CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-196/S-019

Trade Name: Xyrem®

Generic Name: sodium oxybate

Sponsor: Jazz Pharmaceuticals

Approval Date: April 11, 2014

This "Prior Approval" supplemental new drug applications provide for the addition of information about drug reactions with ibuprofen, diclofenac and extended-release valproate to the "Dosage and Administration, "Drug Interactions", and "Clinical Pharmacology" sections of the labeling.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-196/S-019

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21196/S-019

SUPPLEMENT APPROVAL

Jazz Pharmaceuticals
Attention: Joel Selcher, PhD
Senior Director, Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Dr. Selcher:

Please refer to your Supplemental New Drug Application (sNDA) dated June 18, 2013, received June 20, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xyrem (sodium oxybate) oral solution.

We acknowledge receipt of your amendments dated November 25, 2013, and January 27, 2014.

This "Prior Approval" supplemental new drug application provides for the addition of information about drug reactions with ibuprofen, diclofenac, and extended-release valproate to the "Dosage and Administration", "Drug Interactions", and "Clinical Pharmacology" sections of the labeling.

APPROVAL & LABELING

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 and 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 that includes labeling changes 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).

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}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

ERIC P BASTINGS
04/11/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-196/S-019

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----------

Dosage and Administration, Dose Adjustment with Co-administration of Divalproex Sodium (2.4) 04/2014

----------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).
- Concomitant use with divalproex sodium: an initial reduction in Xyrem dose of at least 20% is recommended (2.4, 7.1).

----------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 (5.5).
- Confusion/Anxiety: Monitor for impaired motor/cognitive function (5.6).
- Parasomnias: evaluate episodes of sleepwalking (5.7).
- High sodium content in Xyrem: Monitor patients with heart failure, hypertension, or impaired renal function (5.8).

----------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: 4/2014

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.

1.2 Excessive Daytime Sleepiness in Narcolepsy

Xyrem (sodium oxybate) oral solution is indicated for the treatment of excessive daytime sleepiness (EDS) in narcolepsy.

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 both doses of 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. Patients should remain in bed following ingestion of the first and second doses, and should not take the second dose until 2.5 to 4 hours after the first dose. Patients may need to set an alarm to awaken for the second dose. Rarely, patients may take up to 2 hours to fall asleep.

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)*].

2.4 Dose Adjustment with Co-administration of Divalproex Sodium

Pharmacokinetic and pharmacodynamic interactions have been observed when Xyrem is co-administered with divalproex sodium. For patients already stabilized on Xyrem, it is recommended that addition of divalproex sodium should be accompanied by an initial reduction in the nightly dose of Xyrem by at least 20%. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting Xyrem dose when introducing Xyrem. Prescribers should monitor patient response and adjust dose accordingly. [see *Drug Interactions (7.1)* and *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, sedating anti-epileptic drugs, 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)*and *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

7.1 Alcohol, sedative hypnotics, and CNS depressants

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.

7.2 Divalproex Sodium

Concomitant use of Xyrem with divalproex sodium resulted in a 25% mean increase in systemic exposure to Xyrem (AUC ratio range of 0.8 to 1.7) and in a greater impairment on some tests of attention and working memory. An initial Xyrem dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking Xyrem [see *Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)*]. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of Xyrem and divalproex sodium is warranted.

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)* and *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 commonalities 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

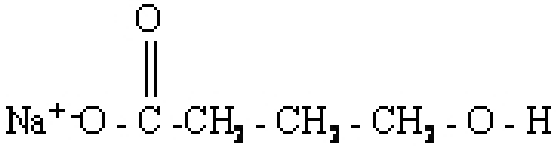
the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid-sequence induction (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 (age 18 to 50 years) were conducted with Xyrem and divalproex sodium, diclofenac, and ibuprofen:

- Divalproex sodium: Co-administration of Xyrem (6 g per day as two equal doses of 3 grams dosed four hours apart) with divalproex sodium (valproic acid, 1250 mg per day) increased mean systemic exposure to sodium oxybate as shown by AUC by approximately 25% , while C_{max} was comparable. Co-administration did not appear to affect the pharmacokinetics of valproic acid. A greater impairment on some tests of attention and working memory was observed with co-administration of both drugs than with either drug alone [see *Drug Interactions (7.1)* and *Dosage and Administration (2.4)*].
- Diclofenac: Co-administration of Xyrem (6 g per day as two equal doses of 3 grams dosed four hours apart) with diclofenac (50 mg/dose twice per day) showed no significant differences in systemic exposure to sodium oxybate . Co-administration did not appear to affect the pharmacokinetics of diclofenac.
- Ibuprofen: Co-administration of Xyrem (6 g per day as two equal doses of 3 grams dosed four hours apart) with ibuprofen (800 mg/dose four times per day also dosed four hours apart) resulted in comparable systemic exposure to sodium oxybate as shown by plasma C_{max} and AUC values. Co-administration did not affect the pharmacokinetics of ibuprofen.

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. 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 recommended 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 2 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.

Solutions prepared following dilution should be consumed within 24 hours.

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 the first and second doses. Instruct patients not to take their second dose until 2.5 to 4 hours after the first dose.

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.

Distributed By:

Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304

Protected by U.S. Patent Nos. 6,472,431; 6,780,889; 7,262,219; 7,851,506; 8,263,650; 8,324,275; 8,461,203

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

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. You should remain in bed after taking the first and second doses of Xyrem.
- 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: April 2014

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

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.**
- Take your dose within 24 hours after mixing Xyrem with water. If you do not take your dose within this time, you will need to throw the mixture away.

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)

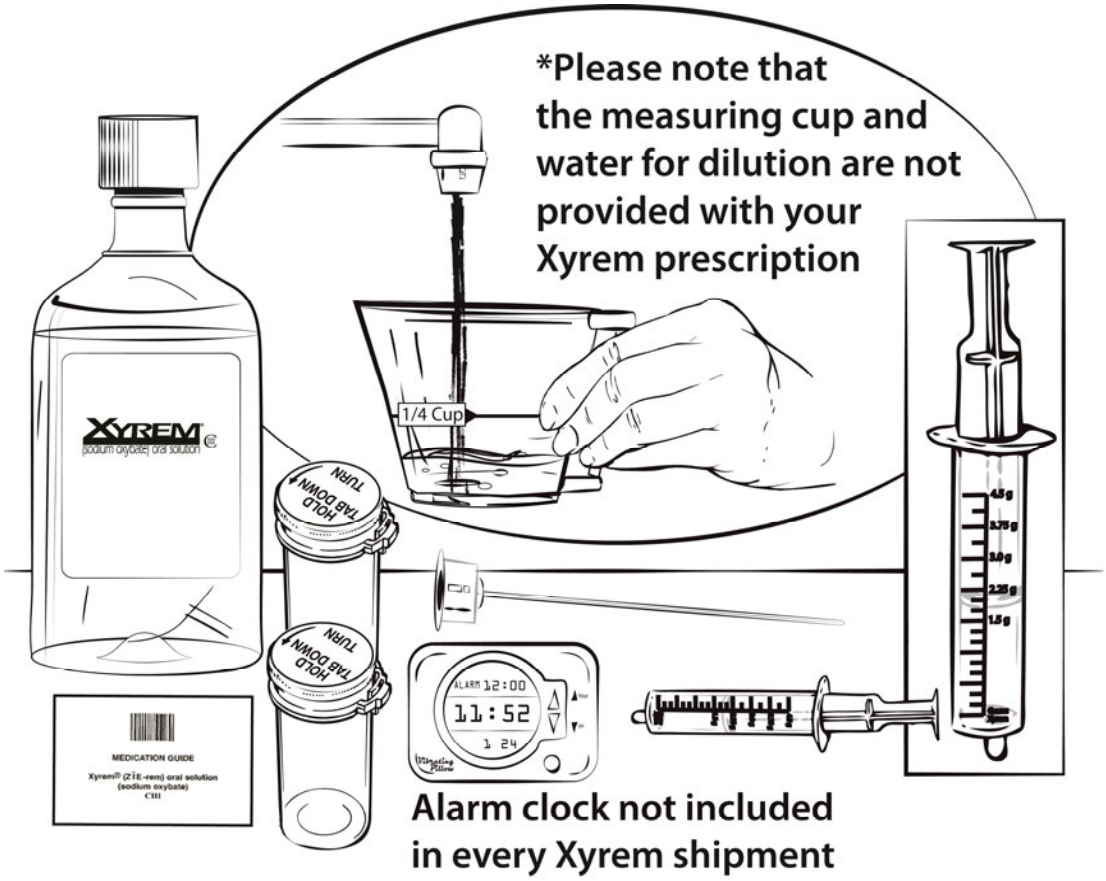


Figure A

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.

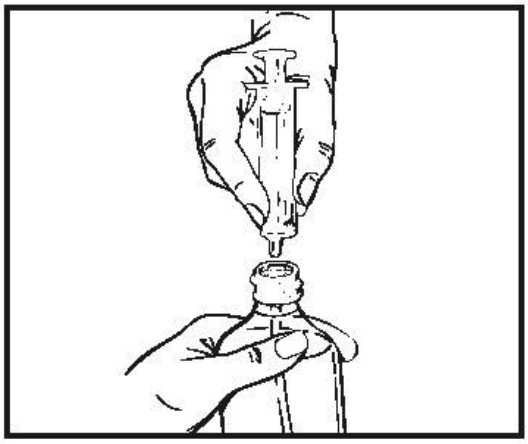


Figure F

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.**

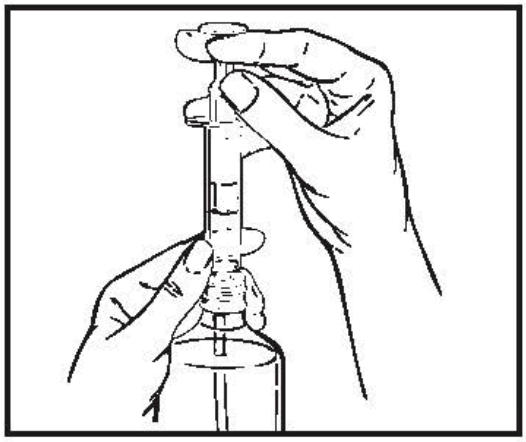


Figure G

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.**

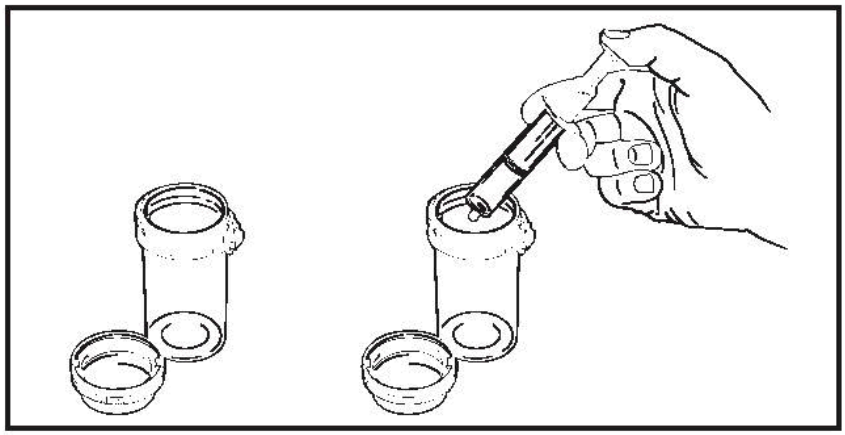


Figure H

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.

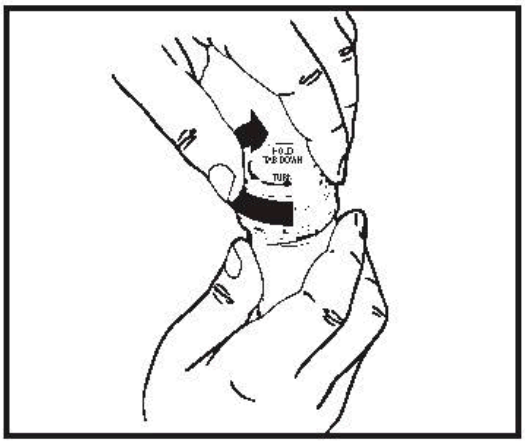


Figure I

- 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: June 2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-196/S-019

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD. Deputy Director, DNP.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	21,196 S-019
Applicant Name	Jazz Pharmaceuticals
Date of Submission	6/18/13
PDUFA Goal Date	4/10/14
Proprietary Name / Established (USAN) Name	Xyrem/Sodium Oxybate
Dosage Forms / Strength	Oral solution
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Ranjit Mani, MD
Pharmacology/Toxicology Review	Raman Baweja, Ph.D.

Supplemental New Drug Application S-019 was submitted to describe the results of drug-drug interaction studies of Xyrem with ibuprofen, diclofenac, and divalproex sodium.

As discussed by Dr. Mani and Dr. Baweja, no pharmacokinetic interaction was observed between Xyrem and ibuprofen, and between Xyrem and diclofenac. There was, however, a pharmacokinetic interaction between Xyrem and divalproex sodium, with a 25% increase in Xyrem AUC during co-administration with divalproex sodium. There was also a pharmacodynamic correlate to these pharmacokinetic changes, with greater impairment on measures of reaction time, vigilance and memory during co-administration of Xyrem and divalproex sodium.

As discussed by Dr. Mani and Dr. Baweja, there was considerable inter-subject variability in the extent of increase in exposure of Xyrem during co-administration with divalproex sodium. The extent of the dose reduction of Xyrem that would be necessary to avoid an excess of adverse events when Xyrem is co-administered with divalproex sodium may vary between patients. The following language will therefore be added to Section 2 "Dosage and Administration" of the Xyrem labeling:

2.4 Dose Adjustment with Co-administration of Divalproex Sodium
Pharmacokinetic and pharmacodynamic interactions have been observed when Xyrem is co administered with divalproex sodium. For patients already stabilized on Xyrem, it is recommended that addition of divalproex sodium should be accompanied by an initial

reduction in the nightly dose of Xyrem by at least 20%. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting Xyrem dose when introducing Xyrem. Prescribers should monitor patient response and adjust dose accordingly. [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

The Xyrem-divalproex sodium drug-drug interaction will also be described in section 7 “Drug Interactions” and section 12 “Clinical Pharmacology” of the Xyrem labeling.

I will issue an approval letter for the above labeling changes.

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

/s/

ERIC P BASTINGS
04/11/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-196/S-019

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21196 (S-019)**
Sponsor:	**Jazz Pharmaceuticals**
Drug:	**Xyrem® (Sodium Oxybate)**
Proposed Indication:	**Narcolepsy**
Material Submitted:	**Supplemental NDA**
Correspondence Date:	**6/18/13**
Date Received / Agency:	**6/20/13**
Date Review Completed:	**4/10/14**
Reviewer:	**Ranjit B. Mani, M.D.**

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Background

This submission consists of a Supplemental New Drug Application (sNDA) for Xyrem® (sodium oxybate) oral solution that seeks to amend the Prescribing Information for that product so as to include the pharmacokinetic results of 3 drug-drug interaction studies of Xyrem® with ibuprofen, with diclofenac, and with divalproex sodium, selected clinical pharmacodynamic data from the same drug-drug interaction studies, and a few other items, including changes to text requested by the Agency during the course of this review.

This sNDA was originally submitted on June 18, 2013. In response to requests from the Agency made during the review of the original submission, the sponsor then submitted an Amendment to this sNDA on November 25, 2013, containing revised proposed labeling and a corrected report for one of the three drug-drug interaction studies included in the original submission.

Xyrem® (sodium oxybate oral solution) was originally approved by the Agency on July 17, 2002, for the treatment of cataplexy in narcolepsy, under NDA 21196. A sNDA that proposed an expansion of the originally approved claim was approved on November 18, 2005; the approved expanded indication for Xyrem® was (and still is) as follows: “The treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.”

Several Prior Approval Labeling supplements for Xyrem® have also been approved since Xyrem® was originally approved for marketing on July 17, 2002. The current text of the Prescribing Information for Xyrem® was approved by the Agency on December 17, 2012.

Xyrem® was originally approved under the Subpart H (21 CFR 314.520) regulations, which have remained applicable to this product. Xyrem® is a Schedule III Controlled Substance available only through a Restricted Distribution Program that is managed by a Central Pharmacy. A deemed Risk Evaluation and Mitigation Strategy (REMS) for Xyrem® is currently in existence, with a significantly-modified REMS currently under discussion between the Agency and sponsor.

Among the core pharmacokinetic properties of sodium oxybate are the following: absolute oral bioavailability of 88%; T_{max} ranging from 0.5 to 1.25 hours; elimination mainly via metabolism to carbon dioxide and water; and an elimination half-life of 0.5 to 1 hour.

The sponsor’s basis for conducting drug-drug interaction studies for sodium oxybate with ibuprofen, diclofenac, and divalproex sodium is as follows. The absorption of gamma-hydroxybutyrate is aided by sodium- and/or proton-dependent monocarboxylate transporter activity in the intestine, kidney, and

blood-brain barrier; the activity of those monocarboxylate transporters are inhibited by non-steroidal anti-inflammatory drugs, such as ibuprofen and diclofenac; and valproic acid also inhibits monocarboxylate transporter activity in the intestine and at the blood-brain barrier. In addition, valproic acid inhibits gamma-hydroxybutyrate dehydrogenase, the enzyme that converts gamma-hydroxybutyrate to succinic acid semialdehyde (which in turn is metabolized via its conversion to succinic acid [by succinic semi-aldehyde dehydrogenase] to carbon dioxide and water through the tricarboxylic acid cycle).

Summary Of Clinical Findings

The three drug-drug interaction studies whose reports are included in this submission are as follows:

- Study 12-006, a randomized, double-blind, placebo-controlled, three-period crossover study whose primary objective was to evaluate the pharmacokinetics and pharmacodynamics of Xyrem® co-administered with ibuprofen; a secondary objective was to evaluate the safety and tolerability of Xyrem® with and without the co-administration of ibuprofen. In this study, ibuprofen was administered in a dose of 800 mg QID (at 4 hour intervals) on 3 consecutive days, with Xyrem® also being administered in two 3 gm doses 4 hours apart on the third day. Xyrem® was also administered alone in two 3 gm doses 4 hours apart on a single separate day during the study.

- Study 12-007, a randomized, double-blind, placebo-controlled, three-period crossover study whose primary objective was to evaluate the pharmacokinetics and pharmacodynamics of Xyrem® co-administered with diclofenac; a secondary objective was to evaluate the safety and tolerability of Xyrem® with and without the co-administration of diclofenac. In this study, diclofenac was administered in a dose of 50 mg QID (at 4 hour intervals) on 3 consecutive days, with Xyrem® also being administered in two 3 gm doses 4 hours apart on the third day. Xyrem® was also administered alone in two 3 gm doses 4 hours apart on a single separate day during the study.

- Study 12-008, a randomized, double-blind, placebo-controlled, five-period crossover study whose primary objective was to evaluate the pharmacokinetics and pharmacodynamics of Xyrem® co-administered with divalproex sodium extended-release tablets; a secondary objective was to evaluate the safety and tolerability of Xyrem® with and without the co-administration of divalproex sodium extended-release tablets. In this study, divalproex sodium extended-release was administered in a dose of 1250 mg once every morning for 14 consecutive days, with Xyrem® also being administered in two 3 gm doses 4 hours apart on the 12^{th} or 14^{th} day of dosing with divalproex sodium.

Common to each of the 3 studies were the following:

- Their conduct at a single US clinical study site.

- The enrollment of a planned 24 healthy men and women aged 18 to 50 years.

- The use of the following tests for assessing the pharmacodynamic effects of the drugs investigated: Karolinska Sleepiness Scale; Simple Reaction Time Task; Digit Vigilance Task; Choice Reaction Time Task; Tracking Task; and Numeric Working Memory Task.

- The use of the following safety outcome measures: adverse events, vital signs, safety laboratory tests (hematology, clinical chemistry, and urinalysis), 12-lead electrocardiograms, and pulse oximetry. (The Columbia-Suicide Severity Rating Scale was used as a safety outcome measure in Study 12-008 only).

- The measurement of plasma and urine concentrations of sodium oxybate as pharmacokinetic outcome measures in each study (plasma concentrations of ibuprofen, diclofenac, and valproic acid were measured as pharmacokinetic measures in Studies 12-006, 12-007, and 12-008, respectively).

The results of the drug-drug interaction studies may be summarized as follows

- No pharmacokinetic interaction was observed between Xyrem® and ibuprofen in Study 12-006, and between Xyrem® and diclofenac in Study 12-007.

- In Study 12-008, the co-administration of divalproex sodium increased the mean exposure to Xyrem®, based on AUC parameters, by about 25% with an AUC ratio that ranged from 0.83 to 1.71; there was considerable inter-subject variability as indicated by a coefficient of variation for AUC parameters between 31% and 43%. The co-administration of Xyrem® in that study had no effect on the pharmacokinetics of valproic acid. The Agency Clinical Pharmacology reviewer has concluded that while a reduction in Xyrem® dosage should be recommended for patients with narcolepsy who are concomitantly administered divalproex sodium, given the inter-subject variability in exposure data seen in Study 12-008, no specific recommendations can be made as to how much the dose of Xyrem® should be reduced under those circumstances.

- No pharmacodynamic interactions (based on measures derived from the aforementioned test battery) were observed between Xyrem® and ibuprofen in Study 12-006, and between Xyrem® and diclofenac in Study 12-007.

- In Study 12-008, the administration of Xyrem® in combination with divalproex sodium resulted in greater impairment on selected measures derived from components of the pharmacodynamic battery assessed at one or more timepoints after dosing, as compared with the administration of Xyrem® alone. The selected measures on which impairments were observed to be greater for the Xyrem® plus divalproex sodium combination versus Xyrem® alone were as follows: Simple Reaction Time Mean, Digit Vigilance Accuracy, Tracking Distance from Target, and Numeric Working Memory Mean Reaction Time. There were no differences between the 2 dosing regimes (i.e., Xyrem® plus divalproex sodium versus Xyrem® alone) on the Karolinska Sleepiness Scale.

- In all three studies, the administration of Xyrem® alone or in combination with the other drug (i.e., ibuprofen, diclofenac or divalproex sodium) resulted in a higher

incidence of selected adverse reactions, in comparison with the administration of the other drug alone. The most common of those adverse events was somnolence, and the adverse event profile of Xyrem® in those studies was broadly consistent with that described in the current Prescribing Information. The incidence of the more common adverse events (e.g., somnolence) was also comparable when Xyrem® was administered in combination with the other drug and when Xyrem® was administered alone in each study.

- There were no deaths, serious adverse events, or discontinuations due to adverse events in any of the three drug-drug interaction studies in this submission. Data for vital signs, safety laboratory tests, electrocardiograms, and the Columbia-Suicide Severity Rating Scale yielded no findings of concern.

The Agency had separately concluded after a review of post-marketing data that the occurrence of falls (and resulting injuries) at night in patients prescribed Xyrem® necessitated changes to Section 2 (DOSAGE AND ADMINISTRATION) and Section 17 (PATIENT COUNSELING INFORMATION) of the Prescribing Information for Xyrem® so as to adequately address that risk. Those proposed changes were conveyed to the sponsor during the review of the current sNDA and have been incorporated into the draft Prescribing Information submitted by the sponsor on November 25, 2013.

An error was noted that had not been observed previously by this reviewer in the description of Trial N2 in Section 14.1 (CLINICAL STUDIES) of the currently-approved Prescribing Information. The current description of that trial, which evaluated the efficacy of Xyrem® as a treatment for cataplexy in narcolepsy, includes the following sentence: "*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*" (emphasis added). The correct text for that sentence is as follows: "*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 2 weeks*" (emphasis added). The report of Trial N2 (formally named Study OMC-SXB-21) was submitted on 12/16/00 during the period of review of the original NDA for Xyrem® which was submitted on 9/30/00; I have confirmed from the Agency efficacy review of the original NDA for Xyrem® that the period of randomized withdrawal in Study OMC-SXB-21 (Trial N2 in the Prescribing Information) lasted 2 weeks and not 4 weeks.

Conclusions

There is no pharmacokinetic or pharmacodynamic interaction between Xyrem® and ibuprofen, or between Xyrem® and diclofenac.

The administration of Xyrem® and divalproex sodium together to healthy subjects resulted in an increase in plasma sodium oxybate exposure of about 25% compared with the administration of Xyrem® alone. However there was considerable inter-subject variability in the extent of that increase in exposure: thus, while a reduction in Xyrem® dose is warranted when that drug is

administered together with divalproex sodium, precise recommendations regarding the extent of that dose reduction cannot be made. The combination of Xyrem® with divalproex sodium was associated with greater impairment on selected tests of attention and working memory at some timepoints after dosing compared with the administration of Xyrem® alone; however, the two treatments did not differ in the severity of sleepiness (as measured by the Karolinska Sleepiness Scale) or in their adverse event profiles.

The results of the 3 drug-drug interaction studies (12-006, 12-007, and 12-007) should be described in the Prescribing Information for Xyrem®, together with the recommendation that the dose of Xyrem® should be reduced when that drug is administered concomitantly with divalproex sodium.

