secure place, out of the reach of children and pets.

Alcohol or Sedative Hypnotics

Advise patients not to drink alcohol or take other sedative hypnotics if they are taking Xyrem.

Sedation

Inform patients that after taking Xyrem they are likely to fall asleep quickly (often within 5 and usually within 15 minutes), but the time it takes to fall asleep can vary from night to night. The sudden onset of sleep, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization. Instruct patients to remain in bed following ingestion of their first dose, and not to take their second dose until 2.5 to 4 hours later.

Food Effects on Xyrem

Inform patients to take the first dose at least 2 hours after eating.

Respiratory Depression

Inform patients that Xyrem can be associated with respiratory depression.

Operating Hazardous Machinery

Inform patients that until they are reasonably certain that Xyrem does not affect them adversely (e.g., impair judgment, thinking, or motor skills) they should not operate hazardous machinery, including automobiles or airplanes.

Suicidality

Instruct patients or families to contact a healthcare provider immediately if the patient develops depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or suicidal ideation.

Sleepwalking

Instruct patients and their families that Xyrem has been associated with sleepwalking and to contact their healthcare provider if this occurs.

Sodium Intake

Instruct patients who are sensitive to salt intake (e.g., those with heart failure, hypertension, or renal impairment) that Xyrem contains a significant amount of sodium and they should limit their sodium intake.

MEDICATION GUIDE
Xyrem® (ZĪE-rem)
(sodium oxybate)
oral solution C III

Read this Medication Guide carefully before you start taking Xyrem and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about Xyrem?

Xyrem can cause serious side effects including slow breathing or changes in your alertness. Do not drink alcohol or take medicines intended to make you fall asleep while you are taking Xyrem because they can make these side effects worse**.** Call your doctor right away if you have any of these serious side effects.

- The active ingredient of Xyrem is a form of gamma-hydroxybutyrate (GHB). GHB is a chemical that has been abused and misused. Abuse and misuse of Xyrem can cause serious medical problems, including:
    - seizures
    - trouble breathing
    - changes in alertness
    - coma
    - death
- Do not drive a car, use heavy machinery, fly an airplane, or do anything that is dangerous or that requires you to be fully awake for at least 6 hours after you take Xyrem. You should not do those activities until you know how Xyrem affects you.
- Xyrem is available only by prescription and filled through the central pharmacy in the Xyrem Success Program. Before you receive Xyrem, your doctor or pharmacist will make sure that you understand how to use Xyrem safely and effectively. If you have any questions about Xyrem, ask your doctor or call the Xyrem Success Program® at 1-866-997-3688.

What is Xyrem?
Xyrem is a prescription medicine used to treat the following symptoms in people who fall asleep frequently during the day, often at unexpected times (narcolepsy):

- suddenly weak or paralyzed muscles when they feel strong emotions (cataplexy)
- excessive daytime sleepiness (EDS) in people who have narcolepsy

It is not known if Xyrem is safe and effective in children.

Xyrem is a controlled substance (CIII) because it contains sodium oxybate that can be a target for people who abuse prescription medicines or street drugs. Keep your Xyrem in a safe place to protect it from theft. Never give your Xyrem to anyone

else because it may cause death or harm them. Selling or giving away this medicine is against the law.

Who should not take Xyrem?

Do not take Xyrem if you:

- take other sleep medicines or sedatives (medicines that cause sleepiness)
- drink alcohol
- have a rare problem called succinic semialdehyde dehydrogenase deficiency

Before you take Xyrem, tell your doctor if you:

- have short periods of not breathing while you sleep (sleep apnea)
- snore, have trouble breathing, or have lung problems. You may have a higher chance of having serious breathing problems when you take Xyrem.
- have or had depression or have tried to harm yourself. You should be watched carefully for new symptoms of depression.
- have liver problems
- are on a salt-restricted diet. Xyrem contains a lot of sodium (salt) and may not be right for you.
- have high blood pressure
- have heart failure
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if Xyrem can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Xyrem passes into your breast milk. You and your doctor should decide if you will take Xyrem or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially, tell your doctor if you take other medicines to help you sleep (sedatives). Do not take medicines that make you sleepy with Xyrem.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take Xyrem?

- Read the **Instructions for Use** at the end of this Medication Guide for detailed instructions on how to take Xyrem.
- Take Xyrem exactly as your doctor tells you to take it.
- Never change your Xyrem dose without talking to your doctor.
- Xyrem can cause sleep very quickly. You should fall asleep soon. Some patients fall asleep within 5 minutes and most fall asleep within 15 minutes. Some patients take less time to fall asleep and some take more time. The time it takes you to fall asleep might be different from night to night.
- Take your first Xyrem dose at bedtime while you are in bed. Take your second Xyrem dose 2 ½ to 4 hours after you take your first Xyrem dose. You may want to set an alarm clock to make sure you wake up to take your second Xyrem dose.

- If you miss your second Xyrem dose, skip that dose and do not take Xyrem again until the next night. Never take 2 Xyrem doses at 1 time.
- Wait at least 2 hours after eating before you take Xyrem.
- You should see your doctor every 3 months for a check-up while taking Xyrem. Your doctor should check to see if Xyrem is helping to lessen your symptoms and if you feel any side effects while you take Xyrem.
- If you take too much Xyrem, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of Xyrem?

Xyrem can cause serious side effects, including:

- See **"What is the most important information I should know about Xyrem?"**
- **Breathing problems, including:**
  - slower breathing
  - trouble breathing
  - short periods of not breathing while sleeping (sleep apnea). People who already have breathing or lung problems have a higher chance of having breathing problems when they use Xyrem.
- **Mental health problems, including:**
  - confusion
  - seeing or hearing things that are not real (hallucinations)
  - unusual or disturbing thoughts (abnormal thinking)
  - feeling anxious or upset
  - depression
  - thoughts of killing yourself or trying to kill yourself

Call your doctor right away if you have symptoms of mental health problems.

- **Sleepwalking.** Sleepwalking can cause injuries. Call your doctor if you start sleepwalking. Your doctor should check you.