Additional changes to the Prescribing Information are to address the risk of falls in patients prescribed Xyrem® and to correct the description of a clinical efficacy study of Xyrem® in cataplexy.

1. Introduction

This submission consists of a Supplemental New Drug Application (sNDA) for Xyrem® (sodium oxybate) oral solution that seeks to amend the Prescribing Information for that product so as to include the pharmacokinetic results of 3 drug-drug interaction studies of Xyrem® with ibuprofen, with diclofenac, and with divalproex sodium, selected clinical pharmacodynamic data from the same drug-drug interaction studies, and a few other items, including changes to text requested by the Agency during the course of this review.

The 3 clinical pharmacokinetic studies whose results are to be described in the Prescribing Information for Xyrem® are: Study 12-006, Study 12-007, and Study 12-008

Under this sNDA, the sponsor has proposed changes of a substantive nature to the DOSAGE AND ADMINISTRATION (Section 2), DRUG INTERACTIONS (Section 7) and CLINICAL PHARMACOLOGY (Section 12) components of the Prescribing Information for Xyrem®.

This sNDA was originally submitted on June 18, 2013 (as per the date on the sponsor's cover letter), and its review begun. On November 1, 2013, the Agency requested that the report of Study 12-007, one of the 3 drug-drug interaction studies whose reports were already contained in submission of June 18, 2013, be corrected. On November 14, 2013, the Agency also requested that additional changes be made to the Prescribing Information that were unrelated to the contents of the original submission of this supplemental NDA. In response to those requests the sponsor submitted an Amendment to this Supplemental NDA on November 25, 2013, containing revised proposed labeling and a corrected report for Study 12-007.

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

Several Prior Approval Labeling Supplements for Xyrem® have also been approved since Xyrem® was originally approved for marketing on July 17, 2002. The current text of the Prescribing Information for Xyrem® was approved by the Agency on December 17, 2012: that Agency action was in response to Supplement #013 submitted on August 13, 2007, and further amended on February 3, 2011, April 24, 2012, and October 3, 2012. The text of the Prescribing Information was converted from its earlier ("legacy") format to Physician Labeling Rule (PLR) format with that approval.

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

Substance available only through a Restricted Distribution Program that is managed by a central pharmacy. A deemed Risk Evaluation and Mitigation Strategy (REMS) for Xyrem® is currently in existence, with a significantly-modified REMS currently under discussion between the Agency and sponsor.

2. Contents Of Submissions

The contents of the two main submissions reviewed here are listed below.

- The original submission of this sNDA (dated June 18, 2013, as per the sponsor's cover letter) had the following key components.
  - Cover letter
  - Draft labeling (including annotated labeling)
  - Complete reports of Studies 12-007, 12-008, and 12-009.
  - Statistical datasets for Studies 12-007, 12-008, and 12-009.

- The Amendment to this sNDA submitted on November 25, 2013 had the following main components
  - Cover letter
  - Draft labeling (including annotated labeling)
  - Complete report of Study 12-007.

3. Contents Of Review

The contents of this sNDA will be reviewed under the following primary headings and in the same consecutive order as below.

- Main pharmacokinetic properties of sodium oxybate
- Basis for drug-drug interaction studies newly described in current submission
- Study 12-006
- Study 12-007
- Study 12-008
- Other items contributing to currently-proposed changes to Prescribing Information for Xyrem®
- Sponsor's proposed changes to Prescribing Information for Xyrem®
- Summary of Agency Clinical Pharmacology review
- Financial disclosure certification
- Reviewer's summary comments
- Reviewer's proposed labeling
- Recommendation
- Appendix 1: Final Prescribing Information.

4. Main Pharmacokinetic Properties Of Sodium Oxybate

Key pharmacokinetic properties of sodium oxybate are listed below, based on the current Prescribing Information for Xyrem®.

- Non-linear pharmacokinetics which are similar after single or repeated dosing
- Absolute oral bioavailability of 88%
- T_{max} ranging from 0.5 to 1.25 hours
- Plasma levels that increase more than dose-proportionally
- Delayed absorption and reduction in exposure after administration with a high fat meal
- Less than 1% binding to plasma protein
- Elimination mainly via metabolism, with < 5% of the drug appearing unchanged in the urine within 6 to 8 hours after dosing and negligible fecal excretion
- Elimination half-life of 0.5 to 1 hour
- Metabolism to carbon dioxide and water primarily via the tricarboxylic acid cycle and secondarily via beta-oxidation (the primary pathway involves first the conversion of sodium oxybate by gamma-hydroxybutyrate dehydrogenase to succinic semialdehyde, which is in turn converted by succinic semialdehyde dehydrogenase to succinic acid; succinic acid then enters the tricarboxylic acid cycle).

5. Basis For Drug-Drug Interaction Studies Newly Described In Current Submission.

The basis provided by the sponsor for conducting drug-drug interaction studies of Xyrem® with ibuprofen, with diclofenac, and with divalproex sodium is described below.

The absorption of gamma-hydroxybutyrate is aided by sodium- and/or proton-dependent monocarboxylate transporter activity in the intestine, kidney, and blood-brain barrier.

The activity of the aforementioned monocarboxylate transporters are inhibited by non-steroidal anti-inflammatory drugs; ibuprofen and diclofenac are both non-steroidal anti-inflammatory drugs.

Valproic acid also inhibits monocarboxylate transporter activity in the intestine and at the blood brain; in addition, valproic acid inhibits gamma-hydroxybutyrate dehydrogenase, the enzyme that converts gamma-hydroxybutyrate to succinic acid semialdehyde.

6. Study 12-006

6.1 Study Protocol

6.1.1 Title

A Randomized, Double-Blind, Placebo-Controlled, Three-Period Crossover Study To Evaluate The Pharmacokinetics And Pharmacodynamics Of Xyrem® (Sodium Oxybate) Co-Administered With Ibuprofen In Healthy Subjects.

6.1.2 Objectives

6.1.2.1 Primary Objective

To evaluate the pharmacokinetics and pharmacodynamics of Xyrem® co-administered with ibuprofen.

6.1.2.2 Secondary Objective

To evaluate and compare the safety and tolerability of Xyrem® with and without co-administration of ibuprofen.

6.1.3 Design, Dose, Sample Size, And Duration

This was a randomized, double-blind, placebo-controlled, three-period crossover study.

24 subjects were to be enrolled in the study and were to receive one of Treatments A, B, and C during each study period in randomized order, as depicted in the following study schema table which I have copied from the submission.

		Treatment Periods Treatment Days Randomized Treatments						
Screening	**Baseline**	**Period 1**		**Period 2**		**Period 3**		**Final Day**
Days -21 through -2	Day -1	Days 1 - 3	Days 4 - 5	Days 6 - 8	Days 9 -10	Days 11 - 13	Days 14-15	Day 15
		A, B, or C	Washout	A, B, or C	Washout	A, B, or C	Washout	

Regimen A = Ibuprofen placebo (qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period) + Xyrem two 3 g doses 4 h apart on the 3rd day of the period
Regimen B = Ibuprofen (800 mg/dose qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period) + Xyrem two 3 g doses 4 h apart on the 3rd day of the period
Regimen C = Ibuprofen (800 mg/dose qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period) + Xyrem placebo two doses 4 h apart on the 3rd day of the period

On days when Xyrem® or Xyrem® placebo was to be co-administered with ibuprofen or ibuprofen placebo (Days 3, 8, and 13 in the above table):

- Xyrem® or Xyrem® placebo was to be administered at 0 hours and 4 hours
- Ibuprofen was to be administered at -1 hours and 3 hours.

On the days when Xyrem®/Xyrem® placebo was to be co-administered with ibuprofen/ibuprofen placebo:

- A light breakfast was to be administered about 2 hours before the first dose of ibuprofen/ibuprofen placebo
- A standardized lunch was to be administered about 2 hours after the first dose of Xyrem®/Xyrem® placebo
- A standardized dinner was to be administered about 4 hours after the second dose of Xyrem®/Xyrem® placebo.

A dose of ibuprofen of 800 mg QID was evaluated in this study as it is the highest recommended prescription dose.

6.1.4 Key Inclusion Criteria

- Men and women. Age: 18 to 50 years.
- Healthy.
- Non-smoker.
- Body Mass Index between 18 and 30 kg/^{m2}.
- Agreement by female subjects to use a medically-accepted method of contraception (specified) throughout the study period and for 30 days after study completion.
- Agreement by male subjects to refrain from sperm donation for 30 days after study completion and to use adequate contraception throughout the study period and for 30 days after study completion.
- Good general health as determined by investigators via medical history, physical examination, clinical laboratory tests, and electrocardiograms at screening and baseline.
- Negative screens for human immunodeficiency virus antibody, Hepatitis B virus antigen, Hepatitis C virus antibody, and Hepatitis A virus IgM antibody. No clinical history related to such infections.
- Negative drug and alcohol screens.
- Hemoglobin ≥ 12 g/dL at baseline.
- Able to read and understand English, provide written informed consent, and comply with all study procedures and restrictions.
- Willing to refrain from consuming xanthine-containing beverages or alcohol while at the center and willing to refrain from intensive physical exercise during the study.
- Willing to remain in the study facility for 15 days.

6.1.5 Key Exclusion Criteria

- Clinically significant unstable medical abnormality, chronic disease, or history or presence of significant neurological (including seizure and cognitive disorders) or psychiatric disorder, hepatic, renal, endocrine, cardiovascular (including hypertension), gastrointestinal, pulmonary, or metabolic disease, or any other abnormality that could interfere with evaluation of study drug.
- Succinic semialdehyde dehydrogenase deficiency.
- History of or current insomnia.
- Screening or baseline blood oxygen saturation < 95% as measured by pulse oximetry on room air, or suspected respiratory difficulty or other condition that could compromise a subject's ability to breathe or maintain adequate oxygen saturation.
- Diagnosis of sleep apnea or at high risk of sleep apnea, history of loud snoring or observed to stop breathing during sleep.
- Score of > 12 points on the Epworth Sleepiness Scale.
- History or presence of gastrointestinal, hepatic or renal disease or any other condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs.
- Pregnant, nursing, or lactating.
- Any severe drug allergy or a history of allergic or other severe adverse reaction or intolerance to Xyrem®, gamma-hydroxybutyrate, ibuprofen, aspirin, other non-steroidal anti-inflammatory drugs.
- History of or current substance abuse or known drug dependence within the last 2 years prior to screening or positive test for drugs of abuse at screening or baseline.
- Inability to swallow capsules.
- Clinically significant illness within 30 days of screening.
- Clinically significant abnormal finding on physical examination, electrocardiogram, or safety laboratory tests, as determined by the investigator.
- Consumption of more than two alcoholic beverages daily or 15 or more alcoholic beverages weekly within 14 days of screening.
- Alcohol ingestion within 24 hours before admission or at any time through completion of the study or unwilling to refrain from alcohol or drug ingestion through study completion.
- Use of tobacco products or products for smoking cessation within 90 days before screening, including use of nicotine-containing products or history of significant use of tobacco (> 10 cigarettes or equivalent per day) within 3 years prior to Day -1.
- Use of any prescription medication within 14 days or over-the-counter medication within 7 days of dosing (excluding acetaminophen), or intent to use any prescription or over-the-counter medication during the study.
- Self-reporting of the consumption of more than 180 mg of caffeine per day (equal to or greater than 4 cups of coffee or the equivalent in caffeinated beverages).

- Consumption of grapefruit or products containing grapefruit or grapefruit juice, Seville oranges, orange marmalade, pomelos, xanthine-containing products, or quinine-containing products (e.g., tonic water) within 48 hours before admission (Day -1) or any time through study completion.
- Any blood donation within 90 days of dosing.
- Any plasma donation within 7 days of dosing.
- History, or suspicion of inability to comply fully with all procedural aspects of the study.
- On a sodium-restricted diet.

6.1.6 Concomitant Medications

See Exclusion Criteria above.

6.1.7 Schedule

The study schedule is copied below from the submission, and is self-explanatory.

Evaluation	Screening Days -21 through -2	Baseline Day -1	Period 1		Period 2		Period 3		Final Day[1]
			Dosing Days 1-3	Washout Day 4-5	Dosing Days 6-8	Washout Day 9-10	Dosing Days 11-13	Washout Day 14-15	Day 15 [1]
Informed Consent	X								
I/E Criteria	X	X							
Demographics	X								
Medical History[2]	X	X							
Physical Examination[3]	X	X							X
Height[4]	X								
Weight[4]	X	X							X
Alcohol and Drug Screens[5]	X	X							
Pregnancy Test[6]	X	X							X
Laboratory Tests[7]	X	X							X
Epworth Sleepiness Scale	X								
Randomization			X[8]						
Vital signs and temperature[9]	X	X	X	X	X	X	X	X	X
12-Lead ECG[10]	X	X	X	X	X	X	X	X	X
Pulse oximetry[11]	X	X	X		X		X		X
Drug Administration[12]			X		X		X		
Training for PD Battery		X[13]							
PD Battery[14]			X		X		X		
Blood samples for PK Analysis[15]			X		X		X		
Urine samples for PK[16]			X		X		X		
Adverse Event Assessment			X	X	X	X	X	X	X →
Concomitant Medications	X	X	X	X	X	X	X	X	X
Assess Reason for Study Discontinuation									X

1 Final day or early termination.

2 Includes a review of previous/ongoing medications.

3 Includes a full examination of body systems (except the genitourinary body system) and will also include a brief neurological examination at the study center.

[4] Height and weight will be measured in ordinary indoor clothes, without shoes.

[5] Drug screen to include amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates.

[6] Only for female subjects

[7] Includes serum chemistry (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, creatine kinase, gamma-glutamyl transferase, globulin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, uric acid), serology (Hep A IgM-Ab, HBs-Ag, HCV-Ab, and HIV-Ab; at Screening only), TSH (at Screening only), hematology (complete blood count including platelet count and white blood cell count with differential), coagulation (International Normalized Ratio, partial thromboplastin time), and urinalysis (appearance, bilirubin, color, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, urobilinogen).

[8] Before dosing in Period 1.

[9] Vital signs (systolic and diastolic blood pressure, pulse, and respiratory rate) and temperature will be measured after the subject has been resting supine for at least 5 minutes at Screening, Baseline, the Final Day, and during Periods 1, 2, and 3. On Days 3, 8, and 13, vital signs will be measured before the first dose of ibuprofen/ibuprofen placebo and at -0.5 h, 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 4.25 h, 4.5 h, 4.75 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 8 h, 10 h, and 12 h relative to the first dose of Xyrem/Xyrem placebo, and temperature will be measured before the first dose of ibuprofen/ibuprofen placebo and 10 h after the first dose of Xyrem/Xyrem placebo. On Days 1 & 2, 6 & 7, and 11 &12, vital signs and temperature will be measured 1 h after each dose of ibuprofen/ibuprofen placebo. On Days 4 & 5, 9 & 10, and 14 & 15, vital signs and temperature will be measured in the morning at approximately 8 am. Respiratory rate will be assessed over 30 seconds.

[10] A standard 12-lead ECG will be recorded with the subject resting supine for at least 5 minutes at Screening, Baseline, and the Final Day. In Periods 1, 2, and 3, ECG will be recorded before the first dose of Xyrem/Xyrem placebo and 2 h and 24 h after the first dose of Xyrem/Xyrem placebo.

[11] Oxygen saturation will be recorded at Screening, Baseline, and the Final Day, will be monitored continuously during Periods 1, 2, and 3 on Days 3, 8, and 13 for 10 hours after the first Xyrem/Xyrem placebo dose, and will be recorded at predose and at 0.5 h, 1 h, 2 h, 4 h, 4.5 h, 5 h, 6 h, 8 h, and 10 h after the first dose of Xyrem/Xyrem placebo. Sleeping subjects will be aroused if the pulse oximetry reading falls below 90%.

[12] Ibuprofen or ibuprofen placebo will be administered qid (doses separated by 4 hours during the day, eg, ~8 am, 12 pm, 4 pm, and 8 pm) for 2 days (Days 1 & 2, 6 & 7, and 11 & 12) before co-administration day. On co-administration day (Days 3, 8, and 13), ibuprofen or ibuprofen placebo will be administered at -1 h and 3 h with Xyrem or Xyrem placebo administered at 0 h and 4 h.

[13] Training for the PD Battery must be completed before the first PD assessment.

[14] The PD Battery (including KSS, Simple Reaction Time task, Digit Vigilance task, Choice Reaction Time task, Tracking task, and Numeric Working Memory task) will be administered on Days 3, 8, and 13 at 2 hours before the first dose of Xyrem/Xyrem placebo and at 0.5 h, 1 h, 2.5 h, 4 h (pre 2nd Xyrem/Xyrem placebo dose), 4.5 h, 5 h, 6.5 h, and 8 h after the first dose of Xyrem/Xyrem placebo.

[15] On Days 3, 8, and 13, the following blood samples will be collected for PK analysis: 4 mL (to measure sodium oxybate) at 0 h (predose), 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h (pre 2nd Xyrem/Xyrem placebo dose), 4.25 h, 4.5 h, 4.75 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 8 h, and 10 h relative to the first dose of Xyrem/Xyrem placebo; 4 mL (to measure ibuprofen) at -1 h, -0.5 h, 0 h, 0.5 h, 1 h, 2 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 6 h, 7 h, and 9 h relative to the first dose of Xyrem/Xyrem placebo. Blood samples for PK analysis of each analyte will be taken within ±2 minutes of the specified time points for the first hour after each dose and within ±5 minutes of the specified time points after one hour.

[16] On Days 3, 8, and 13, collect urine to measure sodium oxybate concentrations at predose (-4 to 0 hours) and during 0-4, 4-8, and 8-12 hour intervals after the first dose of Xyrem/Xyrem placebo.

Please note that the pharmacodynamic test battery (see Section 6.1.8.3 for further details about that battery) was to be administered at the following timepoints on Days 3, 8, and 13 (i.e., the days when ibuprofen/ibuprofen placebo and Xyrem®/Xyrem® placebo were jointly administered).

- 2 hours before the first dose of Xyrem®/Xyrem® placebo.

- 0.5, 1.0, 2.5, 4.0, 4.5, 5.0, 6.5, and 8.0 hours after the first dose of Xyrem®/Xyrem® placebo.

Pharmacokinetic sampling was also performed on Days 3, 8, and 13, only, at the timepoints listed in the above table.

6.1.8 Outcome Measures

6.1.8.1 Safety Measures

Adverse events, vital signs, safety laboratory tests (hematology, clinical chemistry, and urinalysis), 12-lead electrocardiograms, and pulse oximetry.

6.1.8.2 Pharmacokinetic Measures

- Plasma and urine concentrations of sodium oxybate
- Plasma concentrations of ibuprofen.

6.1.8.3 Pharmacodynamic Measures

A battery of pharmacodynamic tests was used to evaluate sleepiness and selected cognitive functions. The tests are summarized in the following sponsor table, and were administered in the same consecutive order as in the table.

Karolinska Sleepiness Scale (KSS)	The KSS is a single-question, nine-point self-rating scale used to measure levels of sleepiness during the last 5 minutes. The scale ranges from 1 =very alert to 9 =very sleepy, great effort to stay awake or fighting sleep. A score of 7 or more indicates excessive sleepiness.
Simple Reaction Time Task	The participant was instructed to press the 'YES' response button as quickly as possible every time the word 'YES' was presented on the screen. Stimuli were presented with a varying inter-stimulus interval.
Digit Vigilance Task	A target digit was randomly selected and constantly displayed to the right of the screen. A series of digits was then presented in the center of the screen and the participant was required to press the 'YES' button as quickly as possible every time the digit in the series matched the target digit.
Choice Reaction Time Task	Either the word 'NO' or the word 'YES' was presented on the screen and the participant was instructed to press the corresponding button as quickly as possible. Each stimulus word was chosen randomly with equal probability and there was a varying inter-stimulus interval.
Tracking Task	The participant used a joystick to track a randomly moving target on the screen. The distance off-target per second was recorded
Numeric Working Memory Task	A series of digits was presented for the participant to hold in memory. This was followed by a series of probe digits for each of which the participant had to decide whether or not it was in the original series and press the 'YES' or 'NO' response button as appropriate, as quickly as possible.

The methods used to score the above tests are summarized below in a table taken from the submission.

Task	Major Measures
KSS	Score (1-9)
Simple Reaction Time	Average time taken for each response (ms)
Digit Vigilance	Average time taken to make each detection (ms) Percentage of correct detections (%) Number of times button was pressed when no stimulus was presented ("false alarms" [#])
Choice Reaction Time	Percentage of correct responses (%) Average response time of correct responses (ms)
Tracking	Average distance off target (mm)
Numeric Working Memory	Sensitivity index, reflecting ability to correctly hold digits in working memory (SI); a score of 1 represents perfect performance, a score of zero represents chance performance. Response time (ms)
Power of Attention	Sum of response times from three tasks (Simple Reaction Time, Digit Vigilance, and Choice Reaction Time [ms])
Continuity of Attention	Sum of correct responses in the Choice Reaction Time task and correct detections in the Digit Vigilance task minus the false alarms in the Digit Vigilance task and the average distance off target from the Tracking task (#)

6.1.9 Analysis Plan

Key aspects of the statistical analysis as actually conducted are summarized below.

6.1.9.1 Pharmacokinetic Measures

The following plasma pharmacokinetic parameters were calculated for sodium oxybate and ibuprofen for specific sampling intervals.

Compound	Sampling Interval*	Pharmacokinetic Parameter
Sodium oxybate	0-4 hours	AUC_T, C_{max}, T_{max}
	4-8 hours	AUC_T, C_{max}, T_{max}
	0-10 hours	AUC_t, AUC_∞, C_{max}, T_{max}, λ, $t_{½}$
Ibuprofen	0-4 hours	AUC_T, C_{max}, T_{max}
	4-8 hours	AUC_T, C_{max}, T_{max}
	0-10 hours	AUC_t, AUC_∞, C_{max}, T_{max}, λ, $t_{½}$

*Relative to first dose of Xyrem®, and only dose for ibuprofen

The following urine parameters were calculated for sodium oxybate, alone:

- Urine concentration (C_{urine})
- Amount excreted during each collection interval (A_e)
- Cumulative amount excreted over the entire 12-hour collection period ($CumA_e$)
- Percentage of dose recovered in urine in each collection interval (%Dose)
- Cumulative percentage of dose recovered in urine (Cum%Dose).

Plasma concentrations and parameters for sodium oxybate and ibuprofen were summarized by treatment, using descriptive statistics. Pharmacokinetic parameters were also evaluated by analysis of variance models using log-transformed data. The 90% confidence intervals of the ratios for the various C_{max} and AUC parameters were calculated.

6.1.9.2 Pharmacodynamic Measures

Pharmacodynamic measurements were summarized and further investigated using analysis of covariance models. Changes from baseline at each timepoint were compared between the Xyrem® + ibuprofen placebo and Xyrem® + ibuprofen treatments; and between the Xyrem® placebo + ibuprofen and Xyrem® + ibuprofen treatments.

6.1.9.3 Safety Measures

These were summarized using descriptive statistics.

6.2 Summary Study Results

This study was conducted at a single clinical site in the United States by a Contract Research Organization: Celerion of Neptune, NJ.

6.2.1 Pharmacokinetic Results

In the following sponsor table, the sodium oxybate pharmacokinetic parameters for the Xyrem® + ibuprofen combination are compared with those for the Xyrem® plus ibuprofen placebo combination.

Parameter (Units)	Geometric LS Means[a]		% Mean Ratio Test/ Reference[b]	% Difference[c]	p-value	90% Confidence Interval
	Test SXB + IBU N=20	Reference SXB + Ipbo N=20				
C_{max} 0-4 h (µg/mL)	86.8	91.4	95.0	-5.05	0.0742	90.6, 99.6
C_{max} 4-8 h (µg/mL)	79.0	83.5	94.6	-5.40	0.0956	89.6, 99.9
C_{max} (µg/mL)	89.1	94.9	93.9	-6.08	0.0103	90.4, 97.5
AUC_{τ} 0-4 h (µg*h/mL)	129	136	95.5	-4.53	0.0455	92.0, 99.1
AUC_{τ} 4-8 h (µg*h/mL)	136	141	96.4	-3.63	0.1557	92.3, 100.6
AUC_{0-t} (µg*h/mL)	269	280	95.9	-4.13	0.0177	93.2, 98.6
AUC_{0-inf} (µg*h/mL)	271	283	95.9	-4.13	0.0194	93.2, 98.6

SXB=Sodium oxybate, IBU=ibuprofen, Ipbo = ibuprofen placebo
SXB + IBU: Ibuprofen (800 mg qid 4 hours apart on the first and second day and two doses on the third day of the period) + Xyrem two 3 g doses 4 hours apart on the third day of the period (test) (Treatment B).
SXB + Ipbo (qid 4 hours apart on the first and second day and two doses on the third day of the period) + Xyrem two 3 g doses 4 hours apart on the third day of the period (reference) (Treatment A).
[a] Geometric least-squares (LS) means were calculated by exponentiating the LS means from the ANOVA. The ANOVA mixed-effects model includes sequence, subject within sequence, period, and treatment.
[b] % Mean Ratio = 100*(test/reference)
[c] % Difference = difference between treatments (test - reference) expressed as a percentage of reference

The sponsor points out that the percentage mean ratio for the Xyrem® + ibuprofen combination versus the Xyrem® plus ibuprofen placebo combination ranged from 93.9% to 96.4% and that the 90% confidence intervals for those comparisons were all within the 80-125% range.

The next sponsor table displays comparisons of the ibuprofen pharmacokinetic parameters for the Xyrem + ibuprofen combination with the Xyrem® placebo plus ibuprofen combination. The results are self-explanatory.

Parameter (Units)	Geometric LS Means[a]		% Mean Ratio Test/ Reference[b]	% Difference[c]	p-value	90% Confidence Interval
	Test SXB + IBU N=20	Reference Spbo + IBU N=20				
C_{max} 0-4[d] h (µg/mL)	60.6	61.3	98.9	-1.10	0.6832	94.4, 104
C_{max} 4-8[d] h (µg/mL)	48.4	51.9	93.4	-6.58	0.1272	86.8, 101
C_{max} (µg/mL)	61.3	62.3	98.4	-1.59	0.4526	94.9, 102
AUC_{τ} 0-4[d] h (µg*h/mL)	145	149	97.2	-2.81	0.2004	93.6, 101
AUC_{τ} 4-8[d] h (µg*h/mL)	138	142	97.5	-2.52	0.5094	91.3, 104
AUC_{0-t} (µg*h/mL)	343	351	97.8	-2.18	0.2623	94.6, 101
AUC_{0-inf} (µg*h/mL)	442[e]	407[f]	109	8.69	0.3982	86.5, 137

SXB=Sodium oxybate, Spbo = Sodium oxybate placebo, IBU=ibuprofen
SXB + IBU: Ibuprofen (800 mg qid 4 hours apart on the first and second day and two doses on the third day of the period) + Xyrem two 3 g doses 4 hours apart on the third day of the period (test) (Treatment B).
Spbo + IBU: Ibuprofen (800 mg qid 4 hours apart on the first and second day and two doses on the third day of the period) + Xyrem placebo two doses 4 hours apart on the third day of the period (reference) (Treatment C).

[a] Geometric LS means were calculated by exponentiating the LS means from the ANOVA. The ANOVA mixed-effects model includes sequence, subject within sequence, period, and treatment.
[b] % Mean Ratio = 100*(test/reference)
[c] % Difference = difference between treatments (test - reference) expressed as a percentage of reference
[d] Times are relative to the ibuprofen dose
[e] N=9
[f] N=7

The renal excretion of sodium oxybate increased about two-fold when Xyrem® was administered with ibuprofen compared with the administration of Xyrem® with ibuprofen placebo.

6.2.2 Pharmacodynamic Results

The administration of Xyrem® whether alone or in combination with ibuprofen resulted in an increase in sleepiness as compared with baseline (on the Karolinska Sleepiness Scale) and impaired performance on most of the other components of the cognitive test battery. Those impairments were most apparent over the hour following the administration of each dose of Xyrem®. The co-administration of ibuprofen did not appear to influence the pharmacodynamic effect of Xyrem®.

6.2.3 Safety Results

There were no deaths, serious adverse events, or discontinuations due to adverse events.

The number (%) of subjects with adverse events that occurred in ≥ 2 subjects is summarized in the following table, which I have copied from the submission.

Adverse Event	Days 1 & 2[a] of each treatment regimen		Days 3, 4, & 5 of each treatment regimen			Total
	Ibuprofen placebo	Ibuprofen	Xyrem placebo + ibuprofen	Xyrem + ibuprofen placebo	Xyrem + ibuprofen	
Any AE	0	3 (14%)	10 (48%)	18 (86%)	18 (86%)	20 (95%)
Somnolence	0	0	3 (14%)	16 (76%)	15 (71%)	20 (95%)
Euphoric mood	0	0	1 (5%)	7 (33%)	10 (48%)	13 (62%)
Dizziness	0	0	0	3 (14%)	5 (24%)	8 (38%)
Headache	0	0	4 (19%)	1 (5%)	3 (14%)	7 (33%)
Nausea	0	0	0	3 (14%)	2 (10%)	4 (19%)
Constipation	0	2 (10%)	0	0	0	2 (10%)
Fatigue	0	0	1 (5%)	0	1 (5%)	2 (10%)
Pruritus	0	1 (5%)	1 (5%)	0	1 (5%)	2 (10%)

[a] Prior to Xyrem or Xyrem placebo

As the above table indicates, somnolence as well as several other adverse events were much more frequent in the two Xyrem® groups than with ibuprofen alone.

No vital sign, electrocardiogram, or laboratory results of clinical significance were observed in this study; I have reviewed those data.

6.3 Sponsor's Conclusions

I have summarized the sponsor's main conclusions below.

6.3.1 Pharmacokinetic Conclusions

The exposure to sodium oxybate, based on plasma C_{max} and AUC, was slightly reduced following the co-administration of Xyrem® and ibuprofen as compared with the administration of Xyrem alone. However, the interaction between Xyrem® and ibuprofen did not appear to be clinically significant. The co-administration of Xyrem® with ibuprofen did not appear to affect the pharmacokinetics of ibuprofen.

6.3.2 Pharmacodynamic Conclusions

The administration of Xyrem® resulted in sleepiness and caused impairment of attention, working memory, and skilled coordination in healthy subjects, as was expected. The extent of those effects was not influenced by the co-administration of ibuprofen.

6.3.3 Safety Conclusions

No new safety signals were observed for Xyrem® or ibuprofen in this population.

7. Study 12-007

7.1 Protocol

7.1.1 Title

A Randomized, Double-Blind, Placebo-Controlled, Three-Period Crossover Study To Evaluate The Pharmacokinetics And Pharmacodynamics Of Xyrem® (Sodium Oxybate) Co-Administered With Diclofenac In Healthy Subjects.

7.1.2 Objectives

7.1.2.1 Primary Objective

To evaluate the pharmacokinetics and pharmacodynamics of Xyrem® co-administered with diclofenac.

7.1.2.2 Secondary Objective

To evaluate and compare the safety and tolerability of Xyrem® with and without co-administration of diclofenac.

7.1.3 Design, Dose, Sample Size, And Duration

This was a randomized, double-blind, placebo-controlled, three-period crossover study.

24 subjects were to be enrolled in the study and were to receive one of Treatments A, B, and C during each study period in randomized order, as depicted in the following study schema table which I have copied from the submission.

		Treatment Periods Treatment Days Randomized Treatments						
Screening	**Baseline**	**Period 1**		**Period 2**		**Period 3**		**Final Day**
Days -21 through -2	Day -1	Days 1 - 3	Days 4 - 5	Days 6 - 8	Days 9 - 10	Days 11 - 13	Days 14 - 15	Day 15
		A, B, or C	Washout	A, B, or C	Washout	A, B, or C	Washout	

A = Diclofenac placebo (qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period) + Xyrem two 3 g doses 4 h apart on the 3rd day of the period
B = Diclofenac (50 mg qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period) + Xyrem two 3 g doses 4 h apart on the 3rd day of the period
C = Diclofenac (50 mg qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period) + Xyrem placebo two doses 4 h apart on the 3rd day of the period

On days when Xyrem® or Xyrem® placebo was to be co-administered with diclofenac or diclofenac placebo (Days 3, 8, and 13 in the above table):

- Xyrem® or Xyrem® placebo was to be administered at 0 hours and 4 hours
- Diclofenac was to be administered at -1 hours and 3 hours.

On the days when Xyrem®/Xyrem® placebo was to be co-administered with diclofenac/diclofenac placebo:

- A light breakfast was to be administered about 2 hours before the first dose of diclofenac/diclofenac placebo
- A standardized lunch was to be administered about 2 hours after the first dose of Xyrem®/Xyrem® placebo
- A standardized dinner was to be administered about 4 hours after the second dose of Xyrem®/Xyrem® placebo.

A dose of diclofenac of 50 mg QID was evaluated in this study as it is the highest recommended dose.

7.1.4 Key Inclusion Criteria

- Men and women. Age: 18 to 50 years.
- Healthy.
- Non-smoker.
- Body Mass Index between 18 and 30 kg/^{m2}.
- Agreement by female subjects to use a medically-accepted method of contraception (specified) throughout the study period and for 30 days after study completion.
- Agreement by male subjects to refrain from sperm donation for 30 days after study completion and to use adequate contraception throughout the study period and for 30 days after study completion.
- Good general health as determined by investigators via medical history, physical examination, clinical laboratory tests, and electrocardiograms at screening and baseline.
- Negative screens for human immunodeficiency virus antibody, Hepatitis B virus antigen, Hepatitis C virus antibody, and Hepatitis A virus IgM antibody. No clinical history related to such infections.
- Negative drug and alcohol screens.
- Hemoglobin ≥ 12 g/dL at baseline.
- Able to read and understand English, provide written informed consent, and comply with all study procedures and restrictions.
- Willing to refrain from consuming xanthine-containing beverages or alcohol while at the center and willing to refrain from intensive physical exercise during the study.
- Willing to remain in the study facility for 15 days.

7.1.5 Key Exclusion Criteria

- Clinically significant unstable medical abnormality, chronic disease, or history or presence of significant neurological (including seizure and cognitive disorders) or psychiatric disorder, hepatic, renal, endocrine, cardiovascular (including hypertension), gastrointestinal, pulmonary, or metabolic disease, or any other abnormality that could interfere with evaluation of study drug.
- Succinic semialdehyde dehydrogenase deficiency.
- History of or current insomnia.
- Screening or baseline blood oxygen saturation < 95% as measured by pulse oximetry on room air, or suspected respiratory difficulty or other condition that could compromise a subject's ability to breathe or maintain adequate oxygen saturation.
- Diagnosis of sleep apnea or at high risk of sleep apnea, history of loud snoring, or observed to stop breathing during sleep.
- Score of > 12 points on the Epworth Sleepiness Scale.
- History or presence of gastrointestinal, hepatic or renal disease or any other condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs.
- Pregnant, nursing, or lactating.
- Any severe drug allergy or a history of allergic or other severe adverse reaction or intolerance to Xyrem®, gamma-hydroxybutyrate, diclofenac, aspirin, other non-steroidal anti-inflammatory drugs.
- History of or current substance abuse or known drug dependence within the last 2 years prior to screening or positive test for drugs of abuse at screening or baseline.
- Inability to swallow capsules.
- Clinically significant illness within 30 days of screening.
- Clinically significant abnormal finding on physical examination, electrocardiogram, or safety laboratory tests, as determined by the investigator.
- Consumption of more than two alcoholic beverages daily or 15 or more alcoholic beverages weekly within 14 days of screening.
- Alcohol ingestion within 24 hours before admission or at any time through completion of the study or unwilling to refrain from alcohol or drug ingestion through study completion.
- Use of tobacco products or products for smoking cessation within 90 days before screening, including use of nicotine-containing products or history of significant use of tobacco (> 10 cigarettes or equivalent per day) within 3 years prior to Day -1.
- Use of any prescription medication within 14 days or over-the-counter medication within 7 days of dosing (excluding acetaminophen), or intent to use any prescription or over-the-counter medication during the study.
- Self-reporting of the consumption of more than 180 mg of caffeine per day (equal to or greater than 4 cups of coffee or the equivalent in caffeinated beverages).

- Consumption of grapefruit or products containing grapefruit or grapefruit juice, Seville oranges, orange marmalade, pomelos, xanthine-containing products, or quinine-containing products (e.g., tonic water) within 48 hours before admission (Day -1) or any time through study completion.
- Any blood donation within 90 days of dosing.
- Any plasma donation within 7 days of dosing.
- History, or suspicion of inability to comply fully with all procedural aspects of the study.
- On a sodium-restricted diet.

7.1.6 Concomitant Medications

See Exclusion Criteria above.

7.1.7 Schedule

The study schedule is copied below from the submission, and is self-explanatory.

Evaluation	Screening Days -21 through -2	Baseline Day -1	Period 1		Period 2		Period 3		Final Day[1]
			Dosing Days 1-3	Washout Day 4-5	Dosing Days 6-8	Washout Day 9-10	Dosing Days 11-13	Washout Day 14-15	Day 15 [1]
Informed Consent	X								
I/E Criteria	X	X							
Demographics	X								
Medical History[2]	X	X							
Physical Examination[3]	X	X							X
Height[4]	X								
Weight[4]	X	X							X
Alcohol and Drug Screens[5]	X	X							
Pregnancy Test[6]	X	X							X
Laboratory Tests[7]	X	X							X
Epworth Sleepiness Scale	X								
Randomization			X[8]						
Vital signs and temperature[9]	X	X	X	X	X	X	X	X	X
12-Lead ECG[10]	X	X	X	X	X	X	X	X	X
Pulse oximetry[11]	X	X	X		X		X		X
Drug Administration[12]			X		X		X		
Training for PD Battery		X[13]							
PD Battery[14]			X		X		X		
Blood samples for PK Analysis[15]			X		X		X		
Urine samples for PK[16]			X		X		X		
Adverse Event Assessment			X →	X	X	X	X	X	X →
Concomitant Medications	X	X	X	X	X	X	X	X	X
Assess Reason for Study Discontinuation									X

[1] Final day or early termination.

[2] Included a review of previous/ongoing medications.

[3] Included a full examination of body systems (except the genitourinary body system) and also included a brief neurological examination at the study center.

[4] Height and weight were measured in ordinary indoor clothes, without shoes.

[5] Drug screen to include amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates.

[6] Only for female subjects

[7] Included serum chemistry (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, creatine kinase, gamma-glutamyl transferase, globulin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, uric acid), serology (Hep A IgM-Ab, HBs-Ag, HCV-Ab, and HIV -Ab; at Screening only), TSH (at Screening only), hematology (complete blood count including platelet count and white blood cell count with differential), coagulation (International Normalized Ratio, partial thromboplastin time), and urinalysis (appearance, bilirubin, color, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, urobilinogen).

[8] Before dosing in Period 1.

[9] Vital signs (systolic and diastolic blood pressure, pulse, and respiratory rate) and temperature were measured after the subject had been resting supine for at least 5 minutes at Screening, Baseline, the Final Day, and during Periods 1, 2, and 3. On Days 3, 8, and 13 vital signs were measured before the first dose of diclofenac/diclofenac placebo and at -0.5 h, 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 4.25 h, 4.5 h, 4.75 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 8 h, 10 h, and 12 h relative to the first dose of Xyrem/Xyrem placebo, and temperature was measured before the first dose of diclofenac/diclofenac placebo and 10 h after the first dose of Xyrem/Xyrem placebo. On Days 1 & 2, 6 & 7, and 11 & 12, vital signs and temperature were measured 1 h after each dose of diclofenac/diclofenac placebo. On Days 4 & 5, 9 & 10, and 14 & 15, vital signs and temperature were measured in the morning at approximately 8 am. Respiratory rate was assessed over 30 seconds.

[10] A standard 12-lead ECG was recorded with the subject resting supine for at least 5 minutes at Screening, Baseline, and the Final Day. In Periods 1, 2, and 3, ECG was recorded before the first dose of Xyrem/Xyrem placebo and 2 h and 24 h after the first dose of Xyrem/Xyrem placebo.

[11] Oxygen saturation was recorded at Screening, Baseline, and the Final Day, was monitored continuously during Periods 1, 2, and 3 on Days 3, 8, and 13 for 10 hours after the first Xyrem/Xyrem placebo dose, and was recorded at predose and at 0.5 h, 1 h, 2 h, 4 h, 4.5 h, 5 h, 6 h, 8 h, and 10 h after the first dose of Xyrem/Xyrem placebo. Sleeping subjects were aroused if the pulse oximetry reading fell below 90%.

[12] Diclofenac or diclofenac placebo was administered qid (doses separated by 4 hours during the day, eg, ~8 am, 12 pm, 4 pm, and 8 pm) for 2 days (Days 1 & 2, 6 & 7, and 11 & 12) before co-administration day. On co-administration day (Days 3, 8, and 13), diclofenac or diclofenac placebo was administered at -1 h and 3 h with Xyrem or Xyrem placebo administered at 0 h and 4 h.

[13] Training for the PD Battery was to be completed before the first PD assessment.

[14] The PD Battery (including KSS, Simple Reaction Time task, Digit Vigilance task, Choice Reaction Time task, Tracking task, and Numeric Working Memory task) was administered on Days 3, 8, and 13 at 2 hours before the first dose of Xyrem/Xyrem placebo and at 0.5 h, 1 h, 2.5 h, 4 h (pre 2nd Xyrem/Xyrem placebo dose), 4.5 h, 5 h, 6.5 h, and 8 h after the first dose of Xyrem/Xyrem placebo.

[15] On Days 3, 8, and 13, the following blood samples were collected for PK analysis: 4 mL (to measure sodium oxybate) at 0 h (predose), 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h (pre 2nd Xyrem/Xyrem placebo dose), 4.25 h, 4.5 h, 4.75 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 8 h, and 10 h relative to the first dose of Xyrem/Xyrem placebo; 4 mL (to measure diclofenac) at -1 h, -0.5 h, 0 h, 0.5 h, 1 h, 2 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 6 h, 7 h, and 9 h relative to the first dose of Xyrem/Xyrem placebo. Blood samples for PK analysis of each analyte were taken within ±2 minutes of the specified time points for the first hour after each dose and within ±5 minutes of the specified time points after one hour.

[16] On Days 3, 8, and 13, urine was collected to measure sodium oxybate concentrations at predose (-4 to 0 hours) and during 0-4, 4-8, and 8-12 hour intervals after the first dose of Xyrem/Xyrem placebo.

Please note that the pharmacodynamic test battery (see Section 7.1.8.3 for further details about that battery) was to be administered at the following timepoints on Days 3, 8, and 13 (i.e., the days when diclofenac/diclofenac placebo and Xyrem®/Xyrem® placebo were jointly administered).

- 2 hours before the first dose of Xyrem®/Xyrem® placebo
- 0.5, 1.0, 2.5, 4.0, 4.5, 5.0, 6.5, and 8.0 hours after the first dose of Xyrem®/Xyrem® placebo.

Pharmacokinetic sampling was also performed on Days 3, 8, and 13, only, at the timepoints listed in the above table.

7.1.8 Outcome Measures

7.1.8.1 Safety Measures

Adverse events, vital signs, safety laboratory tests (hematology, clinical chemistry, and urinalysis), 12-lead electrocardiograms, and pulse oximetry.

7.1.8.2 Pharmacokinetic Measures

- Plasma and urine concentrations of sodium oxybate
- Plasma concentrations of diclofenac.

7.1.8.3 Pharmacodynamic Measures

A battery of pharmacodynamic tests was used to evaluate sleepiness and selected cognitive functions. The tests are summarized in the following sponsor table, and were administered in the same consecutive order as in the table.

Karolinska Sleepiness Scale (KSS)	The KSS is a single-question, nine-point self-rating scale used to measure levels of sleepiness during the last 5 minutes. The scale ranges from 1 =very alert to 9 =very sleepy, great effort to stay awake or fighting sleep. A score of 7 or more indicates excessive sleepiness.
Simple Reaction Time Task	The participant was instructed to press the 'YES' response button as quickly as possible every time the word 'YES' was presented on the screen. Stimuli were presented with a varying inter-stimulus interval.
Digit Vigilance Task	A target digit was randomly selected and constantly displayed to the right of the screen. A series of digits was then presented in the center of the screen and the participant was required to press the 'YES' button as quickly as possible every time the digit in the series matched the target digit.
Choice Reaction Time Task	Either the word 'NO' or the word 'YES' was presented on the screen and the participant was instructed to press the corresponding button as quickly as possible. Each stimulus word was chosen randomly with equal probability and there was a varying inter-stimulus interval.
Tracking Task	The participant used a joystick to track a randomly moving target on the screen. The distance off-target per second was recorded
Numeric Working Memory Task	A series of digits was presented for the participant to hold in memory. This was followed by a series of probe digits for each of which the participant had to decide whether or not it was in the original series and press the 'YES' or 'NO' response button as appropriate, as quickly as possible.

The methods used to score the above tests are summarized below in a table taken from the submission.

Task	Major Measures
KSS	Score (1-9)
Simple Reaction Time	Average time taken for each response (ms)
Digit Vigilance	Average time taken to make each detection (ms) Percentage of correct detections (%) Number of times button was pressed when no stimulus was presented ("false alarms" [#])
Choice Reaction Time	Percentage of correct responses (%) Average response time of correct responses (ms)
Tracking	Average distance off target (mm)
Numeric Working Memory	Sensitivity index, reflecting ability to correctly hold digits in working memory (SI); a score of 1 represents perfect performance, a score of zero represents chance performance. Response time (ms)
Power of Attention	Sum of response times from three tasks (Simple Reaction Time, Digit Vigilance, and Choice Reaction Time [ms])
Continuity of Attention	Sum of correct responses in the Choice Reaction Time task and correct detections in the Digit Vigilance task minus the false alarms in the Digit Vigilance task and the average distance off target from the Tracking task (#)

7.1.9 Analysis Plan

Key aspects of the statistical analysis, as actually conducted, are summarized below.

7.1.9.1 Pharmacokinetic Measures

The following pharmacokinetic parameters were calculated for sodium oxybate and diclofenac for specific sampling intervals.

Compound	Sampling Interval*	Pharmacokinetic Parameter
Sodium oxybate	0-4 hours	AUC_T, C_{max}, T_{max}
	4-8 hours	AUC_T, C_{max}, T_{max}
	0-10 hours	AUC_t, AUC_∞, C_{max}, T_{max}, λ, $t_{½}$
Diclofenac	0-4 hours	AUC_T, C_{max}, T_{max}
	4-8 hours	AUC_T, C_{max}, T_{max}
	0-10 hours	AUC_t, AUC_∞, C_{max}, T_{max}, λ, $t_{½}$

*Relative to first dose of Xyrem®, and only dose for diclofenac

The following urine parameters were calculated for sodium oxybate, alone:

- Urine concentration (C_{urine})
- Amount excreted during each collection interval (A_e)
- Cumulative amount excreted over the entire 12-hour collection period ($CumA_e$)
- Percentage of dose recovered in urine in each collection interval (%Dose)
- Cumulative percentage of dose recovered in urine (Cum%Dose).

Plasma concentrations and parameters for sodium oxybate and diclofenac were summarized by treatment using descriptive statistics. Pharmacokinetic parameters were also evaluated by analysis of variance models using natural log-transformed data. The 90% confidence intervals of the ratios for the various C_{max} and AUC parameters were calculated.

7.1.9.2 Pharmacodynamic Measures

Pharmacodynamic measurements were summarized and further investigated using analysis of covariance models. Changes from baseline at each timepoint were compared between the Xyrem® + diclofenac placebo and Xyrem® + diclofenac treatments; and between the Xyrem® placebo + diclofenac and Xyrem® + diclofenac treatments.

7.1.9.3 Safety Measures

The results for the safety measures were summarized using descriptive statistics.

7.2 Summary Study Results

This study was conducted at a single clinical site in the United States by a Contract Research Organization: Celerion of Neptune, NJ.

7.2.1 Pharmacokinetic Results

In the following sponsor table, the sodium oxybate pharmacokinetic parameters for the Xyrem® + diclofenac combination are compared with those for the Xyrem® plus diclofenac placebo combination.

Parameter (Units)	Geometric LS Means[a]		% Mean Ratio Test/ Reference[b]	% Difference[c]	p-value	90% Confidence Interval
	Test SXB + DICLO N=18	Reference SXB + Dpbo N=18				
C_{max} 0-4 h (µg/mL)	90.6	83.5	109	8.54	0.0969	100, 118
C_{max} 4-8 h (µg/mL)	69.5	74.5	93.4	-6.63	0.0961	87.3, 99.9
C_{max} (µg/mL)	91.2	85.5	107	6.70	0.1528	98.9, 115
AUC_{τ} 0-4 h (µg*h/mL)	122	121	101	1.11	0.6607	96.8, 106
AUC_{τ} 4-8 h (µg*h/mL)	124	125	99.0	-0.98	0.6800	95.1, 103
AUC_{0-t} (µg*h/mL)	250	249	101	0.60	0.6752	98.2, 103
AUC_{0-inf} (µg*h/mL)	253	252	101	-0.51	0.7347	98.0, 103

SXB=Sodium oxybate, DICLO=diclofenac, Dpbo=diclofenac placebo
Note: Subjects 10004, 10005, and 10019 were excluded from the statistical analysis due to vomiting within 2 times the Xyrem median t_{max}. Subject 10015 was excluded from the statistical analysis as subject dropped from the study.
SXB + DICLO: Diclofenac administered as 50 mg immediate-release (IR) tablet (overencapsulated) qid (doses separated by 4 hours during the day, eg, ~8 am, 12 pm, 4 pm, and 8 pm) for 2 days before co-administration day. On co-administration day, 50 mg diclofenac administered at -1 h and 3 h with 3 g of Xyrem administered at 0 h and 4 h (Treatment B).
SXB + Dpbo: Diclofenac placebo administered as one capsule qid (doses separated by 4 hours during the day, eg, ~8 am, 12 pm, 4 pm, and 8 pm) for 2 days before co-administration day. On co-administration day, one diclofenac placebo capsule administered at -1 h and 3 h with 3 g of Xyrem administered at 0 h and 4 h (Treatment A).
[a] Geometric least-squares (LS) means were calculated by exponentiating the LS means from the ANOVA. The ANOVA mixed-effects model includes sequence, subject within sequence, period, and treatment.
[b] % Mean Ratio = 100*(test/reference)
[c] % Difference = difference between treatments (test - reference) expressed as a percentage of reference

The sponsor points out that the percentage mean ratio for the sodium oxybate + diclofenac combination versus the sodium oxybate plus diclofenac placebo combination ranged from 93.4% to 109.0% and that the 90% confidence intervals for those comparisons were all within the 80-125% range.