The most common side effects of Xyrem include:

- nausea
- dizziness
- vomiting
- bedwetting
- diarrhea

Your side effects may increase when you take higher doses of Xyrem.
Xyrem can cause physical dependence and craving for the medicine when it is not taken as directed.

These are not all the possible side effects of Xyrem. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Xyrem?

- **Always store Xyrem in the original bottle or in pharmacy containers with child-resistant caps provided by the pharmacy.**
- **Keep Xyrem in a safe place out of the reach of children and pets.**
- **Get emergency medical help right away if a child drinks your Xyrem.**
- Store Xyrem between 68°F to 77°F (20°C to 24°C). When you have finished using a Xyrem bottle:
    - empty any unused Xyrem down the sink drain
    - cross out the label on the Xyrem bottle with a marker
    - place the empty Xyrem bottle in the trash

General information about the safe and effective use of Xyrem

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Xyrem for a condition for which it was not prescribed. Do not give Xyrem to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Xyrem. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Xyrem that is written for health professionals.

For more information, go to www.XYREM.com or call the Xyrem Success Program at 1-866-997-3688.

What are the ingredients in Xyrem?

Active Ingredients: sodium oxybate

Inactive Ingredients: purified water and malic acid

This Medication Guide has been approved by the U. S. Food and Drug Administration.

Distributed By:

Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304

Revised: December 2012

Instructions for Use
Xyrem® (ZĪE-rem)
(sodium oxybate)
oral solution C III

Read these Instructions for Use carefully before you start taking Xyrem and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

Note:

- **You will need to split your prescribed Xyrem dose into 2 separate pharmacy containers for mixing.**
- **You will need to mix Xyrem with water before you take your dose.**

Supplies you will need for mixing and taking Xyrem: See Figure A.

- bottle of your Xyrem medicine
- press-in bottle adaptor with straw attached
- syringe for drawing up your Xyrem dose
- a measuring cup containing about ¼ cup of water (not provided with your Xyrem prescription)
- 2 **empty** pharmacy containers with child-resistant caps
- alarm clock by your bedside (alarm clock may be included in your first shipment of Xyrem)

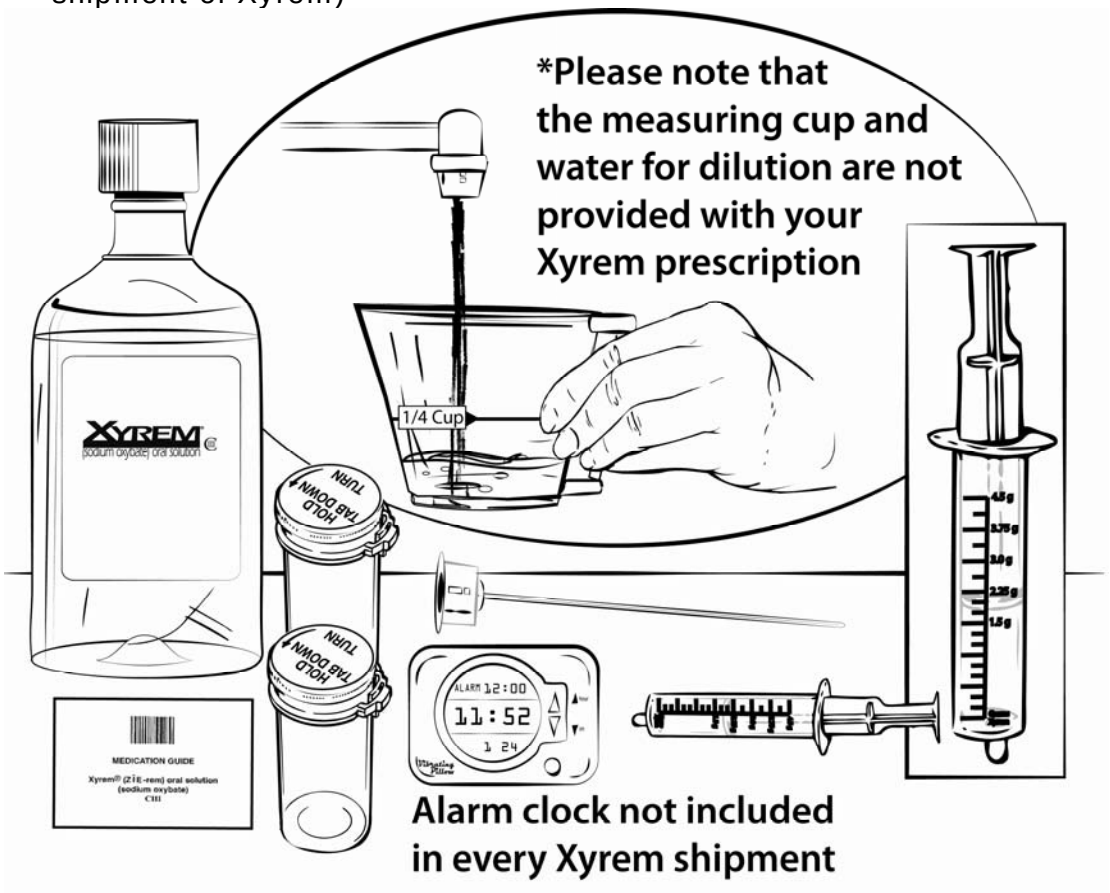


Figure A

Step 1. Take the Xyrem bottle, press-in-bottle adaptor, and syringe out of the box.
Step 2. Remove the bottle cap from the Xyrem bottle by pushing down while turning the cap counterclockwise (to the left). See Figure B.

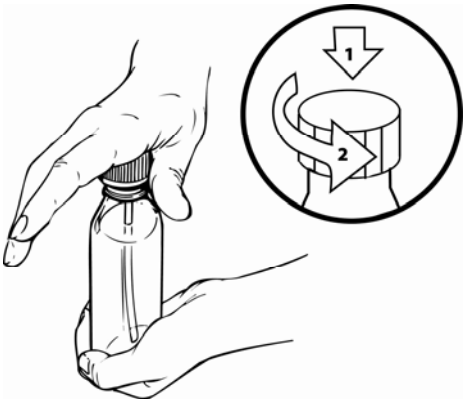


Figure B

Step 3.

- The press-in-bottle adaptor may already be put in place by the pharmacy. If it is not already in place, you will have to do it yourself. After removing the cap from the Xyrem bottle, set the bottle upright on a tabletop.
- While holding the Xyrem bottle in its upright position, insert the press-in-bottle-adaptor into the neck of the Xyrem bottle. See Figure C.

Figure C

- Tilt the straw toward the edge of the bottom of the bottle to be sure you can draw out your dose of the medicine. You only need to do this the first time you open the bottle. See Figure D.

Figure D

- After you draw out your dose of the medicine, leave the adaptor in the bottle for all your future uses. See Figure E.

Figure E

Step 4.

- Take the syringe out of the plastic wrapper. Use only the syringe provided with your Xyrem prescription.
- While holding the Xyrem bottle upright on the tabletop, insert the tip of the syringe into the opening on top of the Xyrem bottle and press down firmly. See Figure F.

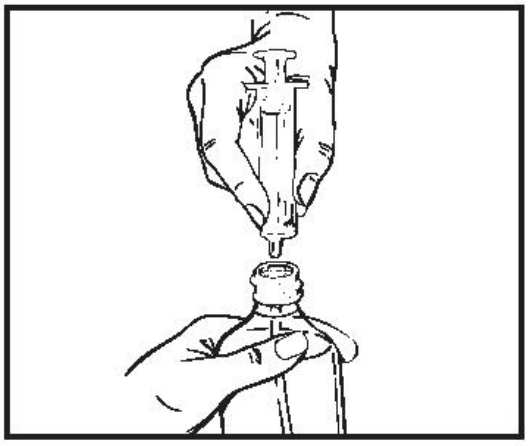


Figure F

Step 5.

- Hold the bottle and syringe down with one hand, and draw up one-half (1/2) of your total prescribed nightly dose with the other hand by pulling up on the plunger. For example, if your total nightly dose of Xyrem is 4.5 grams a night, you will need to draw up 2 separate doses of 2.25 grams each, one for each pharmacy container. See Figure G.

Note: **The Xyrem medicine will not flow into the syringe unless you keep the bottle upright.**

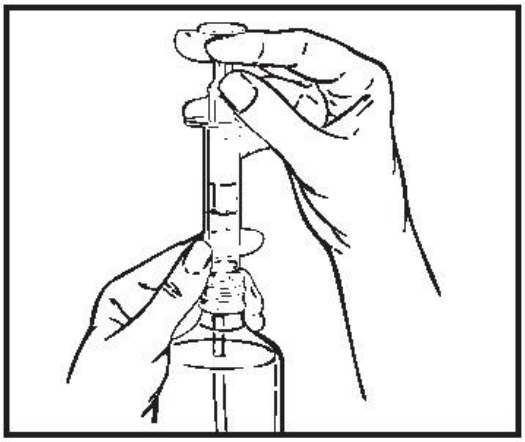


Figure G

Step 6.

- After you draw up each separate Xyrem dose, remove the syringe from the opening of the Xyrem bottle. Put the tip into 1 of the **empty** containers with child-resistant caps provided by the pharmacy.
- **Make sure the pharmacy container is empty and does not contain any medicine from your previous night's dose.**
    - Empty each separate Xyrem dose into 1 of the **empty** pharmacy containers by pushing down on the plunger. (See Figure H).
- Using a measuring cup, pour about ¼ cup of water into **each** container. **Be careful to add only water to each container and not more Xyrem. All shipped bottles of Xyrem contain the concentrated medicine. Water for mixing the medicine is not provided in the shipment.**

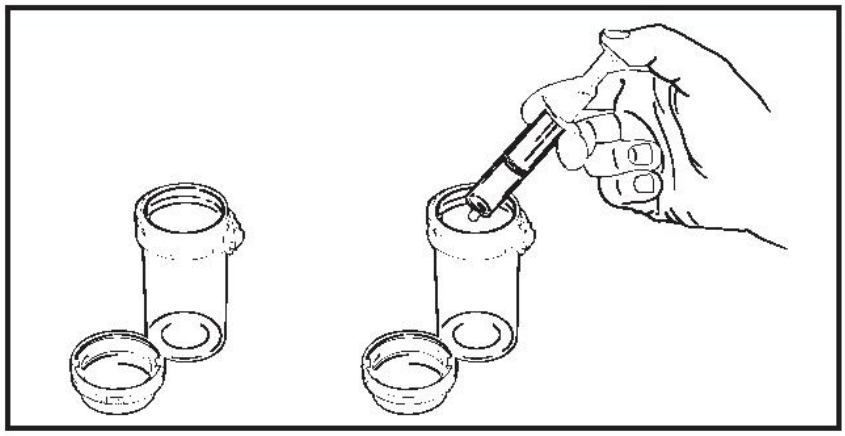


Figure H

Step 7.

- Place the child-resistant caps provided on the filled pharmacy containers and turn each cap clockwise (to the right) until it clicks and locks into its child-resistant position. See Figure I.

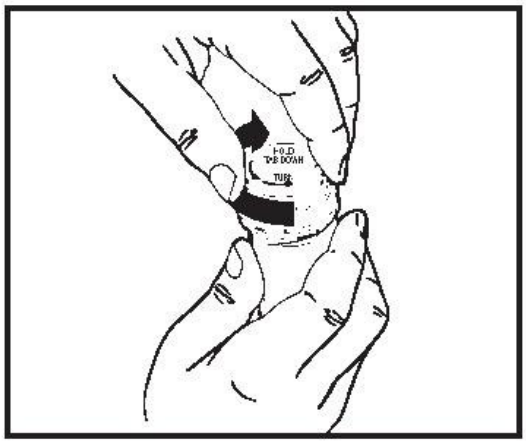


Figure I

- Put the cap back on the Xyrem bottle and store it in a safe and secure place. Store in a locked place if needed. Keep Xyrem out of the reach of children and pets.
- Rinse the syringe out with water and squirt the liquid into the sink drain.