The next sponsor table (corrected as submitted in the Amendment to this labeling supplement on November 25, 2013) displays comparisons of the diclofenac pharmacokinetic parameters for the sodium oxybate + diclofenac combination with the sodium oxybate placebo plus diclofenac combination. The results are self-explanatory.

Parameter (Units)	Geometric LS Means[a]		% Mean Ratio Test/ Reference[b]	% Difference[c]	p-value	90% Confidence Interval
	Test SXB + DICLO N=18	Reference Spbo + DICLO N=18				
C_{max} 0-4 h[d](ng/mL)	909	907	100	0.21	0.9855	82.0, 123
C_{max} 4-8[d] h(ng/mL)	592	506.2	117	17.0	0.3608	87.4, 157
C_{max} (ng/mL)	978	904	108	8.20	0.4622	90.1, 130
AUC_{τ} 0-4[d] h(ng*h/mL)	1028	1002	103	2.57	0.6308	93.7, 112
AUC_{τ} 4-8[d] h (ng*h/mL)	751	740	102	1.53	0.8785	85.6, 120
AUC_{0-t} (ng*h/mL)	2060	1933	107	6.55	0.1160	99.7, 114
AUC_{0-inf} (ng*h/mL)[c]	2130[e]	2019[e]	106	5.51	0.3967	94.1, 118

DICLO=Diclofenac; SXB=Sodium oxybate; Spbo=Sodium oxybate placebo.
Note: Subjects 10004, 10005, and 10019 were excluded from the statistical analysis due to vomiting within 2 times the Xyrem median t_{max}. Subject 10015 was excluded from the statistical analysis as subject dropped from the study.
SXB + DICLO: Diclofenac (50 mg qid 4 hours apart on the first and second day and two doses on the third day of the period) + Xyrem two 3 g doses 4 hours apart on the third day of the period (test) (Treatment B).
Spbo + DICLO: Diclofenac (50 mg qid 4 hours apart on the first and second day and two doses on the third day of the period) + Xyrem placebo two doses 4 hours apart on the third day of the period (reference) (Treatment C).
[a] Geometric LS means were calculated by exponentiating the LS means from the ANOVA. The ANOVA mixed-effects model includes sequence, subject within sequence, period, and treatment.
[b] % Mean Ratio = 100*(test/reference)
[c] % Difference = difference between treatments (test - reference) expressed as a percentage of reference
[d] Times are relative to the diclofenac dose
[e] N=12

The renal excretion of sodium oxybate was similar when Xyrem® was administered with diclofenac compared with the administration of Xyrem® with diclofenac placebo.

7.2.2 Pharmacodynamic Results

The administration of Xyrem® whether alone or in combination with diclofenac resulted in an increase in sleepiness as compared with baseline (on the Karolinska Sleepiness Scale) and impaired performance on most of the other components of the cognitive test battery. These impairments were apparent at multiple timepoints following the administration of each dose of Xyrem®. On selected tests of attention (Digit Vigilance Accuracy, Digit Vigilance Mean Reaction Time, and Choice Reaction Time Mean), the combination of Xyrem® and diclofenac produced less impairment at various timepoints than Xyrem® alone (note that those results do not in any way imply that the efficacy of Xyrem® as a treatment for narcolepsy may be reduced when that drug is administered in combination with diclofenac).

On most pharmacodynamic tests, there was greater evidence of impairment with the combination of diclofenac and Xyrem® than with diclofenac alone. However, diclofenac alone showed a decrease from baseline at multiple timepoints in the Numeric Working Memory Sensitivity Index.

7.2.3 Safety Results

There were no deaths, serious adverse events, or discontinuations due to adverse events in this study.

The number (%) of subjects with adverse events that occurred in ≥ 2 subjects is summarized in the following table, which I have copied from the submission.

Adverse Event	Days 1 & 2[a]		Days 3, 4, & 5			Total
	Diclofenac placebo N = 21[b] n (%)[c]	Diclofenac N = 22[b] n (%)[c]	Xyrem placebo + diclofenac N = 20[b] n (%)[c]	Xyrem + diclofenac placebo N = 21[b] n (%)[c]	Xyrem + diclofenac N = 21[b] n (%)[c]	N = 22[b] (n %)[c]
Any AE	3 (14)	3 (14)	3 (15)	16 (76)	15 (71)	18 (82)
Somnolence	1 (5)	0	1 (5)	8 (38)	11 (52)	14 (64)
Headache	1 (5)	0	1 (5)	5 (24)	4 (19)	9 (41)
Nausea	0	0	1 (5)	8 (38)	5 (24)	9 (41)
Dizziness	1 (5)	0	1 (5)	6 (29)	6 (29)	8 (36)
Euphoric mood	0	0	1 (5)	4 (19)	5 (24)	7 (32)
Vomiting	0	0	0	4 (19)	3 (14)	5 (23)
Feeling hot	1 (5)	0	0	1 (5)	2 (10)	2 (9)
Abdominal discomfort	0	0	0	2 (10)	0	2 (9)
Dry mouth	0	0	0	0	2 (10)	2 (9)
Affect lability	0	0	1 (5)	1 (5)	1 (5)	2 (9)

[a] Prior to Xyrem or Xyrem placebo
[b] Number of subjects dosed
[c] Number (%) of subjects with AEs

As the above table indicates, somnolence, together with several other adverse events, were much more frequent in the two Xyrem® groups than with diclofenac alone.

No vital sign, electrocardiogram, or laboratory results of clinical significance were observed in this study; I have reviewed those data.

7.3 Sponsor's Conclusions

I have further summarized the sponsor's main conclusions below.

7.3.1 Pharmacokinetic Conclusions

No significant differences were noted in the plasma pharmacokinetics of sodium oxybate or in its renal excretion, whether Xyrem® was administered alone or in

combination with diclofenac. The co-administration of Xyrem® with diclofenac did not appear to affect the pharmacokinetics of diclofenac.

7.3.2 Pharmacodynamic Conclusions

The administration of Xyrem® and diclofenac appeared to result in a reduced impairment of attention as compared with the administration of Xyrem® alone. However, there was no reduction in sleepiness as measured by the Karolinska Sleepiness Scale when diclofenac was co-administered with Xyrem®, as compared with the administration of Xyrem® alone.

On most pharmacodynamic measures, subjects demonstrated greater impairment with the combination of Xyrem® and diclofenac than with diclofenac alone.

7.3.3 Safety Conclusions

No new safety signals were observed for Xyrem® or diclofenac in the study population.

8. Study 12-008

8.1 Protocol

8.1.1 Title

A Randomized, Double-Blind, Placebo-Controlled, Five-Period Crossover Study To Evaluate The Pharmacokinetics And Pharmacodynamics Of Xyrem® (Sodium Oxybate) Co-Administered With Depakote® ER (Divalproex Sodium Extended-Release Tablets) In Healthy Volunteers.

8.1.2 Objectives

8.1.2.1 Primary Objective

To evaluate the pharmacokinetics and pharmacodynamics of Xyrem® (sodium oxybate) co-administered with divalproex sodium extended-release tablets.

8.1.2.2 Secondary Objective

To evaluate and compare the safety and tolerability of Xyrem® with and without co-administration of divalproex sodium extended-release tablets.

8.1.3 Design, Dose, Sample Size, And Duration

This was a randomized, double-blind, placebo-controlled, five-period crossover study.

24 subjects were to be enrolled in the study.

The five periods of the study were designated as Periods 1, 2, 3, 4, and 5.

There were 3 different treatment regimes administered during the study: Treatments A, B, and C, which are summarized in the following table.

Treatment	Regimen
A	Xyrem® two doses of 3 g each administered 4 hours apart (at about 9 AM and 1 PM)
B	Xyrem® placebo two doses administered 4 hours apart (at about 9 AM and 1 PM)
C	Divalproex sodium extended-release 1250 mg once daily at about 8 AM

The study schema below, taken from the submission, summarizes the dosing regimen for each study period.

		Treatment Periods Treatment Days Randomized Treatments								
Screening	**Baseline**	**Period 1**	**Period 2**	**Period 3**	**Period 4**		**Period 5**		**Washout**	**Final Day**
Days -21 through -2	Day -1	Days 1 & 2	Days 3 & 4	Days 5–14	Days 15–17		Day 18		Days 19 & 20	Day 21
		A or B Day 1	A or B Day 3	C Days 5–14	A or B Day 15	C Days 15–17	A or B Day 18	C Day 18		
Note: A = Xyrem, two 3 g doses, 4 hours apart at approximately 9 AM (1st dose) and 1 PM (2nd dose) B = Xyrem placebo, two doses, 4 hours apart C = Divalproex sodium 1250 mg, once a day at approximately 8 AM A washout period followed each of the treatment periods (Days 2, 4, 16-17, and 19-20).										

Note that:

- The washout period on Days 16-17 was to apply only to Xyrem®
- Divalproex sodium extended-release was to be administered continually beginning on Day 5 and extending through Day 18 (in a dose of 1250 mg once daily at about 8 AM).

On Days 1, 3, 15, and 18:

- A light breakfast was to be administered about 2 hours before dosing with divalproex sodium extended-release
- A standardized lunch was to be administered about 2 hours after the first dose of Xyrem®/Xyrem® placebo
- A standardized dinner was to be administered about 8 hours after the second dose of Xyrem®/Xyrem® placebo.

8.1.4 Key Inclusion Criteria

- Men and women. Age: 18 to 50 years.
- Healthy.

- Non-smoker.
- Body Mass Index between 18 and 30 kg/^{m2}.
- Agreement by female subjects (of child-bearing potential) to use a medically-accepted method of contraception (specified) throughout the study period and for 30 days after study completion.
- Agreement by male subjects to refrain from sperm donation for 30 days after study completion and to use adequate contraception throughout the study period and for 30 days after study completion.
- Good general health as determined by investigators via medical history, physical examination, clinical laboratory tests, and electrocardiograms at screening and baseline.
- Negative screens for human immunodeficiency virus antibody, Hepatitis B virus antigen, Hepatitis C virus antibody, and Hepatitis A virus IgM antibody. No clinical history related to such infections.
- Negative drug and alcohol screens.
- Hemoglobin ≥ 12 g/dL at baseline.
- Able to read and understand English, provide written informed consent, and comply with all study procedures and restrictions.
- Willing to refrain from consuming xanthine-containing beverages or alcohol while at the center and willing to refrain from intensive physical exercise during the study.
- Willing to remain in the study facility for 21 days.

8.1.5 Key Exclusion Criteria

- Clinically significant unstable medical abnormality, chronic disease, or history or presence of significant neurological (including seizure and cognitive disorders) or psychiatric disorder, hepatic, renal, endocrine, cardiovascular (including hypertension), gastrointestinal, pulmonary, or metabolic disease, or any other abnormality that could interfere with evaluation of study drug.
- Succinic semialdehyde dehydrogenase deficiency.
- Previously-demonstrated clinically significant suicidal or homicidal behavior or demonstrated current suicidality as evaluated by the Columbia-Suicide Severity Rating Scale.
- History of or current insomnia.
- Screening or baseline blood oxygen saturation < 95% as measured by pulse oximetry on room air, or suspected respiratory difficulty or other condition that could compromise a subject's ability to breathe or maintain adequate oxygen saturation.
- Diagnosis of sleep apnea or at high risk of sleep apnea, history of loud snoring or observed to stop breathing during sleep.
- Score of > 12 points on the Epworth Sleepiness Scale.
- Urea cycle disorder or elevated plasma ammonia at screening.
- Any severe drug allergy or a history of allergic or other severe adverse reaction or intolerance to Xyrem®, gamma-hydroxybutyrate, divalproex sodium, or any other components of the formulations.

- Inability to swallow capsules.
- Clinically significant illness within 30 days of screening.
- Clinically significant abnormal finding on physical examination, electrocardiogram, or safety laboratory tests, as determined by the investigator.
- History of or current substance abuse or known drug dependence within the last 2 years prior to screening or positive test for drugs of abuse at screening or baseline.
- Consumption of more than two alcoholic beverages daily or 15 or more alcoholic beverages weekly within 14 days of screening.
- Alcohol ingestion within 24 hours before admission or at any time through completion of the study or unwilling to refrain from alcohol or drug ingestion through study completion.
- Use of tobacco products or products for smoking cessation within 90 days before screening, including use of nicotine-containing products or history of significant use of tobacco (> 10 cigarettes or equivalent per day) within 3 years prior to Day -1.
- Use of any prescription medication within 14 days or over-the-counter medication within 7 days of dosing (excluding acetaminophen), or intent to use any prescription or over-the-counter medication during the study.
- Use of any other investigational drug within 30 days or 5 half-lives (whichever is longer) before dosing or plans to use an investigational drug (other than the study drugs) during the study.
- Self-reporting of the consumption of more than 180 mg of caffeine per day (equal to or greater than 4 cups of coffee or the equivalent in caffeinated beverages).
- Consumption of grapefruit or products containing grapefruit or grapefruit juice, Seville oranges, orange marmalade, pomelos, xanthine-containing products, or quinine-containing products (e.g., tonic water) within 48 hours before admission (Day -1) or any time through study completion.
- Any blood donation within 90 days of dosing.
- Any plasma donation within 7 days of dosing.
- History, or suspicion of inability to comply fully with all procedural aspects of the study.
- On a sodium-restricted diet.

8.1.6 Concomitant Medications

See Exclusion Criteria above.

8.1.7 Schedule

The study schedule is copied below from the submission, and is self-explanatory.

Evaluation	Screening Days -21 through -2	Baseline Day -1	Period 1 Days 1 & 2	Period 2 Days 3 & 4	Period 3 Days 5-14	Period 4 Days 15-17	Period 5 Day 18	Wash-out Days 19 & 20	Final Day[1] Day 21
					Depakote ER (divalproex sodium) Dosing Days 5-18				
			Xyrem/ Placebo Dosing Day 1	Xyrem/ Placebo Dosing Day 3	Days 5-14	Xyrem/ Placebo Dosing Day 15	Xyrem/ Placebo Dosing Day 18	Days 19-20	Day 21[1]
Informed Consent	X								
I/E Criteria	X	X							
Demographics	X								
Medical History[2]	X	X							
Physical Examination[3]	X	X							X
Height (H) and Weight[4] (W)	X (H,W)	X (W)							X (W)
Alcohol and Drug Screens[5]	X	X							
Serum Chemistry, Serology, Hematology, Coagulation, Urinalysis[6]	X	X							X
Ammonia	X								
Additional ALT, AST					X[7]				
ESS	X								
C-SSRS Baseline/Screen	X								
C-SSRS Since Last Visit		X[8]			X[8]				X
Randomization			X[9]						
Vital signs and temperature[10]	X	X	X	X	X	X	X	X	X
12-Lead ECG[11]	X	X	X	X		X	X		X
Pulse oximetry[12]	X	X	X	X		X	X		X
Drug Administration[13]			X	X	X	X	X		
PD Battery Training[14]		X							
PD Battery[15]			X	X		X	X		
Blood samples for PK[16]			X	X	X[17]	X	X		
Urine samples for PK[18]			X	X		X	X		
AE Assessment			X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Assess reason for study discontinuation									X

H=height, I/E=inclusion/exclusion, W=weight

1 Final day or early termination

2 Includes a review of previous/ongoing medications.

3 Includes a full examination of body systems (except the genitourinary body system). Physical examinations included assessments of the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, lymph nodes, extremities, and body weight and also included a brief neurological examination at the study center.

4 Height obtained at Screening only; height and weight were measured in ordinary indoor clothes (without shoes).

5 Drug screen to include amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates.

6 Hematology: Complete blood count, including platelet count and white blood cell count with differential; Coagulation: international normalized ratio, partial thromboplastin time; Chemistry: Albumin, Alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, creatine kinase, gamma-glutamyl transferase, globulin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, uric acid, thyroid stimulating hormone (Screening and Final Day only), serology (hepatitis A, B, C, and human immunodeficiency virus screening) (Screening only); Urinalysis: appearance, bilirubin, color, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, urobilinogen.

7 Collect blood sample to measure ALT and AST on Day 12 also.

8 Since Last Visit Version; Baseline and Day 12. The investigator evaluated results of the Baseline and Day 12 C-SSRS (Since Last Visit version) to determine whether, in the investigator's opinion, any subject demonstrated a risk of suicidality that might prevent that subject's continuing in the study.

9 Before dosing in Period 1.

10 Vital signs (blood pressure, respiratory rate, and heart rate) and temperature were taken after the subject had been resting supine for at least 5 minutes. Vital signs and temperature were taken at Screening, Baseline, and the Final Day. On Days 1 and 3, vital signs were taken relative to the first Xyrem or Xyrem placebo dose at predose, 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 4.25 h, 4.5 h, 4.75 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, and 8 h. On Days 5 through 14 (Period 3), 16, and 17, vital signs were taken pre-divalproex sodium dose and 1 h and 12 h after divalproex sodium dose. On Days 15 and 18, vital signs were taken pre-divalproex sodium dose, and relative to the first Xyrem or Xyrem placebo dose at predose, 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 4.25 h, 4.5 h, 4.75 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 8 h, 10h and 12 h. On Days 1 and 3, temperature was taken before the first Xyrem/Xyrem placebo dose, and ~ 4 h and 8 h after the first Xyrem/Xyrem placebo dose. On Days 5 through 14 (Period 3), 16, and 17, temperature was taken pre-divalproex sodium dose and 1 h and 12 h after divalproex sodium dose. On Days 15 and 18, temperature was taken pre-divalproex sodium dose, and relative to the first Xyrem or Xyrem placebo dose at predose, 4 h, 8 h, and 12 h. On Days 2, 4, and 19-21, vital signs and temperature were taken in the morning at ~ 8 am.

11 A standard 12-lead ECG was recorded with the subject resting supine for at least 5 minutes at Screening, Baseline, the Final Day, and pre-Xyrem/Xyrem placebo dose on Days 1, 3, 15, and 18 and at 1 h, 2 h, 8 h, and 24 h post Xyrem/Xyrem placebo dose.

12 Oxygen saturation was recorded at Screening, Baseline, and the Final Day; was monitored continuously during Periods 1, 2 (Days 1 and 3) and during Periods 4 and 5 (Days 15 and 18) for 10 hours after the first Xyrem/Xyrem placebo dose; and was recorded at pre Xyrem/Xyrem placebo dose and at 30 min, 1 h, 2 h, 4 h, 4.5 h, 5 h, 6 h, 8 h, and 10 h after the first Xyrem or Xyrem placebo dose. Sleeping subjects were aroused if the oxygen saturation reading fell below 90%.

13 Divalproex sodium was administered each morning on Days 5 through 18; Xyrem or Xyrem placebo was administered alone on Days 1 and 3, in two doses 4 hours apart; and the first Xyrem or Xyrem placebo dose was administered approximately 1 hour after divalproex sodium on Days 15 and 18, with the second dose administered 4 hours after the first dose.

14 Subject training on PD Battery was to be completed before PD Battery administration on Day 1.

15 PD Battery was administered on Days 1, 3, 15, and 18 at 2 h before the first Xyrem/Xyrem placebo dose, and at 30 min, 1 h, 2.5 h, 4 h (pre 2nd Xyrem/Xyrem placebo dose), 4.5 h, 5 h, 6.5 h, and 8 h, postdose Xyrem or Xyrem placebo.

16 Blood samples (4 mL) to measure plasma sodium oxybate concentrations were collected on Days 1 & 3 and 15 & 18 at pre Xyrem/Xyrem placebo dose and at 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 4.25 h, 4.5 h, 4.75 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 8 h, 10 h, and 12 h after the first Xyrem or Xyrem placebo dose. Blood samples (4 mL) to measure plasma valproic acid concentrations on Days 15 and 18 were collected at -1 h (pre divalproex sodium dose), 0 h, 1 h, 2 h, 3 h, 7 h, 11 h, 15 h, and 23 h relative to the first dose of Xyrem/Xyrem placebo. PK samples were taken within ±2 minutes of the specified time points for the first hour after dosing and within ±5 minutes of the specified time points after 1 hour.

17 Blood samples (4 mL) for valproic acid concentrations were collected before the dose of divalproex sodium (to determine trough concentrations for assessment of steady state) on Days 13 and 14.

18 Any urine produced was collected at pre Xyrem/Xyrem placebo dose (-4-0 h) and during 0-4, 4-8, 8-12 hour intervals after the first dose of Xyrem/Xyrem placebo to measure sodium oxybate concentrations.

Please note that the pharmacodynamic test battery (see Section 8.1.8.3 for further details about that battery) was to be administered at the following timepoints on Days 1, 3, 15, and 18 (Days 15 and 18 being the days on which divalproex sodium extended-release and Xyrem®/Xyrem® placebo were jointly administered).

- 2 hours before the first dose of Xyrem®/Xyrem® placebo
- 0.5, 1.0, 2.5, 4.0, 4.5, 5.0, 6.5, and 8.0 hours after the first dose of Xyrem®/Xyrem® placebo.

Pharmacokinetic sampling was also performed on Days 1, 3, 15, and 18 only, at the timepoints listed in the above table.

8.1.8 Outcome Measures

8.1.8.1 Safety Measures

Adverse events, vital signs, safety laboratory tests (hematology, clinical chemistry, and urinalysis), 12-lead electrocardiograms, and pulse oximetry. Columbia-Suicide Severity Rating Scale.

8.1.8.2 Pharmacokinetic Measures

- Plasma and urine concentrations of sodium oxybate
- Plasma concentrations of valproic acid.

8.1.8.3 Pharmacodynamic Measures

A battery of pharmacodynamic tests was used to evaluate sleepiness and selected cognitive functions. The tests are summarized in the following sponsor table, and were administered in the same consecutive order as in that table.

Karolinska Sleepiness Scale (KSS)	The KSS is a single-question, nine-point self-rating scale used to measure levels of sleepiness during the last 5 minutes. The scale ranges from 1 =very alert to 9 =very sleepy, great effort to stay awake or fighting sleep. A score of 7 or more indicates excessive sleepiness.
Simple Reaction Time Task	The participant was instructed to press the 'YES' response button as quickly as possible every time the word 'YES' was presented on the screen. Stimuli were presented with a varying inter-stimulus interval.
Digit Vigilance Task	A target digit was randomly selected and constantly displayed to the right of the screen. A series of digits was then presented in the center of the screen and the participant was required to press the 'YES' button as quickly as possible every time the digit in the series matched the target digit.
Choice Reaction Time Task	Either the word 'NO' or the word 'YES' was presented on the screen and the participant was instructed to press the corresponding button as quickly as possible. Each stimulus word was chosen randomly with equal probability and there was a varying inter-stimulus interval.
Tracking Task	The participant used a joystick to track a randomly moving target on the screen. The distance off-target per second was recorded
Numeric Working Memory Task	A series of digits was presented for the participant to hold in memory. This was followed by a series of probe digits for each of which the participant had to decide whether or not it was in the original series and press the 'YES' or 'NO' response button as appropriate, as quickly as possible.

The methods used to score the above tests are summarized below in a table taken from the submission.

Task	Major Measures
KSS	Score (1-9)
Simple Reaction Time	Average time taken for each response (ms)
Digit Vigilance	Average time taken to make each detection (ms) Percentage of correct detections (%) Number of times button was pressed when no stimulus was presented ("false alarms" [#])
Choice Reaction Time	Percentage of correct responses (%) Average response time of correct responses (ms)
Tracking	Average distance off target (mm)
Numeric Working Memory	Sensitivity index, reflecting ability to correctly hold digits in working memory (SI); a score of 1 represents perfect performance, a score of zero represents chance performance. Response time (ms)
Power of Attention	Sum of response times from three tasks (Simple Reaction Time, Digit Vigilance, and Choice Reaction Time [ms])
Continuity of Attention	Sum of correct responses in the Choice Reaction Time task and correct detections in the Digit Vigilance task minus the false alarms in the Digit Vigilance task and the average distance off target from the Tracking task (#)

8.1.9 Analysis Plan

Key aspects of the statistical analysis as actually conducted are summarized below.

8.1.9.1 Pharmacokinetic Measures

The following pharmacokinetic parameters were calculated for sodium oxybate and valproic acid for specific sampling intervals or timepoints.