Step 8.

- At bedtime, and before you take your first Xyrem dose, put your second Xyrem dose in a safe place near your bed.
- You may want to set an alarm clock to make sure you wake up to take the second dose.
- When it is time to take your first Xyrem dose, remove the cap from the container by pressing down on the child-resistant locking tab and turning the cap counterclockwise (to the left).
- Drink all of your first Xyrem dose at bedtime. Put the cap back on the first container before lying down to sleep.

- You should fall asleep soon. Some patients fall asleep within 5 minutes and most fall asleep within 15 minutes. Some patients take less time to fall asleep, and some take more time. The time it takes you to fall asleep might be different from night to night.

Step 9.

- When you wake up 2½ to 4 hours later, take the cap off the second pharmacy container.

- If you wake up before the alarm and it has been at least 2½ hours since your first Xyrem dose, turn off your alarm and take your second Xyrem dose.

- While sitting in bed, drink all of the second Xyrem dose and put the cap back on the second pharmacy container before lying down to continue sleeping.

Distributed By:

Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304

These Instructions for Use have been approved by the U.S. Food and Drug Administration.

Revised December 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021196Orig1s013

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21196 (SLR-013)**
Sponsor:	**Jazz Pharmaceuticals, Inc.**
Drug:	**Xyrem**
Proposed Indication:	**Narcolepsy**
Material Submitted:	**Prior Approval Labeling Supplement**
Correspondence Date:	**8/13/07**
Date Received / Agency:	**8/15/07**
Date Review Completed:	**12/14/12**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This document is an **update** to a review of a Prior Approval Labeling Supplement for Xyrem® (sodium oxybate oral solution [500 mg/mL]) and its Amendments.

The Amendments reviewed here were submitted on the following dates:

- February 3, 2011
- April 24, 2012
- October 3, 2012.

A formal review of this Prior Approval Labeling and its Amendments was earlier completed by me on November 30, 2012. Please see that review for full details.

This review update has been made necessary by further revisions to the Prescribing Information for Xyrem® since my earlier review of this Prior Approval Labeling Supplement and its Amendments was completed on November 30, 2012. Those revisions followed internal Agency deliberations that occurred after that date, and were later agreed to by the sponsor.

The revised Prescribing Information for Xyrem® is in Appendix 1 of this review.

2. Recommendation

I recommend that this Prior Approval Labeling Supplement for Xyrem® be approved using the Prescribing Information listed in Appendix 1.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 12/14/12
cc:
HFD-120
NDA 21196 (SLR-013)

APPENDIX 1: PRESCRIBING INFORMATION

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/s/

RANJIT B MANI
12/14/2012

Review and Evaluation of Clinical Data

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Date Received / Agency:	**8/15/07**
Date Review Completed:	**11/30/12**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

The original submission reviewed here and its Amendments constitute a Prior Approval Labeling Supplement for Xyrem® (sodium oxybate oral solution [500 mg/mL]).

Xyrem® was originally approved by the Agency on July 17, 2002, for the treatment of cataplexy in narcolepsy, under NDA 21196. A supplemental NDA (an efficacy supplement; SE1-005) proposing an expansion of the originally approved claim was approved on November 18, 2005; the approved expanded indication was as follows: "The treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy."

Xyrem® was originally approved under the Subpart H (21 CFR 314.520) regulations, which have remained applicable to this product.

(b) (4)

A Risk Management Plan was instituted as part of the original approval of Xyrem® on February 17, 2002, with a modified version of that Plan being approved on November 18, 2005. The existing Risk Management Plan for Xyrem® was then determined by the Agency (as per a Federal Register notice [Docket No. FDA-2008-N-0174] of March 27, 2008) to constitute a deemed Risk Evaluation and Mitigation Strategy (REMS) under the provisions of the Food and Drug Administration Amendments Act of 2007. As stipulated in that Federal Register notice, the sponsor was also required to submit a proposed REMS for review within 180 days of that notice; in a submission dated August 29, 2008, the sponsor requested that the deemed REMS be approved as such; there have since been many communications between the Agency and the sponsor regarding the REMS, which is currently in the process of being finalized with a text and format that will differ from the deemed REMS. The REMS is being reviewed under a separate Prior Approval Labeling Supplement (Supplement #15).

In addition to responding to labeling recommendations from the Agency (b) (4) the main submission (i.e., that of August 13, 2007) also includes other proposed changes to labeling and, importantly, proposals for conversion of the Prescribing Information section of product labeling to the newer Physician's Labeling Rule (PLR) format.

2. Contents Of Review

The main headings the rest of review will be as follows:

- Main elements in original submission of this Prior Approval Labeling Supplement
- List of Amendments to current Prior Approval Labeling Supplement
- Reviewer's summary comments
- Recommendations
- Appendix 1: Prescribing Information

Note that the current review does not apply to the REMS for Xyrem® that is currently under separate review. However, the text of the REMS and the elements of labeling addressed in this review are closely related, as might be expected.

3. Main Elements In Original Submission Of This Prior Approval Labeling Supplement

The original submission (dated August 13, 2007) of this Prior Approval Labeling Supplement for Xyrem® (Supplement #13 under NDA 21196) provided for the conversion of pertinent sections of the existing Xyrem® labeling to PLR format.

In addition, the same submission proposed significant changes to the following elements, as well as other modifications:

- (b) (4)
- The text of the following sections of the new PLR Prescribing Information: Indications and Usage , Warnings and Precautions, Pharmacokinetics, Adverse Reactions, Drug Abuse and Dependence, Clinical Pharmacology, Non-Clinical Toxicology
- The text of the Medication Guide
- Items constituting part of the REMS (which as already noted are currently being reviewed separately under another Prior Approval Labeling Supplement).

4. List Of Amendments To Current Prior Approval Labeling Supplement

Three amendments to the current Prior Approval Labeling Supplement have been received since August 13, 2007, and are briefly listed below.