Compound	Sampling Interval* Or Timepoint	Pharmacokinetic Parameter
Sodium oxybate	0-4 hours	AUC_T, C_{max}, T_{max}
	4-8 hours	AUC_T, C_{max}, T_{max}
	0-12 hours	AUC_t, AUC_∞, C_{max}, T_{max}, λ, $t_{½}$
Valproic acid	Steady state	AUC_T, C_{maxss}, T_{maxss}, C_{minss}, T_{minss}

*Relative to first dose of Xyrem®

The following urine parameters were calculated for sodium oxybate, alone:

- Urine concentration (C_{urine})
- Amount excreted during each collection interval (A_e)
- Cumulative amount excreted over the entire 12-hour collection period ($CumA_e$)
- Percentage of dose recovered in urine in each collection interval (%Dose)
- Cumulative percentage of dose recovered in urine (Cum%Dose)
- Renal clearance calculated as $CumA_e/AUC_{0\text{-}infinity}$.

Plasma concentrations and parameters for sodium oxybate and valproic acid were summarized by treatment using descriptive statistics. Pharmacokinetic parameters were also evaluated by analysis of variance models using natural log-transformed data. The 90% confidence intervals of the ratios for the various C_{max} and AUC parameters were calculated.

8.1.9.2 Pharmacodynamic Measures

Pharmacodynamic measurements were summarized by treatment and further investigated using analysis of covariance models, using baselines as the covariates. Changes from baseline at each timepoint were compared between the Xyrem® alone and Xyrem® + divalproex sodium treatments; and between the Xyrem® placebo + divalproex sodium and Xyrem® + divalproex sodium treatments.

8.1.9.3 Safety Measures

The results for the safety measures were summarized using descriptive statistics.

8.2 Summary Study Results

This study was conducted at a single clinical site in the United States by a Contract Research Organization: Celerion of Neptune, NJ.

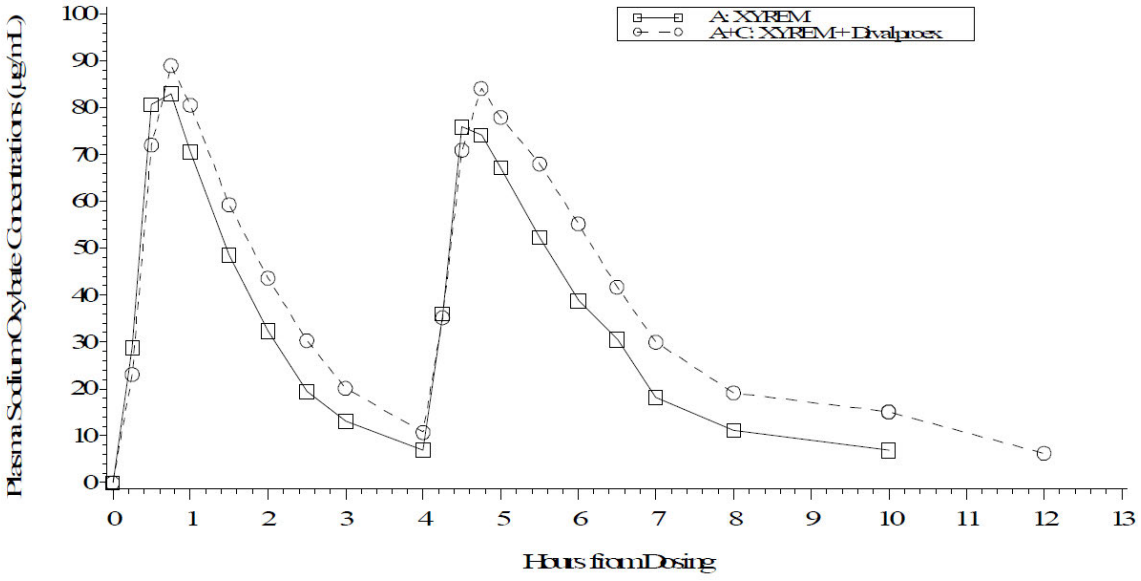
8.2.1 Pharmacokinetic Results

In the following sponsor table, the sodium oxybate pharmacokinetic parameters for the Xyrem® + divalproex sodium combination are compared with those for Xyrem® alone.

Parameter (Units)	Geometric LS Means[a]		% Mean Ratio Test/ Reference[b]	% Difference[c]	90% Confidence Interval	p-value
	Test SXB+DVP (N=18)	Reference SXB (N=18)				
C_{max} 0-4 h (ug/mL)	91.8	92.6	99.1	-0.92	92.7, 106	0.8135
C_{max} 4-8 h (ug/mL)	89.6	84.2	106	6.45	99.7, 114	0.1168
C_{max} (ug/mL)	98.5	95.7	103	2.93	96.5, 110	0.4482
AUC_{τ} 0-4 h (ug*h/mL)	155	133	116	16.2	110, 123	0.0002
AUC_{τ} 4-8 h (ug*h/mL)	175	139	126	26.5	119, 135	<0.0001
AUC_{0-t} (ug*h/mL)	345	277	125	24.6	117, 132	<0.0001
AUC_{0-inf} (ug*h/mL)	350	276[d]	127	26.9	120, 134	<0.0001

SXB = Xyrem two 3 g doses 4 hours apart (Treatment A)
SXB + DVP = Xyrem two 3 g doses 4 hours apart + divalproex sodium 1250 mg ER tablet (Treatment A+C)
Note: Subjects 10013 and 10020 were excluded from the statistical analysis due to vomiting within 2 times the Xyrem median t_{max}.
Parameters were log-transformed prior to analysis.
[a] Geometric LS means were calculated by exponentiating the LS means from the ANOVA. The ANOVA mixed-effects model included sequence, subject within sequence, period, and treatment.
[b] % mean ratio = 100*(test/reference)
[c] % difference = difference between treatments (test – reference) expressed as a percentage of reference
[d] n=17

Mean plasma sodium oxybate plasma concentrations over time are compared over time for Xyrem® administered with and without divalproex sodium in the figure below which is on a linear scale.



The sponsor draws attention to the following results:

- Following the administration of Xyrem® alone and with divalproex sodium, mean concentration-time profiles indicate higher sodium oxybate exposure for the Xyrem® and divalproex sodium combination than for Xyrem® alone. The median sodium oxybate T_{max} for the Xyrem® plus divalproex sodium combination was delayed at 2.75 hours versus that for Xyrem® alone (0.875 hours). After reaching peak concentrations, those for sodium oxybate declined rapidly during both treatments with mean t½ values of 0.722 hours for the Xyrem® plus divalproex sodium combination and 0.875 hours for Xyrem® alone.

- Systemic exposure, measured by the ratios of least squares geometric means was higher to the following extent for the Xyrem® plus divalproex sodium combination when compared with Xyrem® alone: 25% higher for the AUC_{0-t}, 26% higher for the AUC_{τ} for 4 to 8 hours, and 27% for the $AUC_{0-infinity}$. The upper limits for the 90% confidence intervals for the comparisons based on the AUC_{0-t}, AUC_{τ} for 4 to 8 hours, and the $AUC_{0-infinity}$ were higher than the 125% limit specified for equivalence. For the C_{max} at 0-4 hours, C_{max} at 4 to 8 hours, and C_{max}, the 90% confidence intervals for the same comparisons were within the limit of equivalence. The increased AUC values for sodium oxybate observed when Xyrem® and divalproex sodium were combined (as compared with Xyrem® alone) were consistent with the inhibition of gamma-hydroxybutyrate dehydrogenase by valproic acid.

The sponsor also draws attention to an increase in sodium oxybate renal clearance when Xyrem® was administered together with divalproex sodium than when Xyrem® was administered alone, as displayed in the following sponsor table.

Parameter (Units)	Geometric LS Means[a]		% Mean Ratio Test/ Reference[b]	% Difference[c]	90% Confidence Interval	p-value
	Test SXB+DVP (N=18)	Reference SXB (N=18)				
CLr (mL/h)	606	481	126	26.1	114, 139	0.0008
CumAe (ug)	211247	134435	157	57.1	141, 175	< 0.0001

SXB = Xyrem two 3 g doses 4 hours apart (Treatment A)
SXB + DVP = Xyrem two 3 g doses 4 hours apart + divalproex sodium 1250 mg ER tablet (Treatment A+C)
Note: Subjects 10013 and 10020 were excluded from the statistical analysis due to vomiting within 2 times the Xyrem median t_{max}.
Parameters were log-transformed prior to analysis.
[a] Geometric LS means were calculated by exponentiating the LS means from the ANOVA. The ANOVA mixed-effects model included sequence, subject within sequence, period, and treatment.
[b] % mean ratio = 100*(test/reference)
[c] % difference = difference between treatments (test – reference) expressed as a percentage of reference

The increased renal clearance of sodium oxybate that was seen for Xyrem® plus sodium oxybate versus Xyrem® alone is attributed by the sponsor to renal monocarboxylate transporter inhibition by divalproex sodium reducing the renal reabsorption of sodium oxybate.

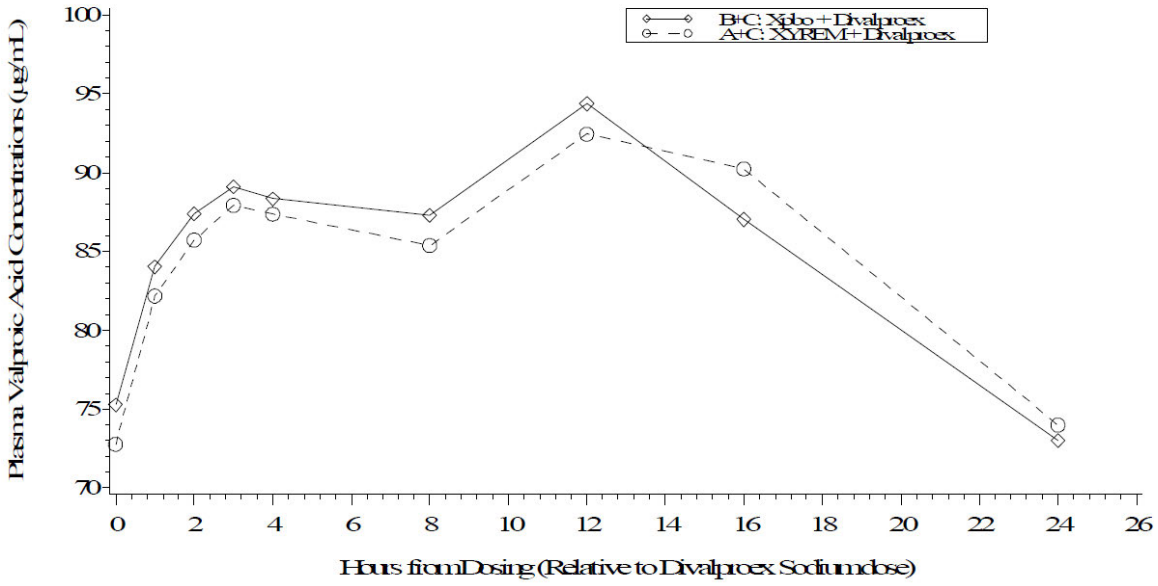
The next sponsor table displays a comparison of the pharmacokinetic parameters of valproic acid for the Xyrem® + divalproex sodium combination versus divalproex sodium alone. The results are self-explanatory, and have been

interpreted by the sponsor as indicating that the co-administration of sodium oxybate did not affect the pharmacokinetics of valproic acid.

Parameter (Units)	Geometric LS Means[a]		% Mean Ratio Test/ Reference[b]	% Difference[c]	90% Confidence Interval	p-value
	Test SXB+DVP (N=18)	Reference SPBO+DVP (N=18)				
C_{maxss} (ug/mL)	95.7	94.8	101	0.90	95.9, 106	0.7626
C_{minss} (ug/mL)	65.0	66.0	98.6	-1.42	91.8, 106	0.7305
AUC_{tau} (ug*h/mL)	1994	2004	99.5	-0.48	95.8, 103	0.8274

SPBO + DVP = sodium oxybate placebo two doses 4 hours apart + divalproex sodium 1250 mg ER tablet (Treatment B+C)
SXB + DVP = sodium oxybate two 3 g doses 4 hours apart + divalproex sodium 1250 mg ER tablet (Treatment A+C)
Note: Subjects 10013 and 10020 were excluded from the statistical analysis due to vomiting within 2 times the Xyrem median t_{max}.
Parameters were log-transformed prior to analysis.
[a] Geometric LS means were calculated by exponentiating the LS means from the ANOVA. The ANOVA mixed-effects model included sequence, subject within sequence, period, and treatment.
[b] % mean ratio = 100*(test/reference)
[c] % difference = difference between treatments (test – reference) expressed as a percentage of reference.

Mean plasma valproic acid concentrations following the administration of divalproex sodium with and without Xyrem® are displayed (on a linear scale) in the following sponsor figure.

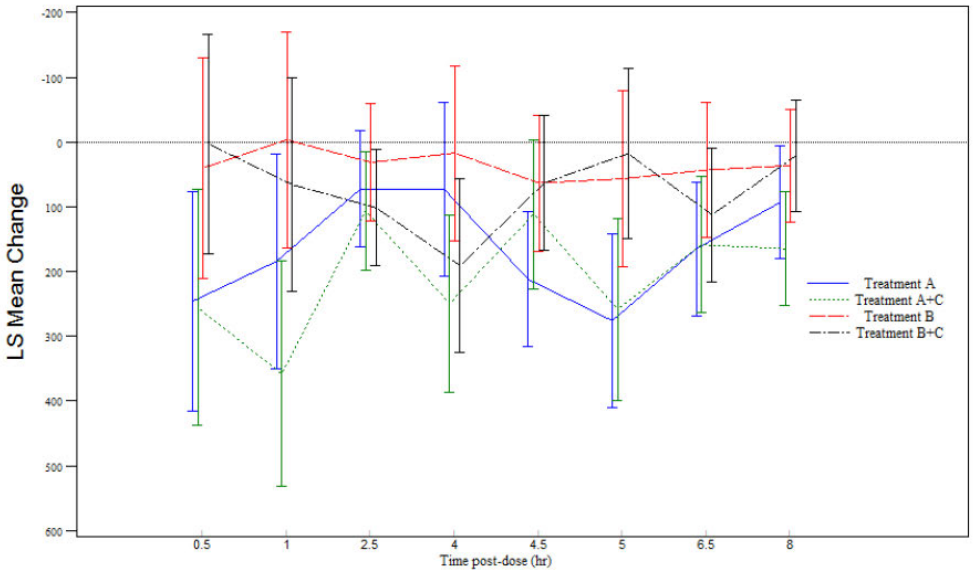


8.2.2 Pharmacodynamic Results

The administration of Xyrem® in combination with divalproex sodium resulted in a greater impairment on selected measures derived from the pharmacodynamic

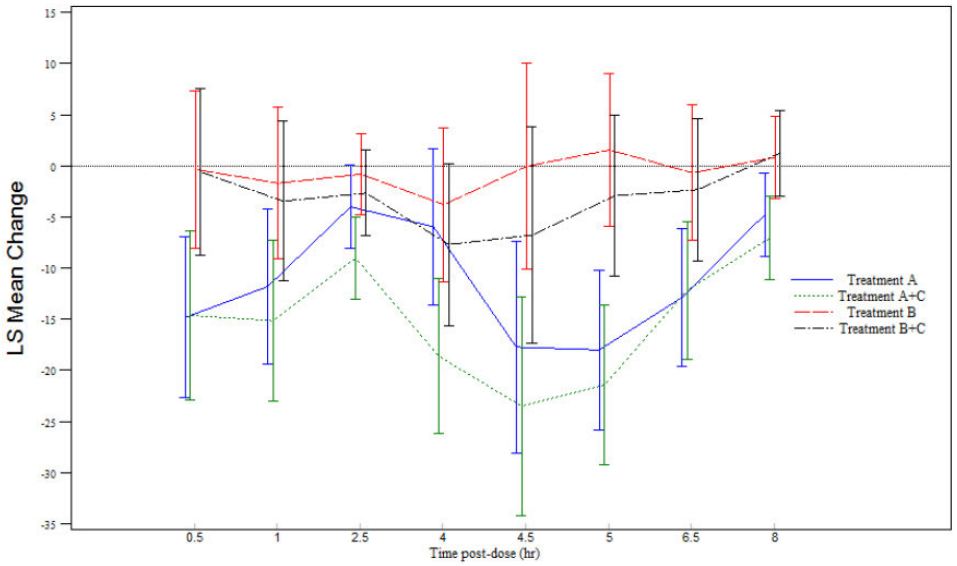
test battery at one or more timepoints after dosing, as compared with the administration of Xyrem® alone. The selected measures on which impairments were observed to be greater for the Xyrem® plus divalproex sodium combination versus Xyrem® alone were as follows (timepoints after the first Xyrem® dose in parentheses): Simple Reaction Time Mean (4 hours), Digit Vigilance Accuracy (4 hours), Tracking Distance from Target (8 hours), and Numeric Working Memory Mean Reaction Time (2.5, 5, and 8 hours). The aforementioned differences were those determined to be "statistically significant" (i.e., nominally statistically significant) by the sponsor. There were no differences between the 2 dosing regimes (i.e., Xyrem® plus divalproex sodium versus Xyrem® alone) on the Karolinska Sleepiness Scale.

The change from baseline in Simple Reaction Time Mean (in milliseconds) with different treatments and treatment combinations in this study is summarized in the following sponsor figure.



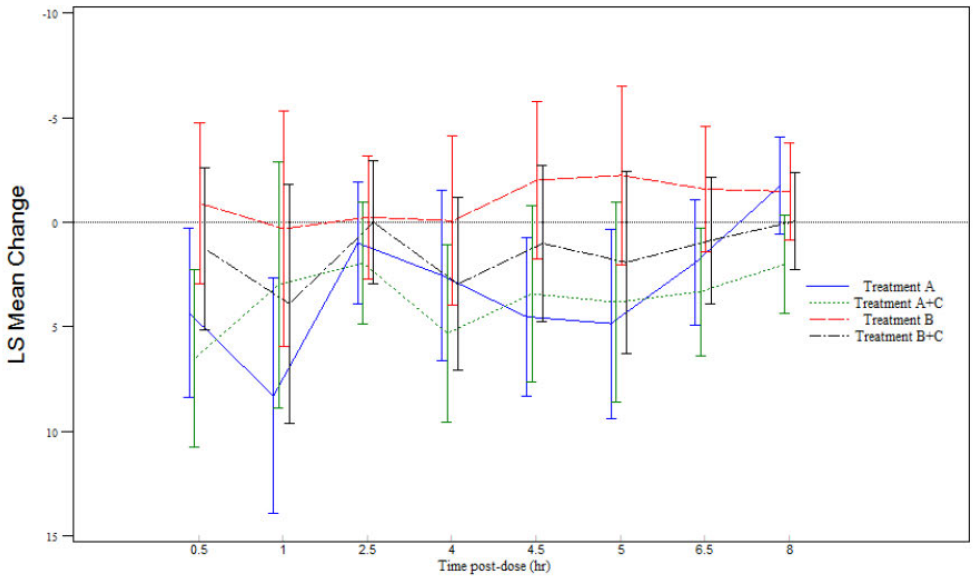
Treatment A=Xyrem two 3 g doses 4 hours apart; Treatment A+C=Xyrem two 3 g doses 4 hours apart + divalproex sodium 1250 mg ER tablet; Treatment B=Xyrem placebo two doses 4 hours apart; Treatment B+C= Xyrem placebo two doses 4 hours apart + divalproex sodium 1250 mg ER tablet

The change from baseline in Digit Vigilance Accuracy (expressed as a percentage) with different treatments and treatment combinations in this study is summarized in the following sponsor figure.



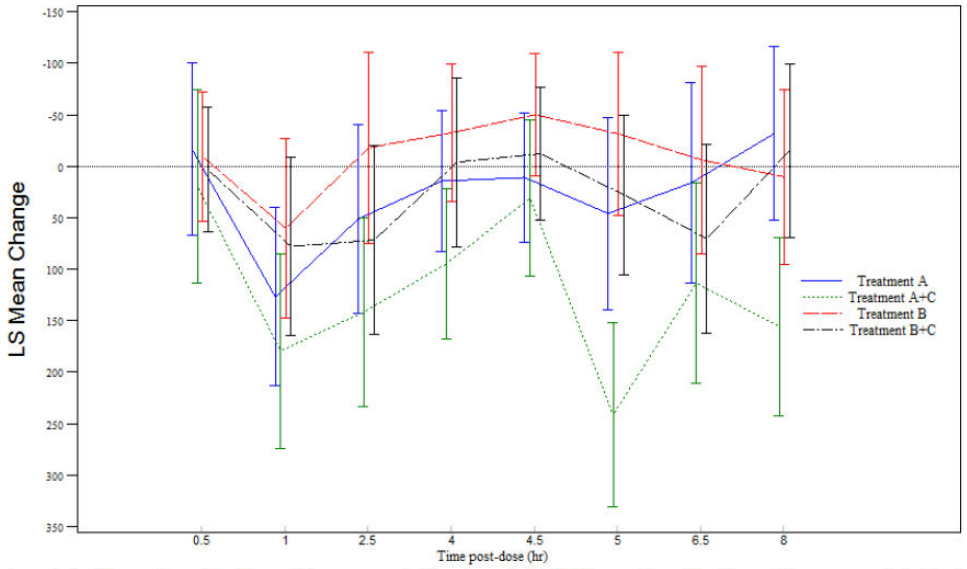
Treatment A=Xyrem two 3 g doses 4 hours apart; Treatment A+C=Xyrem two 3 g doses 4 hours apart + divalproex sodium 1250 mg ER tablet; Treatment B=Xyrem placebo two doses 4 hours apart; Treatment B+C= Xyrem placebo two doses 4 hours apart + divalproex sodium 1250 mg ER tablet

The change from baseline in Tracking Distance from Target (in mm) with different treatments and treatment combinations in this study is summarized in the next sponsor figure.



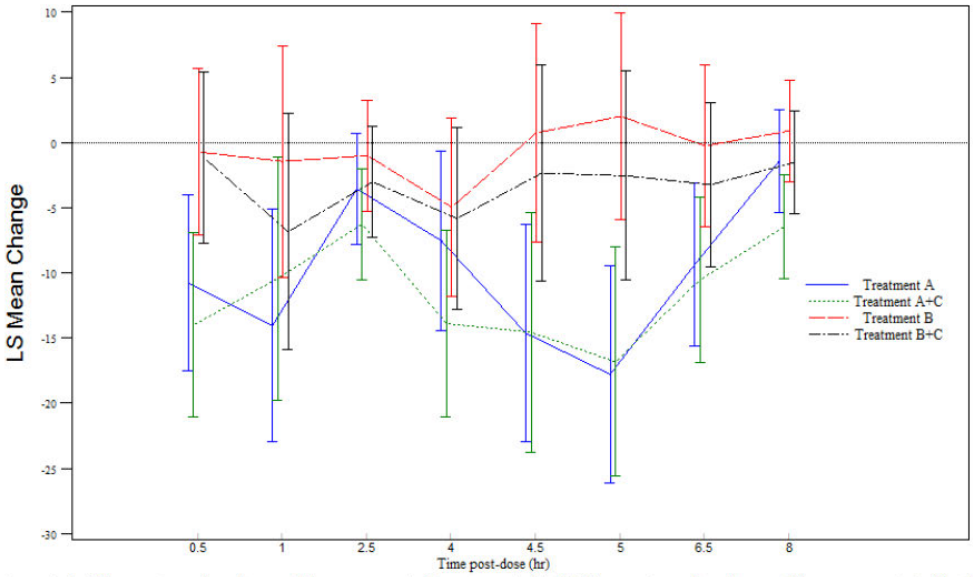
Treatment A=Xyrem two 3 g doses 4 hours apart; Treatment A+C=Xyrem two 3 g doses 4 hours apart + divalproex sodium 1250 mg ER tablet; Treatment B=Xyrem placebo two doses 4 hours apart; Treatment B+C= Xyrem placebo two doses 4 hours apart + divalproex sodium 1250 mg ER tablet

The change from baseline in Numeric Working Memory Mean Reaction Time (in milliseconds) with different treatments and treatment combinations in this study is summarized in the sponsor figure below.



Treatment A=Xyrem two 3 g doses 4 hours apart; Treatment A+C=Xyrem two 3 g doses 4 hours apart + divalproex sodium 1250 mg ER tablet; Treatment B=Xyrem placebo two doses 4 hours apart; Treatment B+C= Xyrem placebo two doses 4 hours apart + divalproex sodium 1250 mg ER tablet

Greater impairment was also seen on the Continuity of Attention measure (derived from the results of multiple individual cognitive tests in the pharmacodynamic battery) for the Xyrem® plus divalproex sodium combination than with Xyrem® alone at a single timepoint (8 hours after first Xyrem® dose). The change from baseline in Continuity of Attention (expressed as a whole number) with different treatments and treatment combinations in this study is summarized in the sponsor figure below.



Treatment A=Xyrem two 3 g doses 4 hours apart; Treatment A+C=Xyrem two 3 g doses 4 hours apart + divalproex sodium 1250 mg ER tablet; Treatment B=Xyrem placebo two doses 4 hours apart; Treatment B+C= Xyrem placebo two doses 4 hours apart + divalproex sodium 1250 mg ER tablet

Choice Reaction Time Accuracy was more impaired for Xyrem® alone than for the Xyrem® plus divalproex sodium combination at 6.5 hours.