4.1 Amendment Submitted February 3, 2011

This Amendment contained an update to the Prescribing Information (plus Medication Guide).

4.2 Amendment Submitted April 24, 2012

This Amendment contained a response to comments received from the Agency on February 17, 2012. These comments applied to the Prescribing Information (plus Medication Guide).

4.3 Amendment Submitted October 3, 2012

This Amendment contained a response to comments from the Agency regarding the draft Prescribing Information (plus Medication Guide) which were received by the sponsor on September 5, 2012.

5. Reviewer's Summary Comments

The main (original) submission reviewed here and its Amendments constitute a Prior Approval Labeling Supplement (Supplement #13) for Xyrem® (sodium oxybate oral solution [500 mg/mL]) approved under NDA 21196. Xyrem® is currently approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.

The modifications to labeling addressed here are applicable to the Prescribing Information (plus Medication Guide) and include, but are not limited to, conversion of the Prescribing Information from a previously-used format to a format that complies with the Physician's Labeling Rule.

The components of this Prior Approval Labeling Supplement have undergone detailed review by me and by other disciplines within the Agency and considerable internal discussion, and has been the subject of multiple communications with the sponsor. Appendix 1 of this review contains the text of the Prescribing Information (and Medication Guide) that is the result of these efforts and has been agreed upon both by the Agency and by the sponsor. A detailed written review of the many elements of this Prior Approval Labeling Supplement by me is impractical.

A Risk Evaluation and Mitigation Strategy for Xyrem® is currently separately under review under a separate Prior Approval Labeling Supplement (Supplement #15) originally submitted to the Agency on August 29, 2008 under the same NDA.

6. Recommendation

I recommend that this Prior Approval Labeling Supplement for Xyrem® be approved using the Prescribing Information listed in Appendix 1.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 11/30/12
cc:
HFD-120
NDA 21196 (SLR-013)

APPENDIX 1: PRESCRIBING INFORMATION

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/s/

RANJIT B MANI
11/30/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021196Orig1s013

OTHER REVIEW(S)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**XYREM (sodium oxybate) oral solution CIII**
Applicant	Jazz Pharmaceuticals
Application/Supplement Number	NDA 021196/S-013
Type of Application	PLR Conversion
Indication(s)	Treatment of cataplexy in narcolepsy; treatment of excessive daytime sleepiness in narcolepsy
Established Pharmacologic Class[1]	Central nervous system depressant
Office/Division	ODEI/DNP
Division Project Manager	Susan Daugherty
Date FDA Received Application	August 13, 2007
Goal Date	February 13, 2008
Date PI Received by SEALD	November 29, 2012
SEALD Review Date	December 5, 2012
SEALD Labeling Reviewer	Elizabeth Donohoe
SEALD Division Director	Laurie Burke

PI = prescribing information

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

(b) (4) 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: (b) (4)

(b) (4) 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: (b) (4)

(b) (4) 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: (b) (4)

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: (b) (4)

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional

Selected Requirements of Prescribing Information

• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment: (b) (4)

YES 7. A horizontal line must separate HL and Table of Contents (TOC).
Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.
Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment: (b) (4)

YES

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

(b) (4) 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: (b) (4)

Patient Counseling Information Statement

(b) (4) 26. Must include <u>one</u> of the following three **bolded** verbatim statements (without quotation marks):

<u>If a product **does not** have FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

<u>If a product **has** FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment: (b) (4)

Revision Date

(b) (4) 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: (b) (4)

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS**".

Comment:

Selected Requirements of Prescribing Information

(b) (4) 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: (b) (4)

(b) (4) 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: (b) (4)

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

(b) (4) 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS

Selected Requirements of Prescribing Information

8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: (b) (4)

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: (b) (4)

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

(b) (4) 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment: (b) (4)

Selected Requirements of Prescribing Information

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *The statement in 6.2 contains wording that strongly implies a causal realtaionship; if the review division approves this language then that is an acceptable modification of the Postmarketing Experience limitation statement.*

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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/s/

ELIZABETH A DONOHOE
12/05/2012

ERIC R BRODSKY
12/05/2012
I agree. Eric Brodsky, signing for Laurie Burke, SEALD Director.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	November 14, 2011
To:	Russell Katz, M.D., Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Team Leader, Patient Labeling Team **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling Team **Division of Medical Policy Programs**
From:	Robin Duer, MBA, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs**
Subject:	DMPP Review of Patient Labeling (Medication Guide, Instructions for Use)
Drug Name (established name):	XYREM (sodium oxybate)
Dosage Form and Route:	oral solution
Application Type/Number:	NDA 21-196
Supplement #	013
TSI #	569
Applicant:	Jazz Pharmaceuticals
OSE RCM #:	2008-1454

1 INTRODUCTION

This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Medical Policy Programs (DMPP) to provide a review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for XYREM (sodium oxybate) oral solution.

XYREM (sodium oxybate) is indicated for the treatment of cataplexy in patients with narcolepsy and for excessive daytime sleepiness in patient with narcolepsy. Supplement 013 was originally submitted to the Agency on August 13, 2007 (b) (4) Supplement 013 provided for a prior approval supplement adding supportive data and revised labeling for the use of XYREM for the treatment of (b) (4)

The purpose of the Applicant's February 4, 2011 submission was to provide a revised labeling proposal (S-015) and a prior approval supplement (S-013) for the XYREM labeling (b) (4)
DMPP conferred with DMEPA on November 7, 2011 and a separate DMEPA review of the IFU will be forthcoming.

The Risk Evaluation and Mitigation Strategy (REMS) will be reviewed by DRISK under separate cover.

2 MATERIAL REVIEWED

- Draft XYREM (sodium oxybate) Medication Guide (MG) received on February 4, 2011 and received by DMPP on October 28, 2011
- Draft XYREM (sodium oxybate) Instructions for Use (IFU) received on February 4, 2011 and received by DMPP on October 28, 2011
- Draft XYREM (sodium oxybate) Prescribing Information (PI) received February 4, 2011, revised by the Review Division throughout the current review cycle and received by DMPP on October 28, 2011

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG and IFU are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

ROBIN E DUER
11/12/2011

MELISSA I HULETT
11/14/2011

LASHAWN M GRIFFITHS
11/14/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Labeling Review

Date:	November 9, 2011
Reviewer(s):	Julie Villanueva, PharmD Division of Medication Error Prevention and Analysis
Team Leader	Lubna Merchant, PharmD Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name(s):	Xyrem (Sodium Oxybate) Oral Solution
Application Type/Number:	NDA 21196 / S-013
Applicant/sponsor:	Jazz Pharmaceuticals Inc.
OSE RCM #:	2011-3471

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed changes to the Instructions for Use (IFU) labeling for Xyrem (Sodium Oxybate) Oral Solution for areas of vulnerability that could lead to medication errors. This review is in response to a request from the Division of Neurology Products (DNP).

1.1 BACKGROUND OR REGULATORY HISTORY

Xyrem (NDA 21196) was approved for the treatment of cataplexy in 2002 with a risk management plan. In 2005, Xyrem was approved for the treatment of excessive daytime sleepiness in patients with narcolepsy.

With the implementation of the Food and Drug Administration Amendments Act, Xyrem was found to have a deemed Risk Evaluation and Mitigation Strategy (REMS) in which Jazz Pharmaceuticals submitted a REMS supplement on August 29, 2008.

(b) (4)

The review of Xyrem's REMS (b) (4) In October 2010, DNP requested Jazz Pharmaceuticals to submit a revised REMS proposal for Xyrem. Jazz Pharmaceuticals submitted a revised REMS proposal and revised labeling (insert labeling and medication guide) for Xyrem on February 3, 2011.

In addition, DMEPA has reviewed container labels, carton labeling and the package insert labeling in OSE Review # 2000-0311, OSE Review # 2007-230, and OSE Review # 2008-340. On August 13, 2007, Supplement-013 was submitted by the Applicant,

(b) (4)

1.2 PRODUCT INFORMATION

Xyrem (Sodium Oxybate) Oral Solution is a central nervous system depressant indicated for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy. The recommended starting dose of Xyrem is 4.5 grams nightly divided into two equal doses of 2.25 grams with the first dose given at bedtime and the second dose given 2.5 hours to 4 hours later. The dose can be titrated in weekly intervals by 1.5 grams nightly to a maximum of 9 grams nightly (two equal doses of 4.5 grams). Xyrem is available in an oral solution concentration of (b) (4) and supplied in a 180 mL amber bottle with a child-resistant cap.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1] and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Instructions for Use submitted on February 3, 2011

Additionally, since Xyrem is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Xyrem. The September 30, 2011 AERS search used the following search terms: active ingredient "sodium oxyb%", trade name "Xyre%", and verbatim terms "sodium oxyb%" and "Xyre%". The reaction terms used were the MedDRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues". No time limitation was set.

The reports were manually reviewed to determine if a medication error occurred. (See Appendix A for a complete list of Individual Safety Report (ISR) numbers.) Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the Instructions for Use, the case was considered pertinent to this review. Reports excluded from further analysis are those that did not describe a medication error, such as product quality issues and adverse events, or those that could not inform review of the Instructions for Use, such as dose omissions, drug interactions, and intentional and prescribed overdoses. (See Appendix B for a summary of exclusions.)

We also reviewed the Periodic Safety Update Report (PSUR) submitted by Jazz Pharmaceuticals on September 15, 2011. The exclusion criteria described above were applied to these reports and are incorporated into the summary of exclusions found in Appendix B.

3 RESULTS AND DISCUSSION

The following section discusses the results of our AERS search, our evaluation of the Instructions for Use, and a comment identified in a previous review that was not accepted by the Applicant.

3.1 MEDICATION ERROR CASES

A total of 183 reports were identified from the AERS search (n = 170 reports) and the PSUR (n = 13). Following exclusions as described in Section 2, we evaluated a total of 61 cases relevant to this review. Of note, some cases involved more than one type of error, therefore the numbers equal greater than 61. The relevant medication errors are categorized below.

Overdose (n = 36)

Twenty-four cases indicated that an overdose occurred, but no specific information was given to determine if these cases were accidental or intentional overdoses. In six of the

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

36 cases, an accidental overdose was reported, but no cause was identified. In three of the 36 cases, the patient misunderstood the directions and took more than the prescribed dose, which led to adverse events, such as headache, enuresis, disorientation, and vomiting. Of the 36 cases, one patient prepared Xyrem several times during the night leading to the patient feeling as if he was in a coma. In one of the 36 cases, the patient inadvertently used a (b) (4) that contained doses for the following night. One of the 36 cases describes a patient who did not realize that the dose omitted from the previous night was still in the (b) (4) and subsequently received a double dose in which the patient was sent to the Emergency Room.

Wrong technique (n = 7)

Two cases reported that the patient did not use the provided syringe and subsequently administered the wrong dose resulting in a cataplexy crisis. In another case, the patient emptied undiluted Xyrem into a vial since the press-in-bottle adaptor was not working properly. The patient mistakenly took the undiluted Xyrem and was sent to the Emergency Room. Four of the seven cases report that the patient used another bottle of Xyrem contained in the same shipment to dilute the doses resulting in adverse events, such as fatigue, dizziness, nausea, and hand twitching.

Extra dose (n = 11)

Eight cases indicated that an extra dose of Xyrem was taken by the patient, but no specific information was given regarding if these were taken accidentally or intentionally. In one of the 11 cases, the patient accidentally took the second dose minutes after taking the first dose, which led to the patient falling and fracturing multiple bones. In another case, the patient mistakenly took a third dose thinking it was only the second dose. Of the 11 cases, one patient accidentally took a second unprescribed dose due to changes in the dosing syringe. This case, however, occurred in another country and it is unknown what changes to the dosing syringe were made.

Underdose (n = 7)

Two cases reported an underdose, but no specific information regarding the cause of the error was identified. Three of the seven patients misunderstood the directions and took half of the prescribed dose and were unable to sleep. In one of the seven cases, the patient was unable to read the dose on the syringe and subsequently took a lower dose than prescribed. The patient woke up the next morning feeling disoriented and confused. Another case reports a patient whose prescription was in mL rather than grams and the patient subsequently administered a lower dose without any adverse events occurring.