On a number of the pharmacodynamic tests, including the Karolinska Sleepiness Scale, there was greater evidence of impairment with the combination of divalproex sodium and Xyrem® than for divalproex sodium alone.

The administration of divalproex sodium with Xyrem® placebo did not affect cognitive function or drowsiness to a significant degree, as compared with baseline.

8.2.3 Safety Results

There were no deaths, serious adverse events, or discontinuations due to adverse events.

The number (%) of subjects with adverse events that occurred in ≥ 2 subjects is summarized in the following table, which I have copied from the submission.

Preferred Term	Periods 1 & 2 Days 1-4 SPBO (n=20)	Periods 1 & 2 Days 1-4 SXB (n=20)	Period 3 Days 5-14 DVP (n=20)	Periods 4 & 5 Days 15-18 SPBO+DVP (n=20)	Periods 4 & 5 Days 15-18 SXB+DVP (n=20)	Total (n=20)
Any AE	5 (25%)	19 (95%)	5 (25%)	5 (25%)	20 (100%)	20 (100%)
Somnolence	5 (25%)	16 (80%)	0 (0%)	3 (15%)	18 (90%)	18 (90%)
Euphoric mood	0 (0%)	8 (40%)	0 (0%)	0 (0%)	10 (50%)	13 (65%)
Dizziness	0 (0%)	7 (35%)	0 (0%)	0 (0%)	7 (35%)	10 (50%)
Nausea	0 (0%)	3 (15%)	1 (5%)	0 (0%)	4 (20%)	4 (20%)
Vomiting	0 (0%)	2 (10%)	0 (0%)	0 (0%)	1 (5%)	2 (10%)
Back pain	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	2 (10%)
Limb discomfort	1 (5%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	2 (10%)
Disturbance in attention	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)	2 (10%)
Headache	0 (0%)	1 (5%)	0 (0%)	1 (5%)	0 (0%)	2 (10%)
Oropharyngeal pain	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	2 (10%)

Note: SPBO = Xyrem placebo, 2 doses given 4 hours apart
SXB = Xyrem, two 3-g doses given 4 hours apart
DVP = divalproex sodium 1250 mg given once daily at approximately 08:00

As the above table indicates, somnolence as well as well as several other adverse events were much more frequent with Xyrem® plus divalproex sodium and with Xyrem® alone, than with divalproex sodium alone.

A single subject (#10008), a 30-year-old man developed disorientation, emotional lability, an inability to focus, and hyperacusis beginning 26 minutes after receiving a Xyrem® dose of 3 g and ending 6 hours and 50 minutes later. Those symptoms were of moderate severity. The subject also experienced dizziness and sleepiness after the same dose of Xyrem® although not at exactly the same time, as the previously-mentioned symptoms.

No vital sign, electrocardiogram, or laboratory results of clinical significance were observed in this study; I have reviewed those data in some detail.

Data for the Columbia-Suicide Severity Rating Scale rating at baseline and subsequently revealed no evidence of suicidal ideation or self-injurious behavior.

8.3 Sponsor's Conclusions

8.3.1 Pharmacokinetic Conclusions

The systemic exposure to sodium oxybate was "statistically significantly" higher, based on AUC following the co-administration of divalproex sodium and Xyrem® than after the administration of Xyrem® alone; this increase in exposure was consistent with the inhibition of gammahydroxybutyrate dehydrogenase. There was no difference in systemic exposure to sodium oxybate, based on $C_{max,}$ when Xyrem® was co-administered with divalproex sodium as compared with the administration of Xyrem® alone.

The co-administration of Xyrem® and divalproex sodium did not affect the pharmacokinetics of valproic acid.

The co-administration of Xyrem® and divalproex sodium resulted in a "statistically significant" increase of about 30% in the renal clearance of sodium oxybate relative to the administration of Xyrem® alone. That effect was consistent with renal monocarboxylate transporter inhibition by divalproex sodium resulting in a reduced renal reabsorption of sodium oxybate.

8.3.2 Pharmacodynamic Conclusions

Not unexpectedly, the administration of Xyrem® alone resulted in sleepiness and in impaired attention, working memory, and performance on a tracking task, as compared with baseline. The co-administration of Xyrem® and divalproex sodium resulted in more cognitive impairment as compared with administration of the combination of Xyrem® placebo and divalproex sodium. However, the administration of divalproex sodium with Xyrem® placebo lacked noteworthy or consistent effects on cognition or sleepiness as compared with baseline.

The co-administration of Xyrem® and divalproex sodium resulted in statistically significantly greater deficits than the administration of Xyrem® alone on several cognitive measures at some of the timepoints at which they were assessed. These measures included Numeric Working Memory Mean Reaction Time, Simple Reaction Time Mean, Digit Vigilance Accuracy, Choice Reaction Time Accuracy, Continuity of Attention, and Tracking Distance from Target.

8.3.3 Safety Conclusions

The adverse events observed in this study were consistent with the approved Prescribing Information for Xyrem® and divalproex sodium.

9. Other Items Contributing To Currently-Proposed Changes To Prescribing Information For Xyrem®

The Agency had concluded after a review of post-marketing data pertaining to the occurrence of falls (and resulting injuries) at night in patients prescribed Xyrem® that changes to the DOSAGE AND ADMINISTRATION (Section 2) and PATIENT COUNSELING INFORMATION (Section 17) sections of the Prescribing Information for Xyrem® were needed to address that risk.

The proposed changes to labeling were conveyed by the Agency to the sponsor in an e-mail dated November 14, 2013, and are copied below. The same changes have been incorporated into the draft labeling submitted by the sponsor on November 25, 2013, as an Amendment to this Supplemental NDA.

The Agency-proposed changes to the Prescribing Information for Xyrem® included to address the risk of nocturnal falls are copied verbatim below using the "Track Changes" option to highlight the proposed changes.

SECTION 2 DOSAGE AND ADMINISTRATION

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 both doses of 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, p~~Patients should remain in bed following ingestion of the first and second doses, and should not take the second dose until 2.5 to 4 hours ~~later~~after the first dose. Patients may need to set an alarm to awaken for the second dose. Rarely, patients may take up to 2 hours to fall asleep.

SECTION 17 PATIENT COUNSELING INFORMATION

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 the first and second doses. 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~~after the first dose.

10. Sponsor's Full Proposed Changes To Prescribing Information For Xyrem®

The sponsor's proposed changes to the Prescribing Information for Xyrem® are available in full at the following link. The proposed changes to the Prescribing Information are those contained in the Amendment to this Supplemental NDA which was submitted on November 25, 2013.

\\cdsesub1\evsprod\nda021196\0026\m1\us\1-14-1-3-xyrem-redline-amended-20131120.pdf

A number of the changes proposed consist of minor editorial changes only. The more substantive changes to labeling proposed by the sponsor, with annotations, are copied fully below, in extracts from the proposed label.

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(b) (4)

11. Summary Of Agency Clinical Pharmacology Review

The Agency's Clinical Pharmacology review of this submission was conducted by Raman K Baweja, PhD, of the Division of Clinical Pharmacology 1. Dr Baweja has also discussed this sNDA with me on a number of occasions during the course of his review.

The full text of his review is available at the following link.

http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af8031fb00

In his review, he has presented the results of the three drug-drug interaction studies (12-006, 12-007, and 12-008) included in this sNDA. He has also edited a number of the proposed changes to the Prescribing Information submitted by the sponsor, with his editorial changes being accompanied by specific comments.

The following is a summary of Dr Baweja's main conclusions.

- In Studies 12-006 and 12-007, no drug-drug interactions were observed between Xyrem® and ibuprofen, and between Xyrem® and diclofenac, respectively.

- In Study 12-008, the co-administration of divalproex sodium increased the mean exposure to Xyrem®, based on AUC, by about 25% with an AUC ratio range from 0.83 to 1.71. There was considerable inter-subject variability as indicated by a coefficient of variation for AUCs between 31% and 43%. At the same time, there was no difference in the extent of sleepiness, based on the Karolinska Sleepiness Scale, when the administration of the combination of divalproex

sodium and Xyrem® was compared with the administration of Xyrem® alone; the adverse event profile of the 2 treatments (i.e., Xyrem® plus divalproex sodium vs Xyrem® alone) was also comparable. However, Study 12-008 was conducted in healthy subjects; in contrast, there is already a concern that central nervous system (and resulting respiratory) depression may occur in patients administered Xyrem®, a concern that may be greater if divalproex sodium, also a central nervous system depressant, is co-administered with Xyrem®. Thus if Xyrem® is co-administered with divalproex sodium, a reduction in Xyrem® dose or discontinuation of Xyrem® should be considered (the current approved Prescribing Information already has similar text applying to central nervous system depressants in general).

Notwithstanding the above, the pharmacokinetic and pharmacodynamic data for Study 12-008 are such that no specific (i.e., numerical) adjustments to the dose of Xyrem® have been recommended in the event that Xyrem® is co-administered with divalproex sodium. More specifically, the inter-subject variability in AUC_{0-4hr} and AUC_{0-8hr} ratios for sodium oxybate, and the comparability of sleepiness (based on the Karolinska Sleepiness Scale) and adverse event profile between the Xyrem® plus divalproex sodium and Xyrem® only treatments precluded more definite recommendations regarding how the dose of Xyrem® may be adjusted when divalproex sodium is co-administered.

- All references to (b) (4) have been deleted from the sponsor's proposed labeling (b) (4)

Please see Dr Baweja's review for details of the changes to the sponsor's proposed labeling that he has recommended.

12. Financial Disclosure Certification

Financial disclosure certification has been provided for all 3 clinical studies (12-006, 12-007, and 12-008) whose full reports are included in this submission.

12.1 Components Of Certification

The financial disclosure certification provided by the sponsor applies to two investigators, each of whom was involved in conducting all 3 clinical trials included in the sNDA: (b) (6)

In regard to the above investigators, the sponsor has:

- Certified that it has not entered into any financial agreement with the clinical investigators listed in the application, whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)

- Certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements
- Certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)

The above certification has been provided on FDA Form 3454

12.2 Reviewer's Comments

Based on the information provided above, it is highly unlikely that any financial arrangements for the listed clinical investigators introduced significant bias into the results of the 3 clinical trials included in this sNDA, on account of the clinical investigators' financial arrangements.

13. Reviewer's Summary Comments

13.1 Background

This submission consists of a Supplemental New Drug Application (sNDA) for Xyrem® (sodium oxybate) oral solution that seeks to amend the Prescribing Information for that product so as to include the pharmacokinetic results of 3 drug-drug interaction studies of Xyrem® with ibuprofen, with diclofenac, and with divalproex sodium, selected clinical pharmacodynamic data from the same drug-drug interaction studies, and a few other items, including changes to text requested by the Agency during the course of this review.

This sNDA was originally submitted on June 18, 2013. In response to requests from the Agency made during the review of the original submission, the sponsor then submitted an Amendment to this sNDA on November 25, 2013, containing revised proposed labeling and a corrected report for one of the three drug-drug interaction studies included in the original submission.

Xyrem® (sodium oxybate oral solution) was originally approved by the Agency on July 17, 2002, for the treatment of cataplexy in narcolepsy, under NDA 21196. A sNDA that proposed an expansion of the originally approved claim was approved on November 18, 2005; the approved expanded indication for Xyrem® was (and still is) as follows: "The treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy."

Several Prior Approval Labeling supplements for Xyrem® have also been approved since Xyrem® was originally approved for marketing on July 17, 2002. The current text of the Prescribing Information for Xyrem® was approved by the Agency on December 17, 2012.

Xyrem® was originally approved under the Subpart H (21 CFR 314.520) regulations, which have remained applicable to this product. Xyrem® is a Schedule III Controlled Substance available only through a Restricted Distribution Program that is managed by a Central Pharmacy. A deemed Risk Evaluation and Mitigation Strategy (REMS) for Xyrem® is currently in existence, with a significantly-modified REMS currently under discussion between the Agency and sponsor.

Among the core pharmacokinetic properties of sodium oxybate are the following: absolute oral bioavailability of 88%; T_{max} ranging from 0.5 to 1.25 hours; elimination mainly via metabolism to carbon dioxide and water; and an elimination half-life of 0.5 to 1 hour.

The sponsor's basis for conducting drug-drug interaction studies for sodium oxybate with ibuprofen, diclofenac, and divalproex sodium is as follows. The absorption of gamma-hydroxybutyrate is aided by sodium- and/or proton-dependent monocarboxylate transporter activity in the intestine, kidney, and blood-brain barrier; the activity of those monocarboxylate transporters are inhibited by non-steroidal anti-inflammatory drugs, such as ibuprofen and diclofenac; and valproic acid also inhibits monocarboxylate transporter activity in the intestine and at the blood-brain barrier. In addition, valproic acid inhibits gamma-hydroxybutyrate dehydrogenase, the enzyme that converts gamma-hydroxybutyrate to succinic acid semialdehyde (which in turn is metabolized via its conversion to succinic acid [by succinic semi-aldehyde dehydrogenase] to carbon dioxide and water through the tricarboxylic acid cycle).

13.2 Summary Of Clinical Findings

The three drug-drug interaction studies whose reports are included in this submission are as follows:

- Study 12-006, a randomized, double-blind, placebo-controlled, three-period crossover study whose primary objective was to evaluate the pharmacokinetics and pharmacodynamics of Xyrem® co-administered with ibuprofen; a secondary objective was to evaluate the safety and tolerability of Xyrem® with and without the co-administration of ibuprofen. In this study, ibuprofen was administered in a dose of 800 mg QID (at 4 hour intervals) on 3 consecutive days, with Xyrem® also being administered in two 3 gm doses 4 hours apart on the third day. Xyrem® was also administered alone in two 3 gm doses 4 hours apart on a single separate day during the study.

- Study 12-007, a randomized, double-blind, placebo-controlled, three-period crossover study whose primary objective was to evaluate the pharmacokinetics and pharmacodynamics of Xyrem® co-administered with diclofenac; a secondary objective was to evaluate the safety and tolerability of Xyrem® with and without the co-administration of diclofenac. In this study, diclofenac was administered in a dose of 50 mg QID (at 4 hour intervals) on 3 consecutive days, with Xyrem® also being administered in two 3 gm doses 4 hours apart on the third day.

Xyrem® was also administered alone in two 3 gm doses 4 hours apart on a single separate day during the study.

- Study 12-008, a randomized, double-blind, placebo-controlled, five-period crossover study whose primary objective was to evaluate the pharmacokinetics and pharmacodynamics of Xyrem® co-administered with divalproex sodium extended-release tablets; a secondary objective was to evaluate the safety and tolerability of Xyrem® with and without the co-administration of divalproex sodium extended-release tablets. In this study, divalproex sodium extended-release was administered in a dose of 1250 mg once every morning for 14 consecutive days, with Xyrem® also being administered in two 3 gm doses 4 hours apart on the 12th or 14th day of dosing with divalproex sodium.

Common to each of the 3 studies were the following:

- Their conduct at a single US clinical study site.
- The enrollment of a planned 24 healthy men and women aged 18 to 50 years.
- The use of the following tests for assessing the pharmacodynamic effects of the drugs investigated: Karolinska Sleepiness Scale; Simple Reaction Time Task; Digit Vigilance Task; Choice Reaction Time Task; Tracking Task; and Numeric Working Memory Task.
- The use of the following safety outcome measures: adverse events, vital signs, safety laboratory tests (hematology, clinical chemistry, and urinalysis), 12-lead electrocardiograms, and pulse oximetry. (The Columbia-Suicide Severity Rating Scale was used as a safety outcome measure in Study 12-008 only).
- The measurement of plasma and urine concentrations of sodium oxybate as pharmacokinetic outcome measures in each study (plasma concentrations of ibuprofen, diclofenac, and valproic acid were measured as pharmacokinetic measures in Studies 12-006, 12-007, and 12-008, respectively).

The results of the drug-drug interaction studies may be summarized as follows

- No pharmacokinetic interaction was observed between Xyrem® and ibuprofen in Study 12-006, and between Xyrem® and diclofenac in Study 12-007.
- In Study 12-008, the co-administration of divalproex sodium increased the mean exposure to Xyrem®, based on AUC parameters, by about 25% with an AUC ratio that ranged from 0.83 to 1.71; there was considerable inter-subject variability as indicated by a coefficient of variation for AUC parameters between 31% and 43%. The co-administration of Xyrem® in that study had no effect on the pharmacokinetics of valproic acid. The Agency Clinical Pharmacology reviewer has concluded that while a reduction in Xyrem® dosage should be recommended for patients with narcolepsy who are concomitantly administered divalproex sodium, given the inter-subject variability in exposure data seen in Study 12-008, no specific recommendations can be made as to how much the dose of Xyrem® should be reduced under those circumstances.

- No pharmacodynamic interactions (based on measures derived from the aforementioned test battery) were observed between Xyrem® and ibuprofen in Study 12-006, and between Xyrem® and diclofenac in Study 12-007.

- In Study 12-008, the administration of Xyrem® in combination with divalproex sodium resulted in greater impairment on selected measures derived from components of the pharmacodynamic battery assessed at one or more timepoints after dosing, as compared with the administration of Xyrem® alone. The selected measures on which impairments were observed to be greater for the Xyrem® plus divalproex sodium combination versus Xyrem® alone were as follows: Simple Reaction Time Mean, Digit Vigilance Accuracy, Tracking Distance from Target, and Numeric Working Memory Mean Reaction Time. There were no differences between the 2 dosing regimes (i.e., Xyrem® plus divalproex sodium versus Xyrem® alone) on the Karolinska Sleepiness Scale.

- In all three studies, the administration of Xyrem® alone or in combination with the other drug (i.e., ibuprofen, diclofenac or divalproex sodium) resulted in a higher incidence of selected adverse reactions, in comparison with the administration of the other drug alone. The most common of those adverse events was somnolence, and the adverse event profile of Xyrem® in those studies was broadly consistent with that described in the current Prescribing Information. The incidence of the more common adverse events (e.g., somnolence) was also comparable when Xyrem® was administered in combination with the other drug and when Xyrem® was administered alone in each study.

- There were no deaths, serious adverse events, or discontinuations due to adverse events in any of the three drug-drug interaction studies in this submission. Data for vital signs, safety laboratory tests, electrocardiograms, and the Columbia-Suicide Severity Rating Scale yielded no findings of concern.

The Agency had separately concluded after a review of post-marketing data that the occurrence of falls (and resulting injuries) at night in patients prescribed Xyrem® necessitated changes to Section 2 (DOSAGE AND ADMINISTRATION) and Section 17 (PATIENT COUNSELING INFORMATION) of the Prescribing Information for Xyrem® so as to adequately address that risk. Those proposed changes were conveyed to the sponsor during the review of the current sNDA and have been incorporated into the draft Prescribing Information submitted by the sponsor on November 25, 2013.

An error was noted that had not been observed previously by this reviewer in the description of Trial N2 in Section 14.1 (CLINICAL STUDIES) of the currently-approved Prescribing Information. The current description of that trial, which evaluated the efficacy of Xyrem® as a treatment for cataplexy in narcolepsy, includes the following sentence: "*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*" (emphasis added). The correct text for that sentence is as follows: "*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 2 weeks*"

(emphasis added). The report of Trial N2 (formally named Study OMC-SXB-21) was submitted on 12/16/00 during the period of review of the original NDA for Xyrem® which was submitted on 9/30/00; I have confirmed from the Agency efficacy review of the original NDA for Xyrem® that the period of randomized withdrawal in Study OMC-SXB-21 (Trial N2 in the Prescribing Information) lasted 2 weeks and not 4 weeks.

13.3 Conclusions

There is no pharmacokinetic or pharmacodynamic interaction between Xyrem® and ibuprofen, or between Xyrem® and diclofenac.

The administration of Xyrem® and divalproex sodium together to healthy subjects resulted in an increase in plasma sodium oxybate exposure of about 25% compared with the administration of Xyrem® alone. However there was considerable inter-subject variability in the extent of that increase in exposure: thus, while a reduction in Xyrem® dose is warranted when that drug is administered together with divalproex sodium, precise recommendations regarding the extent of that dose reduction cannot be made. The combination of Xyrem® with divalproex sodium was associated with greater impairment on selected tests of attention and working memory at some timepoints after dosing compared with the administration of Xyrem® alone; however, the two treatments did not differ in the severity of sleepiness (as measured by the Karolinska Sleepiness Scale) or in their adverse event profiles.

The results of the 3 drug-drug interaction studies (12-006, 12-007, and 12-007) should be described in the Prescribing Information for Xyrem®, together with the recommendation that the dose of Xyrem® should be reduced when that drug is administered concomitantly with divalproex sodium.

Additional changes to the Prescribing Information are to address the risk of falls in patients prescribed Xyrem® and to correct the description of a clinical efficacy study of Xyrem® in cataplexy.

14. Reviewer's Proposed Changes To Prescribing Information

This reviewer's own proposed changes to labeling were superimposed on those provided by the Clinical Pharmacology reviewer. These were then further edited by the Division's Deputy Director and eventually finalized with the sponsor. The final Prescribing Information that was agreed upon with the sponsor is in Appendix 1 at the end of this review. Note that the appended Prescribing Information does not include the Medication Guide for Xyrem®.

15. Recommendation

I recommend that this supplemental New Drug Application be approved under the conditions of use described in the Prescribing Information of Xyrem® contained in Appendix 1.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm
cc:
HFD-120
IND

16. Appendix 1: Final Prescribing Information

(b) (4)

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/s/

RANJIT B MANI
04/10/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-196/S-019

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	021196/S-019
Brand Name:	Xyrem™
Generic Name:	Sodium Oxybate
Dosage Form & Strength:	Immediate Release Oral Solution (0.5 g/ml)
Indication:	Narcolepsy
Applicant:	Jazz Pharmaceuticals
Submission:	Standard
Submission Dates:	June 18, 2013, November 25, 2013
OND Division:	OND-1/Division of Neurology Drug Products
OCP Divisions:	OCP/Division of Clinical Pharmacology 1 (DCP 1)
Primary Reviewer:	Raman Baweja, Ph.D.
Secondary Reviewer:	Ramana Uppoor, Ph.D.

Table of Contents

I. Executive Summary:

I.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 1 (OCP/DCP 1) has reviewed the labeling supplement and finds that it is acceptable from an OCP standpoint provided that an agreement is reached between the Sponsor and the Agency regarding the revised labeling language.

I.2 Comments to the Medical Officer

1. The results of three drug drug interaction studies are presented and appropriate labeling edits are being provided. The section on Labeling (see below) also has individual OCP comments for each of the labeling subsections.

2. In the three drug drug interaction studies, the ones of Xyrem with Ibuprofen, and Xyrem with Diclofenac showed no drug drug interaction in either direction for each of these pairs.

3. In the Divalproex sodium ER study it was seen that divalproex sodium increased the mean exposure of Xyrem by about 25% (AUC ratio range of 0.83 to 1.71). The intersubject variability as indicated by the coefficient of variation (% cv) for AUCs was between 31-43%. There was no difference in sleepiness amongst the two treatments (coadministration versus Xyrem alone). Further, both the number of AEs reported as well as the types of AEs were comparable. This drug interaction study was conducted with healthy subjects. In contrast, there is concern for CNS depression (e.g., respiratory depression) in narcolepsy patients which could potentially be a safety concern particularly when Xyrem, a CNS depressant, is coadministered with divalproex sodium which may also produce CNS depression. As per the label of Xyrem, 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. Based on the PK and PD information from this study, no specific dose adjustments are being recommended. However, the current language with respect to coadministration with CNS depressants should be applied to divalproex sodium coadministration.

(b) (4)

I.3 Summary of Clinical Pharmacology Findings

Background: Xyrem (Sodium oxybate) is an oral solution (500 mg/ml) that was approved as an orphan drug in the US in 2002 for the treatment of cataplexy and in 2005 for excessive daytime sleepiness in patients with narcolepsy. It is a Schedule III controlled

substance and is the sodium salt of gamma hydroxybutyrate (GHB) which is a Schedule I controlled substance. The initial dose is 4.5 grams (g) per night administered orally in two equal, divided doses of 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later. Titrating to effect occurs 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. The recommended dose range is 6 g to 9 g per night orally. Doses higher than 9 grams per night have not been studied. Time to peak concentration is 0.5 to 1.25 hours, and its elimination half life is very short, 0.5 hours. Metabolism via the tricarboxylic acid (Krebs) cycle is the major elimination pathway for sodium oxybate producing carbon dioxide which is eliminated from the lungs, and water; beta-oxidation is secondary and minor.
The label mentions that the drug is a hydrophilic compound and that its absolute bioavailability is about 88 % indicating that it is highly permeable.