Wrong dose (n = 1)

This case describes a patient who took a wrong dose, but no specific information regarding the cause of the error was identified.

Administration error (n = 1)

This case reports a drug maladministration error, but no specific information regarding the cause of the error was identified.

3.2 INSTRUCTIONS FOR USE

We noted a case of overdose in which the patient inadvertently took an omitted dose (b) (4) with the current dose, a statement emphasizing to make sure that (b) (4) are empty prior to placing the dose in the pharmacy containers will alleviate this error.

In addition, we identified four cases in which the patient used another bottle of Xyrem, contained in the same shipment, to dilute the doses. The Instructions for Use should also indicate that all shipped bottles contain concentrated medication and that water for dilution is not contained in the shipment. This will prevent patients from assuming that one of the Xyrem bottles is used for dilution. Xyrem should be kept in the original container to prevent patients from inadvertently taking undiluted Xyrem from a container in which the medication was transferred. (b) (4)

We also noted that the directions for dividing the total nightly dose into two equal doses are unclear in the Instructions for Use (IFU). This could be a potential cause for overdoses and should be clearly stated in the IFU.

Additionally, the heading for Step 4 is missing and should be adequately identified. We provide recommendations to address the above issues in section 4.

3.3 COMMENT THAT NEEDS TO BE FORWARDED TO THE APPLICANT

(b) (4)

4 CONCLUSIONS AND RECOMMENDATIONS

The proposed Instructions for Use (IFU) is confusing to patients and requires revision for clarity to minimize the medication errors reported postmarketing. DMEPA is collaborating with Patient Labeling and our recommendations for improving the IFU will be incorporated into the review conducted by Patient Labeling. (b) (4)

DMEPA's recommendations to the IFU include the following:

- Instruct patients to make sure that (b) (4) are empty prior to placing in the next dose (b) (4)
- State that all shipped bottles contain concentrated medication and that water for dilution is not contained in the shipment
- Clarify directions for dividing the total nightly dose into two equal doses
- Identify a Step 4

If you have further questions or need clarifications, please contact Laurie Kelley, project manager, at 301-796-5068.

APPENDICES

Appendix A: All AERS Reports (ISR Numbers)

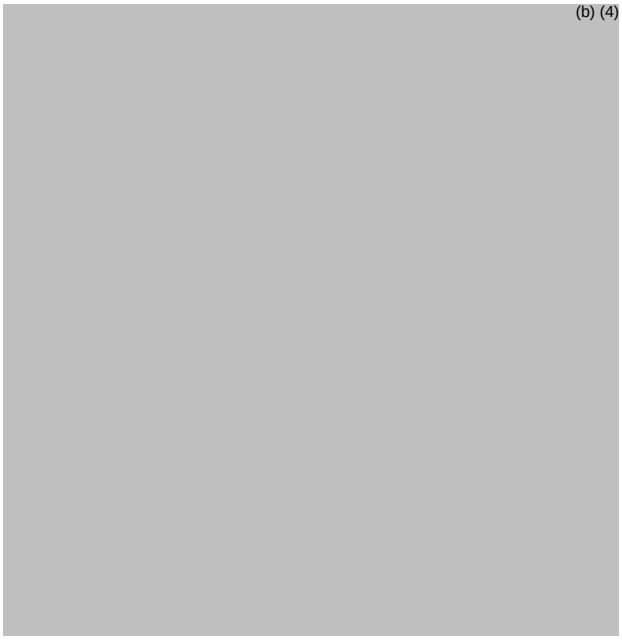
4226833	6087227	6554662	6312489
7402953	7613329	6266268	5278480
7402697	4801853	7569755	7008837
7378026	4905411	6938640	7008840
5444081	5156210	4470821	7179937
7613229	5409800	6717905	7424553
5162249	7362325	6398857	7577657
5823916	4678273	6701814	7577700
5443307	5211507	6526221	4199411
7700726	5117254	5270587	5911392
5825667	4148211	5553405	7008833
6925287	4175897	6326229	7577674
7019974	4220544	5543683	7577686
7589334	4518742	6193625	4200423
7376425	5087472	7725351	7010402
5683316	5047179	7293286	7010426
7719358	5156215	4270386	7056627
4237212	5543632	3869449	7008824
5823915	6264229	5772202	7577652
7308610	6326330	6874012	7577659
7569753	6019888	6424984	7577687
7019969	6723780	6152463	7577697
5166394	6337077	7384230	6970206
6136672	6932550	7289979	7124677
6166493	7361372	7701081	7008841

7008844	7124676	7262158	7021578
7577654	7124678	7297802	5514804
7577699	7008827	5688078	4355646
7124683	6032061	7611229	4219910
7124679	7067645	6427755	7076612
7010399	6424977	5531633	5925673
7008834	5554866	5877454	4357852
7577688	5706028	7179935	4956397
5887765	6542768	6310848	7583383
6970202	6602675	5894668	6697748
6970205	7124672	4443633	5420643
7124680	7124670	5136797	4161931
7124671	7124674	7374399	7436010
7056625	5102496	6310849	7755370
7008830	7488949	4233228	5509464
7124669	7105469	7287815	7700259
7056626	6435436	7553747	
6970203	6490740	6955054	

Appendix B: Summary of ISR Exclusion Criteria

Type of error	***Number of ISRs***
Dose omission	25
Drug interaction	21
No medication error identified	19
Intentional overdose	12
Prescribed overdose	8
Overdose associated with abuse	8
Wrong time	6
Suspected overdose (not specified)	4
Intentional or prescribed underdose	4
Extra dose prescribed or extra dose intentionally taken by the patient	2
Non-compliance	2
Drug diversion	2
Accidental exposure	2
Wrong frequency prescribed	1
Intentional wrong technique	1
Pharmacy transcription error	1