This Supplement: This labeling supplement has three drug drug interaction studies:

(1) Xyrem and Ibuprofen (Study 12-006)

(2) Xyrem and Diclofenac (Study 12-007) and

(3) Xyrem and Divalproex sodium ER (Study 12-008)

(1) Xyrem and Ibuprofen (Study 12-006):

The objective of the study was to evaluate the pharmacokinetics and pharmacodynamics of Xyrem coadministered with ibuprofen. The study was a Phase 1, randomized, double-blind, placebo-controlled, three-period, crossover study in non-smoking healthy subjects. The three treatment arms were Xyrem alone, ibuprofen alone, and the coadministration of the two drugs. Ibuprofen was given as an 800mg/dose four times a day (4 hours apart) for two consecutive days before coadministration day. A four-times-daily dose of 800 mg ibuprofen (total daily dose of 3200 mg) was assessed because this is the highest recommended prescription dose. On day 3, co-administration occurred with 4×200 mg (800 mg/dose) ibuprofen administered at -1 hour and at 3 hours with 3 grams of Xyrem administered at 0 hour and at 4 hour. Xyrem alone treatment comprised of its administration as 3 gram doses each 4 hours apart and this occurred on one day only; this dosing regimen is the lowest effective nightly dose in patients with narcolepsy. In this study 19 males and 1 female completed the study.

Sodium oxybate:

Sodium oxybate has a very short half life and it reached zero level concentrations at each of the 4 hour dosing intervals (0-4 or 4-8) after drug administration. Thus, the relevant PK assessment for sodium oxybate is in looking at the AUC and Cmax values for both treatments of coadministration and of drug alone over the 0-4, and 4-8 hour dosing intervals. The 90% CIs for these sodium oxybate PK parameter values of the dosing intervals of 0-4 hours, and 4-8 hours were all within the accepted 80% to 125% equivalence range. The median t_{max} of the 0-4 and 4-8 hour interval all occurred within

one hour (i.e., 0.75 hr) after each of the two doses of Xyrem which were administered at 0 h and at 4 h; further these Tmaxs had comparable ranges for coadministration treatment and for sodium oxybate alone.

The cumulative percent of dose excreted in urine was about 2 % for drug alone and was about 4 % upon coadministration. This very small percent of drug excreted unchanged was seen in all three drug interaction studies. Renal elimination of sodium oxybate is not a major route of elimination. The drug rapidly and mainly undergoes conversion to a succinate by a dehydrogenase enzyme, and is then metabolized via the Krebs cycle and eliminated as carbon dioxide (CO_2) by the lungs, and as water.

There is no effect of Ibuprofen on the pharmacokinetics of Xyrem.

Ibuprofen:

When ibuprofen was co-administered with Xyrem compared with ibuprofen with Xyrem placebo, the 90% confidence intervals for AUC 0-4, AUC 4-8, Cmax 0-4, and Cmax 4-8 for ibuprofen were all within the 80-125% equivalence range. The point estimate for these AUCs was 97 % for both these intervals indicating comparable exposures from the two treatments. Mean Tmaxs and their ranges were comparable for both treatments.

Co-administration of Ibuprofen with Xyrem did not affect the PK of Ibuprofen.

Overall Conclusion: Neither Xyrem nor Ibuprofen affected the pharmacokinetics of the other drug.

Comment 1:

On coadministration days, ibuprofen was dosed one hour earlier relative to the dose of Xyrem. This was done to gauge the maximal effect of ibuprofen whose Tmax is around 1 hour on the kinetics of Xyrem which has a very short half of about 0.5 hours. Had the two drugs been coadministered at the same time, it would be expected that most of the dose of Xyrem would have been eliminated by the time ibuprofen was reaching its Cmax. Thus, a good strategy has been applied to obtain beneficial information on drug drug interaction.

A similar dosing scheme was used in the Xyrem – diclofenac interaction study that follows.

Comment 2:

Appropriate labeling text is being provided to the sponsor related to this drug drug interaction between Xyrem and ibuprofen.

(2) Xyrem and Diclofenac (Study 12-007):

This study assessed the pharmacokinetics and pharmacodynamics of Xyrem when given with diclofenac. This was a Phase 1, randomized, double-blind, placebo-controlled, three-period, crossover study in non-smoking healthy subjects. The three treatment arms were Xyrem alone, diclofenac alone, and the coadministration of the two drugs. Diclofenac was given as a 50mg/dose four times a day (4 hours apart) for two consecutive days before coadministration day. A four-times-daily dose of 50 mg diclofenac (total daily dose of 200 mg) was assessed because this is the highest recommended daily dose. On day 3, co-administration occurred with 50 mg dose of diclofenac administered at -1 hour and at 3 hours with 3 grams of Xyrem administered at 0 hour and at 4 hour. Xyrem alone treatment comprised of its administration as 3 gram doses each 4 hours apart and this occurred on one day only; this dosing regimen is the lowest effective nightly dose in patients with narcolepsy. Eighteen healthy subjects comprising of 16 males and 2 females completed the study.

Sodium oxybate:

The percent mean ratio of the sodium oxybate plasma exposure (AUC 0-4 or AUC 4-8) for the co-administration of Xyrem + diclofenac versus Xyrem alone were about 100 % and the 90% confidence intervals (CIs) for these comparisons were within the 80-125% equivalence range. Similarly, Cmax 0-4 and 4-8 had CI values within 80-125%. The median T_{max} of 0-4 and 4-8 hour interval occurred in 0.75 hour after each of the respective two doses of Xyrem (i.e., Xyrem doses administered at 0 h and at 4 h), and Tmaxs had comparable ranges for Xyrem + diclofenac versus Xyrem alone treatments.

The cumulative percent of sodium oxybate dose excreted in urine was about 2.5 % from coadministration and from Xyrem alone treatments.

There was no effect of Diclofenac on the pharmacokinetics of Xyrem.

Diclofenac:

When diclofenac was co-administered with Xyrem compared with diclofenac with Xyrem placebo, the 90% confidence intervals for the comparisons of AUC 0-4, AUC 4-8, and Cmax 0-4 for diclofenac were within the 80-125% equivalence range; Cmax 4-8 h showed 90% CI of 87% - 157%.

The point estimate for AUC 0-4, and for AUC 4-8 was about 103 % indicating comparable exposures from both treatments. Mean Tmaxs were 1 hour with very comparable ranges from both treatments.

A check of the individual values for Cmax 4-8 hours showed that one subject had a high value of 1630 ng/ml upon coadministration relative to the values of the other subjects, and, in this coadministration arm only. Without this value the mean point estimate is 1.11

instead of 1.17. Also, this value of 1630 ng/ml is not unusual, as in the other interval of Cmax 0-4 hour higher values were also seen but they were seen in both the treatment arms.

Co-administration of Diclofenac with Xyrem did not appear to affect the PK of Diclofenac.

Overall Conclusion: Neither Xyrem nor Diclofenac affected the pharmacokinetics of the other drug.

Comment 1:

The dosing strategy of administering diclofenac one hour earlier than Xyrem dosing was designed to obtain the maximal effect of diclofenac with its Tmax of about 1 hour on Xyrem which has a very short half of about 0.5 hours.

Comment 2:

Appropriate labeling text is being provided to the sponsor related to this drug drug interaction between Xyrem and Diclofenac.

(3) Xyrem and Divalproex sodium ER (Study 12-008):

The study was designed to evaluate the pharmacokinetics and pharmacodynamics of Xyrem coadministered with divalproex sodium ER tablets. The rationale for the dose of Xyrem of 6 grams per day given in two equal, divided doses was based on its clinical dose in narcolepsy. The 1250 mg dose of divalproex sodium ER tablets is slightly above the initial therapy dose for epilepsy monotherapy. This was a Phase 1, randomized, double-blind, placebo-controlled, five-period, crossover study in 18 healthy male subjects. The three treatments arms were Xyrem alone, divalproex sodium alone, and the coadministration of the two drugs. Divalproex sodium was given once daily for 10 consecutive days before coadministration day. Co-administration occurred with the continuation of the daily 1250 mg divalproex sodium ER tablets in the morning with 3 grams of Xyrem administered at 0 hour and again at 4 hour. Xyrem alone treatment comprised of its administration as 3 gram doses each 4 hours apart and this occurred on one day only. Twenty subjects entered the study and completed the study.

Sodium oxybate:

The 90 % CI for AUC 0-4 was within range (110 -123 %) with a point estimate of 116%. The upper bound of the 90% CI was higher than the 125% limit specified for equivalence for AUC 4-8 (90 % CI was 119 – 135% with a point estimate of 126%. The overall increase in exposure accounting for the two four-hour intervals is 25 % (AUC ratio range of 0.83 to 1.71). The coefficient of variation (% cv) for AUCs was between 31-43% and

for Cmaxs it was 13-23%. The Cmax's were comparable between treatments and the 90 % CI's were within the limits for equivalence. Tmaxs seen were around 0.75 hours.

A check of AUC ratios of individual subjects for coadministration : Xyrem alone for the 0-4 hour interval shows that 5 subjects had ratios below 1.0, 7 subjects had ratios between 1.0 and 1.2, and 8 subjects had ratios > 1.2 including a subject who had a value of 1.47 (Figure 7). Similarly, for the 4-8 hour interval, there were 4 subjects with ratios below 1.0, 3 subjects with ratios between 1.0 and 1.2, and 13 subjects with ratios above 1.2 including 4 subjects with values > 1.4; the highest ratio seen was 1.7 (Figure 8). The high ratios observed in both the intervals cannot be explained on the basis of gender (as all the subjects in the study were males), or age (comparable ages of healthy adults between 26 – 44 years), or body mass index (17 % difference between subjects).

Pharmacodynamics (PD): Of the twelve tests conducted, *5* showed that greater impairment was seen with coadministration treatment than with Xyrem alone treatment. Briefly, co-administration of Xyrem and divalproex sodium produced statistically significantly greater deficits than Xyrem alone in Numeric Working Memory Mean Reaction Time at 2.5, 5, and 8 h; in Simple Reaction Time Mean, and in Digit Vigilance Accuracy at 4 h; and in Continuity of Attention, and Tracking Distance from Target at 8h.

The study showed that co-administration of Xyrem and divalproex sodium produced greater impairments to attention than were seen with either drug alone. There was no difference amongst the two treatments in sleepiness.

Safety: In terms of Adverse Events (AEs) a total of 146 treatment-emergent AEs were reported by 20 of the 20 (100%) subjects treated, with 59 AEs in 19 subjects during treatment with Xyrem, and 61 AEs in 20 subjects during treatment with Xyrem + divalproex sodium. The most frequently reported AEs (reported in 2 or more subjects during any treatment) were somnolence, euphoric mood, dizziness, nausea, and vomiting. For example, somnolence was reported by 18 (90%) subjects receiving Xyrem + divalproex sodium, and 16 (80%) subjects receiving Xyrem alone.

The number of AEs reported as well as the types of AEs were similar between coadministration treatment and Xyrem alone treatment.

An issue of concern with Xyrem is that clinically significant respiratory depression has occurred in Xyrem-treated patients and this is mentioned as a black box Warning in the Full Prescribing Information of labeling. The concurrent use of Xyrem with other CNS depressants, including as for example opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs (AEDs), general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death (as per label). 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. As per the Depakote ER prescribing information, divalproex sodium may

produce CNS depression, especially when combined with another CNS depressant (and Xyrem is a CNS depressant). There is concern for respiratory depression in narcolepsy patients which could potentially be a safety concern particularly when Xyrem, a CNS depressant, is coadministered with divalproex sodium which may also produce CNS depression.

There is no PK/PD relationship known or established between Xyrem levels and PD of respiratory depression and it is therefore unknown if respiratory depression is related to AUC or Cmax.

Summary: From a PK standpoint the overall increase in exposure of Xyrem is about 25 % (AUC point estimate range of 0.83 to 1.71). The first interval of AUC (0-4) showed that the two treatments were comparable as the 90 % CI was within the 80 -125 % range (110 -123 %). The % coefficient variation (% cv) for AUCs as between 31-43% which relative to the mean increase in exposure of 25%, shows that there is considerable inter-subject variability in both treatments. Co-administration of Xyrem and divalproex sodium showed greater impairments to attention than were seen with either drug alone. There was no difference amongst the two treatments in sleepiness. The number of AEs reported as well as the types of AEs in this study in healthy subjects were similar between coadministration treatment and Xyrem alone treatment. There is no PK/PD relationship known or established between Xyrem levels and PD of CNS depression (e.g., respiratory depression) and it is therefore unknown if CNS (respiratory) depression is related to AUC or Cmax.

It is recognized that CNS depression is a concern when Xyrem either alone or in combination with valproic acid is administered and that its dose adjustment upon coadministration should be considered from a safety standpoint. However, specific dosing recommendation cannot be provided as, from a PK standpoint intersubject variability of 31- 43 % for AUC is considerable and PD endpoint, like sleepiness, was comparable between treatments in this study in healthy subjects. Further, both the number of AEs as well as the types of AEs in this study were similar. However, safety concern does remain for narcolepsy *patients* for CNS depression.

The cumulative percent of dose excreted in urine was about 2.5 % of the dose for drug alone and was 4.3 % upon coadministration. Urinary excretion is not the main route of elimination for Xyrem.

Divalproex sodium ER increased the exposure of Xyrem by 25%.

Valproic acid:

Valproic acid as measured by the ratio between treatments (of coadministration : drug alone) for the PK parameters of AUCtau (24 hours), Cmaxss, and Cminss were all close to 1.00. The 90% CIs for these comparisons were contained within 80% to 125%. Tmaxss were about 12.0 hours for both treatments.

Co-administration of Valproic acid with Xyrem did not affect the PK of Valproic acid.

Overall Conclusion: Valproic acid increased the exposure of Xyrem by about 25% and this is being mentioned in the Labelling of the drug. In turn, the co-administration of valproic acid with Xyrem did not affect the PK of valproic acid.

I.4 **Labeling**

The sponsor has provided labeling writeups for these three drug drug interaction studies in the following sections:

1) The Highlights section – Dosage and Administration

2) Section 2.4 DOSAGE AND ADMINISTRATION/Dose Adjustment with Co-administration of Divalproex Sodium

3) (b) (4)

4) Section 12.3 CLINICAL PHARMACOLOGY/Pharmacokinetics – Drug Interaction Studies

OCP labeling Comments are provided below after edits to each of the sections. Text and sentences related to Pharmacodynamics are to be reviewed by the Medical Officer.

Labeling Recommendation to be sent to the Sponsor:

The following describes the proposed changes: the underlined text is the proposed change to the label language; the ~~Strikethrough text~~ is the recommendation for deletion from an OCP perspective.

1) The Highlights section – Dosage and Administration: Appears this way on original

2) Section 2.4 DOSAGE AND ADMINISTRATION/Dose Adjustment with Co-administration of Divalproex Sodium

Pharmacokinetic and pharmacodynamic interactions have been observed when Xyrem is co-administered with divalproex sodium. (b) (4)

[see *Drug Interactions (7.1)*; *Clinical Pharmacology (12.3)*].

3) Section 7.1 DRUG INTERACTIONS

[redacted]

- *Divalproex sodium:* Concomitant use of Xyrem with divalproex sodium resulted in 25% mean increase in systemic exposure of Xyrem (AUC ratio range of [redacted] Prescribers are advised to monitor patient response [redacted] if concomitant use is warranted. [redacted]

[redacted]

OCP Comment: The Medical Officer is reviewing the PD of diclofenac.

4) Section 12.3 CLINICAL PHARMACOLOGY/Pharmacokinetics – Drug Interaction Studies

Drug interaction studies in healthy adults (age 18 to 50 years) were conducted with Xyrem and divalproex sodium, diclofenac, and ibuprofen. [See *Drug Interactions (7.1)* and *Dosage and Administration (2.4)*].

- Co-administration of Xyrem (6 g per day as two equal doses of 3 grams dosed four hours apart) with divalproex sodium (valproic acid, 1250 mg per day) increased mean systemic exposure to sodium oxybate as shown by AUC by approximately 25%, C_{max} was comparable. Co-administration did not appear to affect the pharmacokinetics of valproic acid. [redacted]

- Co-administration of Xyrem (6 g per day as two equal doses of 3 grams dosed four hours apart) with diclofenac (50 mg/dose [redacted] showed no significant differences in systemic exposure to sodium oxybate. Co-administration did not affect the pharmacokinetics of diclofenac. [redacted]

(b) (4)

- Co-administration of Xyrem (6 g per day as two equal doses of 3 grams dosed four hours apart) with ibuprofen (800 mg/dose qid) also dosed four hours apart resulted in comparable systemic exposure to sodium oxybate as shown by plasma C_{max} and AUC values. Co-administration did not affect the pharmacokinetics of ibuprofen. (b) (4)

OCP Comment: The Medical Officer is reviewing the PD of diclofenac.

Appendix

Individual Study Reviews

(1) Xyrem – Ibuprofen -- Clinical Study Report 12-006

Study Title: A randomized, double-blind, placebo-controlled, three-period, crossover study to evaluate the Pharmacokinetics and Pharmacodynamics of Xyrem® (sodium oxybate) co-administered with Ibuprofen in healthy volunteers (Study 12-006)

Study Dates: The study was initiated on 13 August 2012, and was completed on 22 September 2012

Sponsor: Jazz Pharmaceuticals, 3180 Porter Drive, Palo Alto, CA 94304

Clinical Research Organization: Celerion, 1930 Heck Ave, Neptune, NJ 07753

Bioanalytical Laboratories: (b) (4) (b) (4) (for sodium oxybate and ibuprofen concentrations)

Objective of the Study: The primary objective of this study was to evaluate the PK and PD of Xyrem coadministered with ibuprofen. The secondary objective of this study was to evaluate and compare the safety and tolerability of Xyrem with and without co-administration of ibuprofen.

Formulations used:

Xyrem® (sodium oxybate) oral solution, 500 mg/mL, Lot No: 3097264; Expiry Date: 31 May 2017

Xyrem placebo (sodium citrate oral solution), Lot No: 3103243; Retest Date: 31 July 2014

Motrin® IB (ibuprofen) tablets 200 mg, Lot No: CPA124; Expiration Date: 31 July 2014

Motrin® IB (overencapsulated in gelatin capsules)
Lot No: 74831B0; Expiration Date: 31 July 2014

Ibuprofen placebo capsules (gelatin capsules containing microcrystalline cellulose)
Lot No: 74831A0; Expiration Date: 31 July 2014

Rationale for the Doses Selected:

The therapeutic dose range established for Xyrem in clinical trials with narcolepsy patients is 6 to 9 grams (g) per day given in two equal, divided doses at bedtime

and then again 2.5 to 4 hours later. Two 3 g doses of Xyrem, administered 4 hours apart, were evaluated, as this dosing regimen was found to be the lowest effective nightly dose in patients with narcolepsy.
A four-times-daily dose of 800 mg ibuprofen (total daily dose of 3200 mg) was assessed because this is the highest recommended prescription dose. In this study, Motrin® IB 200 mg ibuprofen tablets were used to enable overencapsulation and therefore maintain the blinding of the study.

Study Design:

This was a Phase 1, randomized, double-blind, placebo-controlled, three-period, crossover study in non-smoking healthy subjects where 19 males and 1 female completed the study. Subjects met the inclusion and exclusion criteria. Following screening and baseline procedures, eligible subjects were entered into the study to receive one of the following treatments per period in randomized order:

A. Ibuprofen placebo was administered as four capsules qid (doses separated by 4 hours during the day, at 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before coadministration day. On co-administration day, four ibuprofen placebo capsules were administered at -1 h and at 3 h with 3 g of Xyrem administered at 0 h and at 4 h.

B. Ibuprofen was administered as four 200 mg tablets (overencapsulated) (800 mg/dose) qid (doses separated by 4 hours during the day, at 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before co-administration day. On co-administration day, 4×200 mg (800 mg/dose) ibuprofen was administered at -1 h and at 3 h with 3 g of Xyrem administered at 0 h and at 4 h.

C. Ibuprofen was administered as four 200 mg tablets (overencapsulated) (800 mg/dose) qid (doses separated by 4 hours during the day, at 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before co-administration day. On co-administration day, 4×200 mg (800 mg/dose) ibuprofen was administered at -1 h and at 3 h with Xyrem placebo (volume equivalent to 3 g of Xyrem oral solution) administered at 0 h and at 4 h

Subjects were randomized to one of the above treatments on Day 1, followed by a washout period on days 4 and 5, and then crossed over to one of the other treatments on Day 6, again followed by a washout period on days 9 and 10. The final crossover occurred on Day 11.

Study Schema

		Treatment Periods Treatment Days Randomized Treatments						
Screening	**Baseline**	**Period 1**		**Period 2**		**Period 3**		**Final Day**
Days -21 through -2	Day -1	Days 1 - 3	Days 4 – 5	Days 6 – 8	Days 9 -10	Days 11 - 13	Days 14-15	Day 15
		A, B, or C	Washout	A, B, or C	Washout	A, B, or C	Washout	

Regimen A = Ibuprofen placebo (qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period) + Xyrem two 3 g doses 4 h apart on the 3rd day of the period

Regimen B = Ibuprofen (800 mg/dose qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period) + Xyrem two 3 g doses 4 h apart on the 3rd day of the period

Regimen C = Ibuprofen (800 mg/dose qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period) + Xyrem placebo two doses 4 h apart on the 3rd day of the period

The crossover design allowed for within-the-same-subject comparison of Xyrem dosed alone and in combination with ibuprofen. The effect of sodium oxybate on ibuprofen was also evaluated. This study used a double-blind approach. The Xyrem and Xyrem placebo oral solutions were matched to ensure that the subjects and investigators were double-blinded. In addition, the ibuprofen tablets which were overencapsulated, and the ibuprofen placebo capsules were also matched to ensure double-blinding.

Subjects took ibuprofen or ibuprofen placebo with 240 mL of water, and Xyrem or Xyrem placebo (each dose diluted with 60 mL of water) with 180 mL of water. On non-Xyrem/Xyrem placebo dosing days, standard meals were provided, and there were no food or fluid restrictions. On co-administrations days (Days 3, 8, and 13), subjects received a light breakfast about 2 hours before the first dose of ibuprofen or ibuprofen placebo, a standardized low-fat meal (lunch) approximately 2 hours after the first dose of Xyrem or Xyrem placebo, and a standardized meal (dinner) approximately 4 hours after the second dose of Xyrem or Xyrem placebo. After the last plasma PK sample was collected, subjects were allowed food and fluid ad lib and a standardized snack was provided.

The light breakfast consisted of cornflakes cereal with up to one cup of skim milk, 200 mL of orange juice, and 200 mL of water (or equivalent meal <300 calories and <1 g fat). The standardized low-fat lunch was typically <500 calories and had about 20% to 30% fat content (i.e., calories derived from fat).

Sampling Schema:

Sodium Oxybate

Blood samples of 4 mL each were collected on Days 3, 8, and 13 at 0 h (predose), 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h (pre 2nd Xyrem/Xyrem placebo dose), 4.25 h, 4.5 h, 4.75 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 8 h, and 10 h relative to the first dose of Xyrem or Xyrem placebo. These blood samples were dispensed into labeled sodium heparin tubes.

Urine to measure sodium oxybate concentrations was collected on Days 3, 8, and 13, at predose (-4 to 0 hours) and during 0-4, 4-8, and 8-12 hour intervals after the first dose of Xyrem or Xyrem placebo.

Ibuprofen

Blood samples (4 mL) to measure ibuprofen concentrations were collected on Days 3, 8, and 13 at -1 h, -0.5 h, 0 h, 0.5 h, 1 h, 2 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 6 h, 7 h, and 9 h relative to the first dose of Xyrem or Xyrem placebo. These blood samples were dispensed into labeled sodium heparin tubes.

Analytical Method:

The PK analyses were performed by a central bioanalytical laboratory. Bioanalytical assays (for plasma and urine samples) were conducted at (b) (4) using validated methods that consisted of extraction and then analysis using Applied Biosystems LC/MS/MS. The method was specific for the moieties of sodium oxybate and ibuprofen.

Sodium oxybate

The validation aspects of the assay are that the method for plasma was linear over the range of 1.00 - 160 mcg/mL with a lower limit of quantitation (LLOQ) of 1.0 µg/mL. The internal standard used was sodium oxybate – d6 (deuterated). The freeze thaw cycle covered 4 cycles of freeze (-20°C) and thaw (37°C) and showed that the compound is stable. Accuracy was 100 +/- 2%, and precision was within 3 %.

Sodium oxybate was linear from 5.0 to 480 mcg/mL in human urine. The lower limit of quantitation (LLOQ) for analysis in urine was 5.0 µg/mL. Accuracy was 100 +/- 5%, and precision was within 4.5 %.

Ibuprofen

The lower limit of quantitation (LLOQ) for the analysis of ibuprofen in plasma was 0.5 µg/mL. Linearity was from 0.5 mcg/ml to 100 mcg/ml. The internal standard used was the deuterated form of ibuprofen (d3). Accuracy was 100 +/- 1.5%, and precision

was within 5 %. Ibuprofen was stable in human plasma over 4 cycles of freeze (-20°C or -70°C) and thaw (room temperature or 37 ± 3 °C).

The method was specific for the moieties of sodium oxybate and ibuprofen, and is validated.

Results:

Pharmacokinetics: A total of 20 subjects including 19 males and 1 female completed the study.