Appendix C: Container Label



Appendix D: Carton Label

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/s/

JULIE M VILLANUEVA
11/09/2011

LUBNA A MERCHANT
11/10/2011

CAROL A HOLQUIST
11/10/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 16, 2008
To:	Russell Katz, MD, Director Division of Neurology Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention
From:	Melina Griffis, R.Ph, Safety Evaluator Division of Medication Error Prevention
Subject:	Xyrem Labeling Review
Drug Name(s):	Xyrem (sodium oxybate) Oral Solution (b) (4)
Submission Number:	S-013
Application Type/Number:	NDA 21-196
Applicant/sponsor:	Jazz Pharmaceuticals
OSE RCM #:	2008-340

CONTENTS

EXECUTIVE SUMMARY

As part of a prior approval labeling supement submitted by the Applicant, the Division of Medication Error Prevention reviewed the carton, container and insert labeling and noted that improvements could be made to the currently approved carton and container labeling to increase readability of information presented on the labeling. We refer you to our comments in section 5 of this review.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a consult from the Division of Neurology to evaluate the Applicant's responses (submitted as prior approval supplement 013 dated August 13, 2007) to the Division of Medication Error Prevention comments on the carton and container labels for Xyrem and to identify any outstanding areas of concern from a medication errors perspective.

1.2 REGULATORY HISTORY

(b) (4)

On August 13, 2007 the Applicant submitted a prior approval supplement (S-013) providing additional pharmacokinetics information and conversion of the prescribing information to the new label format. In this submission the Applicant also provided a response to the Division of Medication Error Prevention comments (b) (4) Although the Applicant included a response to the Division of Medication Error Prevention comments as of the date of this review, (b) (4)

It should be noted that on November 13, 2006 Supplement-012 was approved (b) (4) This change was in response to numerous medication errors (4,590) received by the Applicant in which dosing errors were caused by confusion in the units of measure. A formal post marketing review of these errors is currently ongoing by the Division of Medication Error Prevention.

1.3 PRODUCT INFORMATION

Xyrem is the approved name for sodium oxybate oral solution. Sodium oxybate is a central nervous system depressant indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. The exact mechanism of action is unknown. The dose of Xyrem should be titrated to effect and the recommended starting dose is 4.5 g/night divided into 2 equal doses of 2.25 g each (separated by 4 hours). This dose can be increased in increments of 1.5 g/night (0.75 g per dose) to a maximum dose of 9 g/night (4.5 g per dose).

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention medication error staff to conduct a label, labeling, and/or packaging risk assessment (see section 3 Results). The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. The Division defines a medication error as

any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton labeling and container labels communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because the Division of Medication Error Prevention staff analyze reported misuse of drugs, the staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on August 13, 2007 the following labels for our review (see Appendices A and B for images):

- Container Label (b) (4)
- Carton Label (b) (4)

Additionally, we compared the submitted labels to the currently approved carton and container labels to identify any outstanding areas of concern from a medication errors perspective.

3 RESULTS

The Division of Medication Error Prevention notes that the proposed revised labels are generally consistent with the requests and comments forwarded to the Applicant on (b) (4) However, some of the revisions are inconsistent with the requests, and represent areas of concern from a medication errors perspective. These differences are noted below.

3.1 COMMENTS FORWARDED BUT NOT ACCEPTED BY SPONSOR

(b) (4)

4 DISCUSSION

The Division of Medication Error Prevention notes that the revised labels are generally consistent with the requests and comments forwarded to the Applicant on (b) (4)

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

5 CONCLUSIONS AND RECOMMENDATIONS

Based upon our assessment of the labels and labeling, the Division of Medication Error Prevention has identified the following area of needed improvement. To minimize the potential for confusion, and to improve readability, (b) (4)

The Division of Medication Error Prevention would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy our division on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Daniel Brounstein, Project Manager, at 301-796-0674.

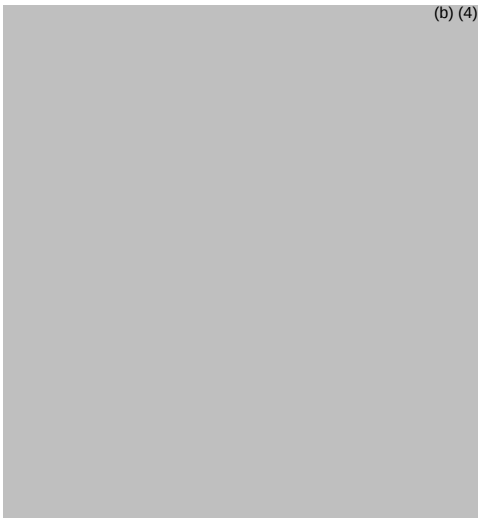
5.1 COMMENTS TO THE APPLICANT

Based upon our assessment of the labels and labeling, the Division of Medication Error Prevention has identified the following area of needed improvement.

(b) (4)

Appendix A: Container Label (b) (4)

(b) (4)



Appendix B: Carton Label: (b) (4)

(b) (4)

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/s/

Melina Griffis
5/16/2008 11:38:36 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/16/2008 11:56:22 AM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: DMETS			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Russell Katz, MD, Division Director, DNP	
DATE 2/20/08	IND NO.	NDA NO. 21-196	TYPE OF DOCUMENT Labeling Supplement	DATE OF DOCUMENT 8/13/07
NAME OF DRUG Xyrem	PRIORITY CONSIDERATION medium		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE March 31, 2008

NAME OF FIRM: Jazz Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This labeling supplement was in response to DNP's [redacted] (b) (4) . I have preliminarily reviewed the carton and container labels [redacted] (b) (4) Please review the carton and container labeling to determine whether the sponsor's changes are acceptable.

The submission can be found in the EDR and the pathway is following:
\\CDSESUB1\NONECTD\N21196\S_013\2007-08-13

Thanks

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Tamy Kim, PharmD, Regulatory Project Manager, DNP Food and Drug Administration	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

Phone: 301-796-1125 Email: tamy.kim@fda.hhs.gov	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tamy E. Kim

2/20/2008 03:27:04 PM