Sodium oxybate

Means and standard deviations (SD) for plasma sodium oxybate PK parameters are presented in Table 1. The statistical analysis of sodium oxybate PK parameters is in Table 2. Mean sodium oxybate concentrations with and without ibuprofen co-administration are plotted over time in Figure 1.

Table 1 Sodium Oxybate Plasma PK Parameters

PK Parameter	Units		Treatment A sodium oxybate + ibuprofen placebo (reference)			Treatment B sodium oxybate + ibuprofen		
			0-4 h	4-8 h	0-10 h	0-4 h	4-8 h	0-10 h
C_{max}	(µg/mL)	N	20	20	20	20	20	20
		Mean	92.5	85.3	96.0	87.6	80.6	89.7
		SD	16.87	19.62	17.41	13.15	15.95	12.27
		Geometric Mean	91.0	82.9	94.3	86.6	78.8	88.9
		Geometric SD	1.21	1.29	1.22	1.16	1.26	1.14
t_{max}	(h)	N	20	20	20	20	20	20
		Median	0.750	4.63	2.63	0.500	4.63	0.750
		Min, Max	0.25, 1.00	4.50, 5.00	0.25, 4.75	0.25, 0.75	4.50, 4.75	0.25, 4.75
AUC_{τ}	(µg*h/mL)	N	20	20	--	20	20	--
		Mean	139	149	--	132	141	--
		SD	38.6	54.9	--	35.1	45.1	--
		Geometric Mean	133	138	--	127	134	--
		Geometric SD	1.35	1.51	--	1.32	1.43	--
AUC_{0-t}	(µg*h/mL)	N	--	--	20	--	--	20
		Mean	--	--	291	--	--	277
		SD	--	--	97.2	--	--	84.1
		Geometric Mean	--	--	275	--	--	264
		Geometric SD	--	--	1.44	--	--	1.39
AUC_{0-inf}	(µg*h/mL)	N	--	--	20	--	--	20
		Mean	--	--	294	--	--	280
		SD	--	--	98.4	--	--	84.8
		Geometric Mean	--	--	277	--	--	267
		Geometric SD	--	--	1.44	--	--	1.39
λz	(1/h)	N	--	--	20	--	--	20
		Mean	--	--	1.30	--	--	1.27
		SD	--	--	0.461	--	--	0.405
$t_{1/2}$	(h)	N	–	–	20	–	–	20
		Mean	--	--	0.587	--	--	0.596
		SD	--	--	0.1737	--	--	0.1772

The percent mean ratio of sodium oxybate AUC and Cmax over the 0-4, and 4-8 hour intervals for the co-administration of Xyrem + ibuprofen versus Xyrem + ibuprofen placebo ranged from about 94 % to 96%, and the 90% confidence intervals (CIs) for these comparisons were well within the 80-125% equivalence range (Table 2). The

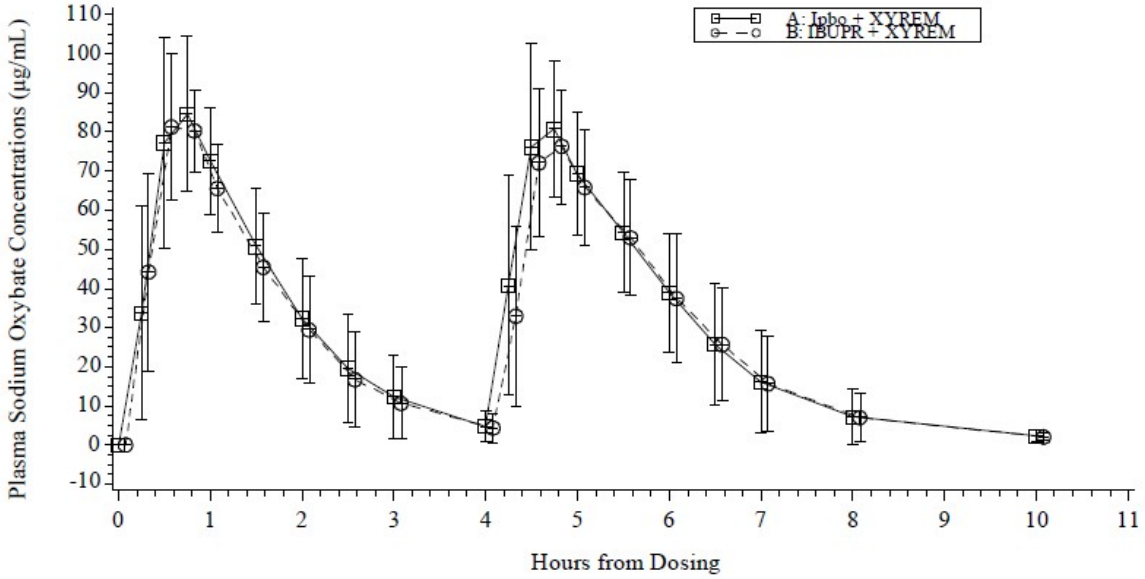
median t_{max} of the 0-4 and 4-8 hour interval all occurred within one hour (i.e., 0.75 hr) after each of the two doses of Xyrem which were administered at 0 h and at 4 h; further these Tmaxs had comparable ranges for coadministration treatment and for sodium oxybate alone.

There is no effect of ibuprofen on the pharmacokinetics of sodium oxybate.

Table 2 Statistical Comparisons of Plasma Sodium Oxybate PK Parameters: SXB + IBU versus SXB + Ipbo

Parameter (Units)	Geometric LS Means[a]		% Mean Ratio Test/ Reference[b]	% Difference[c]	p-value	90% Confidence Interval
	Test SXB + IBU N=20	Reference SXB + Ipbo N=20				
C_{max} 0-4 h (µg/mL)	86.8	91.4	95.0	-5.05	0.0742	90.6, 99.6
C_{max} 4-8 h (µg/mL)	79.0	83.5	94.6	-5.40	0.0956	89.6, 99.9
C_{max} (µg/mL)	89.1	94.9	93.9	-6.08	0.0103	90.4, 97.5
AUC_{τ} 0-4 h (µg*h/mL)	129	136	95.5	-4.53	0.0455	92.0, 99.1
AUC_{τ} 4-8 h (µg*h/mL)	136	141	96.4	-3.63	0.1557	92.3, 100.6
AUC_{0-t} (µg*h/mL)	269	280	95.9	-4.13	0.0177	93.2, 98.6
AUC_{0-inf} (µg*h/mL)	271	283	95.9	-4.13	0.0194	93.2, 98.6

Figure 1 Mean (+/-SD) Plasma Sodium Oxybate Concentration with and without Ibuprofen Co-administration



Treatment A=Xyrem + ibuprofen placebo (Ipbo)
Treatment B=Xyrem + ibuprofen (IBUPR)

Urinary excretion of sodium oxybate: A very small fraction of the dose administered is excreted as unchanged sodium oxybate in the urine and this fact is also mentioned in the current labeling for this drug. In this study the cumulative percent of dose excreted in urine was about 2 % for drug alone and was about 4 % upon coadministration. Renal excretion increased approximately 2 fold when Xyrem was co-administered with ibuprofen compared with Xyrem + ibuprofen placebo (CLr=874 mL/h for Xyrem + ibuprofen and 464 mL/h for Xyrem + ibuprofen placebo). Overall the renal route of elimination for sodium oxybate is insignificant.

Comments:

Comment 1: Sodium oxybate has a very short half life which reached zero level concentrations at each of the 4 hour dosing intervals (i.e., 0-4 or 4-8) after drug administration. A check of the C4 hour and C8 hour concentrations of subjects showed that these values were 5 % of the observed Cmax, indicating clearly that almost all of the drug had been eliminated with its very short half life of around 0.5 hours in a given 4 hour dosing interval. So the relevant PK assessment is in looking at the AUC and Cmax values for both treatments over the 0-4, and 4-8 hour dosing intervals.

This comment applies to the assessment of sodium oxybate in all three drug drug interaction studies.

Comment 2: The 90% CIs for the relevant sodium oxybate PK parameter values of the dosing intervals of 0-4 hours, and 4-8 hours were all within the accepted 80% to 125% equivalence range. Further, Tmaxs for both treatments were comparable.

There is no effect of ibuprofen on the pharmacokinetics of Xyrem.

Comment 3: The light breakfast of corn flakes given to subjects 3 hours before Xyrem dosing as well as the timing of the other meals given 2 hours or 4 hours after Xyrem dosing should have no influence on the pharmacokinetics of sodium oxybate which as mentioned has a very short half life.

Comment 4: On coadministration days, ibuprofen was dosed one hour earlier relative to the dose of Xyrem. This was done to gauge the maximal effect of ibuprofen whose Tmax is around 1 hour on the kinetics of Xyrem which has a very short half of about 0.5 hours. Had the two drugs been coadministered at the same time, it would be expected that most of the dose of Xyrem would have been eliminated by the time ibuprofen was reaching its Cmax. Thus, a good strategy has been applied to obtain beneficial information on drug drug interaction.

Comment 5: Even though Xyrem is administered at nighttime, the three drug drug interaction studies conducted on healthy subjects had Xyrem and the coadministered drug given in the morning. This should not affect the outcome of the studies as neither Xyrem nor the coadministered drugs show diurnal variation.

Ibuprofen

Means and standard deviations (SD) for plasma ibuprofen PK parameters are presented in Table 3. The statistical analysis of ibuprofen PK parameters is in Table 4. Mean ibuprofen concentrations with and without Xyrem co-administration are plotted over time in Figure 2.

Table 3 Ibuprofen Plasma PK Parameters

Parameter	Units		Treatment B sodium oxybate + ibuprofen			Treatment C Sodium oxybate placebo + ibuprofen (reference)		
			0-4[a] h	4-8[a] h	0-10[a] h	0-4[a] h	4-8[a] h	0-10[a] h
C_{max}	(µg/mL)	N	20	20	20	20	20	20
		Mean	61.2	49.9	61.9	61.7	52.7	62.7
		SD	10.04	12.62	9.37	8.12	9.38	7.01
		Geometric Mean	60.5	48.2	61.2	61.2	51.9	62.3
		Geometric SD	1.18	1.31	1.16	1.14	1.20	1.11
t_{max}[a]	(h)	N	20	20	20	20	20	20
		Median	1.50	7.00	1.50	1.50	7.00	1.50
		Min, Max	0.50, 2.00	5.00, 8.00	0.50, 7.00	0.50, 1.50	5.00, 8.00	0.50, 7.00
AUC_{τ}	(µg*h/mL)	N	20	20	--	20	20	--
		Mean	146	141	--	150	144	--
		SD	27.0	28.1	--	24.5	27.8	--
		Geometric Mean	144	138	--	149	142	--
		Geometric SD	1.20	1.23	--	1.16	1.21	--
AUC_{0-t}	(µg*h/mL)	N	--	--	20	--	--	20
		Mean	--	--	347	--	--	355
		SD	--	--	64.0	--	--	57.6
		Geometric Mean	--	--	342	--	--	351
		Geometric SD	--	--	1.20	--	--	1.17
AUC_{0-inf}	(µg*h/mL)	N	--	--	9	--	--	7
		Mean	--	--	439	--	--	421
		SD	--	--	87.9	--	--	77.7
		Geometric Mean	--	--	431	--	--	416
		Geometric SD	--	--	1.22	--	--	1.19
λz	(1/h)	N	--	--	9	--	--	7
		Mean	--	--	0.259	--	--	0.293
		SD	--	--	0.0875	--	--	0.0502
$t_{1/2}$	(h)	N	--	--	9	--	--	7
		Mean	--	--	3.26	--	--	2.42
		SD	--	--	2.055	--	--	0.395

When ibuprofen was co-administered with Xyrem compared with ibuprofen with Xyrem placebo, the 90% confidence intervals for AUC 0-4, AUC 4-8, Cmax 0-4, and Cmax 4-8 for ibuprofen were all within the 80-125% equivalence range (Table 4). The point estimate for these AUCs was 97 % for both these intervals indicating comparable exposures from the two treatments. Mean Tmaxs and ranges are comparable for both treatments.

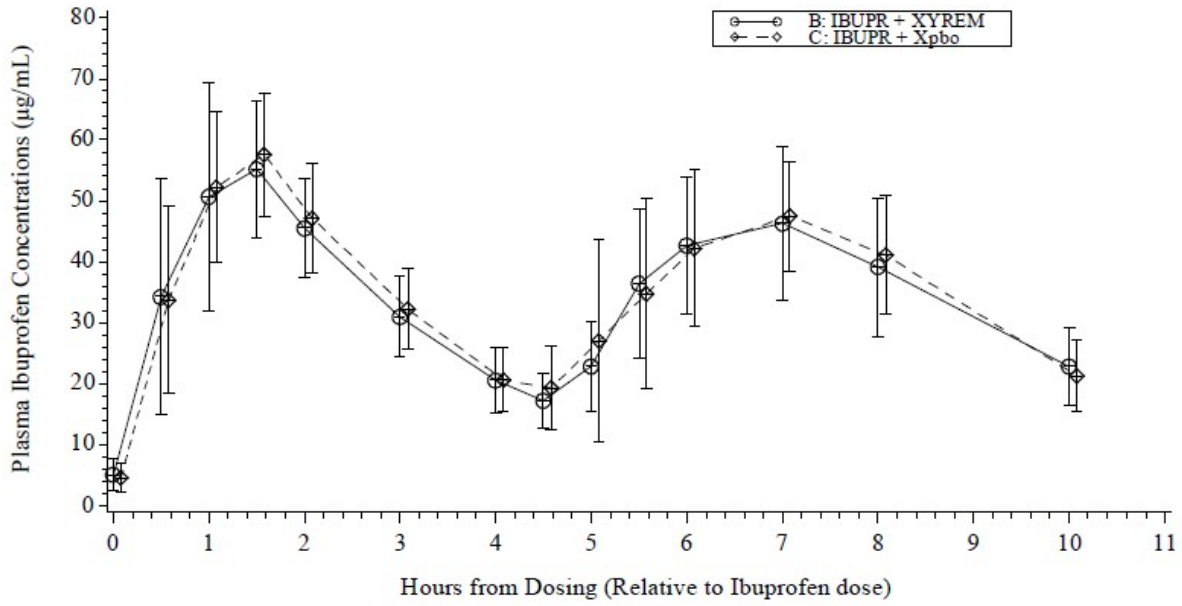
Co-administration of Xyrem with ibuprofen did not affect the PK of ibuprofen. (see also Comment section).

Table 4 Statistical Comparisons of Plasma Ibuprofen PK Parameters: SXB + IBU versus Spbo + IBU

Parameter (Units)	Geometric LS Means[a]		% Mean Ratio Test/ Reference[b]	% Difference[c]	p-value	90% Confidence Interval
	Test SXB + IBU N=20	Reference Spbo + IBU N=20				
C_{max} 0-4[d] h (µg/mL)	60.6	61.3	98.9	-1.10	0.6832	94.4, 104
C_{max} 4-8[d] h (µg/mL)	48.4	51.9	93.4	-6.58	0.1272	86.8, 101
C_{max} (µg/mL)	61.3	62.3	98.4	-1.59	0.4526	94.9, 102
AUC_{τ} 0-4[d] h (µg*h/mL)	145	149	97.2	-2.81	0.2004	93.6, 101
AUC_{τ} 4-8[d] h (µg*h/mL)	138	142	97.5	-2.52	0.5094	91.3, 104
AUC_{0-t} (µg*h/mL)	343	351	97.8	-2.18	0.2623	94.6, 101
AUC_{0-inf} (µg*h/mL)	442[e]	407[f]	109	8.69	0.3982	86.5, 137

SXB=Sodium oxybate, Spbo = Sodium oxybate placebo, IBU=ibuprofen

Figure 2 Mean (SD) Ibuprofen Concentration with and without Sodium Oxybate Co-administration



Treatment B=Xyrem + ibuprofen Treatment
C=Xyrem placebo (Xpbo) + ibuprofen

Comments:

Comment 1: For ibuprofen also the 0-4, and 4-8 hour intervals were chosen for PK assessment. This is because ibuprofen has a half-life of about 2 hours and in the dosing interval of 4 hours (i.e., 2 half-lives) almost 70 % of it should be theoretically eliminated.

This is also what was observed with the data as the concentrations at C4 hours and at C8 hours showed that about 66 % of ibuprofen had been eliminated leaving about 34 % in the body. Since this was a crossover study it was seen that the 34 % amount of ibuprofen remaining was a constant amount from either of the crossover treatments, namely, coadministration of both drugs or drug alone.

Comment 2: Co-administration of ibuprofen with Xyrem did not affect the PK of ibuprofen.

Adverse Events: Most of the adverse events seen in the study were somnolence, euphoric moodiness, dizziness, headache, nausea, constipation, fatigue and itching. Most were mild in severity and none were severe. No deaths or SAEs occurred during the study and no subject discontinued.

Overall Conclusion: Neither Xyrem nor ibuprofen affected the pharmacokinetics of the other drug.

(2) Xyrem – Diclofenac -- Clinical Study Report 12-007

Study Title: A randomized, double-blind, placebo-controlled, three-period, crossover study to evaluate the Pharmacokinetics and Pharmacodynamics of Xyrem® (sodium oxybate) co-administered with Diclofenac in healthy volunteers (Study 12-007)

Study Dates: The study was initiated on 7 August 2012, and was completed on 22 September 2012

Sponsor: Jazz Pharmaceuticals, 3180 Porter Drive, Palo Alto, CA 94304

Clinical Research Organization: Celerion, 1930 Heck Ave, Neptune, NJ 07753

Bioanalytical Laboratories: (b) (4) (b) (4) (for sodium oxybate and diclofenac concentrations)

Objective of the Study: The primary objective of this study was to evaluate the PK and PD of Xyrem coadministered with diclofenac. The secondary objective of this study was to evaluate and compare the safety and tolerability of Xyrem with and without co-administration of diclofenac.

Formulations used:

Xyrem® (sodium oxybate) oral solution, 500 mg/mL, Lot No: 3097264; Expiry Date: 31 May 2017

Xyrem placebo (sodium citrate oral solution), Lot No: 3103243; Retest Date: 31 July 2014

Cataflam® (diclofenac potassium immediate-release tablets) 50 mg, Lot No: FXPB; Expiration Date: 31 August 2014

Cataflam® (overencapsulated in gelatin capsules), Lot No: 74841B0; Expiration Date: 31 August 2014

Diclofenac placebo capsules (gelatin capsules containing microcrystalline cellulose), Lot No: 74841A0; Expiration Date: 31 August 2014

Rationale for the Doses Selected:

The therapeutic dose range established for Xyrem in clinical trials with narcolepsy patients is 6 to 9 grams (g) per day given in two equal, divided doses at bedtime and then again 2.5 to 4 hours later. Two 3 g doses of Xyrem, administered 4 hours apart, were evaluated, as this dosing regimen was found to be the lowest effective nightly dose in patients with narcolepsy.
A four-times-daily dose of 50 mg diclofenac (total daily dose of 200 mg) was assessed because this is the highest recommended daily dose.

Study Design:

This was a Phase 1, randomized, double-blind, placebo-controlled, three-period, crossover study in non-smoking healthy subjects where 18 subjects (16 males and 2 females) completed the study. Subjects met the inclusion and exclusion criteria. Following screening and baseline procedures, eligible subjects were entered into the study to receive one of the following treatments per period, in randomized order:

A. Diclofenac placebo administered as one capsule qid (doses separated by 4 hours during the day, at 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before coadministration day. On co-administration day, one diclofenac placebo capsule was administered at -1 h and at 3 h with 3 g of Xyrem administered at 0 h and at 4 h.

B. Diclofenac administered as 50 mg immediate-release (IR) tablet (overencapsulated) qid (doses separated by 4 hours during the day, at 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before co-administration day. On co-administration day, 50 mg diclofenac was administered at -1 h and at 3 h with 3 g of Xyrem administered at 0 h and at 4 h.

C. Diclofenac administered as 50 mg IR tablet (overencapsulated) qid (doses separated by 4 hours during the day, at 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before co-administration day. On co-administration day, 50 mg diclofenac was administered at -1 h and at 3 h with Xyrem placebo (volume equivalent to 3g of Xyrem oral solution) administered at 0 h and at 4 h.

Subjects were randomized to one of the above treatments on Day 1, followed by a washout period on days 4 and 5, and then crossed over to one of the other treatments on

Day 6, again followed by a washout period on days 9 and 10. The final crossover occurred on Day 11.

Study Schema

		Treatment Periods Treatment Days Randomized Treatments						
Screening	**Baseline**	**Period 1**		**Period 2**		**Period 3**		**Final Day**
Days -21 through -2	Day -1	Days 1 - 3	Days 4 - 5	Days 6 - 8	Days 9 -10	Days 11 - 13	Days 14-15	Day 15
		A, B, or C	Washout	A, B, or C	Washout	A, B, or C	Washout	

A = Diclofenac placebo (qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period) + Xyrem two 3 g doses 4 h apart on the 3rd day of the period
B = Diclofenac (50 mg qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period) + Xyrem two 3 g doses 4 h apart on the 3rd day of the period
C = Diclofenac (50 mg qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period) + Xyrem placebo two doses 4 h apart on the 3rd day of the period

The crossover design allowed for within-the-same-subject comparison of Xyrem dosed alone and in combination with diclofenac. The effect of sodium oxybate on diclofenac was also evaluated. This study used a double-blind approach. The Xyrem and Xyrem placebo oral solution were matched to ensure that the subjects and investigators were double-blinded. In addition, the diclofenac tablets which were overencapsulated, and the diclofenac placebo capsules were also matched to ensure double-blinding.

Subjects took diclofenac or diclofenac placebo with 240 mL of water and Xyrem or Xyrem placebo (each dose diluted with 60 mL of water) with 180 mL of water. On non-Xyrem/Xyrem placebo dosing days, standard meals were provided, and there were no food or fluid restrictions. On co-administrations days (Days 3, 8, and 13), subjects received a light breakfast about 2 hours before the first dose of diclofenac or diclofenac placebo, a standardized low-fat meal (lunch) approximately 2 hours after the first dose of Xyrem or Xyrem placebo, and a standardized meal (dinner) approximately 4 hours after the second dose of Xyrem or Xyrem placebo. After the last plasma PK sample was collected, subjects were allowed food and fluid ad lib and a standardized snack was provided.

The light breakfast consisted of cornflakes cereal with one cup of skim milk, 200 mL of orange juice, and 200 mL of water (or equivalent meal <300 calories and <1 g fat). The standardized low-fat lunch was typically <500 calories and contained about 20% to 30% fat content (i.e., calories derived from fat).

Sampling Schema:

Sodium Oxybate

Blood samples of 4 mL each were collected on Days 3, 8, and 13 at 0 h (predose), 0.25 h, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h (pre 2nd Xyrem/Xyrem placebo dose), 4.25 h, 4.5 h, 4.75 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 8 h, and 10 h relative to the first dose of Xyrem or Xyrem placebo. These blood samples were dispensed into labeled sodium heparin tubes.

Urine to measure sodium oxybate concentrations was collected on Days 3, 8, and 13, at predose (-4 to 0 hours) and during 0-4, 4-8, and 8-12 hour intervals after the first dose of Xyrem or Xyrem placebo.

Diclofenac

Blood samples (4 mL) to measure diclofenac concentrations were collected on Days 3, 8, and 13 at -1 h, -0.5 h, 0 h, 0.5 h, 1 h, 2 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 6 h, 7 h, and 9 h relative to the first dose of Xyrem or Xyrem placebo. These blood samples were dispensed into labeled sodium heparin tubes.

Analytical Method:

The PK analyses were performed by a central bioanalytical laboratory. Bioanalytical assays (for plasma and urine samples) were conducted at (b) (4) using validated methods that consisted of extraction and then analysis using Applied Biosystems LC/MS/MS. The method was specific for the moieties of sodium oxybate and diclofenac.

Sodium oxybate

The validation aspects of the assay are that the method for plasma is linear over the range of 1.00 - 160 mcg/mL with a lower limit of quantitation (LLOQ) of 1.0 µg/mL. The internal standard used was sodium oxybate – d6 (deuterated). The freeze thaw cycle covered 4 cycles of freeze (-20^0 C) and thaw (37^0 C) and showed that the compound is stable. Accuracy was close to 100 % (97 % to 101%), and precision was within 5 %.

Sodium oxybate was linear from 5.0 to 480 mcg/mL in human urine. The lower limit of quantitation (LLOQ) for analysis in urine was 5.0 µg/mL. Accuracy was 100 +/- 3%, and precision was within 4 %.

Diclofenac

The lower limit of quantitation (LLOQ) for analysis of diclofenac in plasma was 5.0 ng/mL. The method is linear over 5 – 1920 ng/ml.The internal standard used was the deuterated form of diclofenac (d4). Accuracy was 100 +/- 3%, and precision was within

4%. Diclofenac was proven stable in human plasma over 4 cycles of freeze (-70 °C) and thaw (room temperature or 37 ± 3 °C).

Overall the method is specific for the moieties of sodium oxybate and diclofenac, and is validated.

Results:

Pharmacokinetics: A total of 18 subjects including 16 males and 2 females completed the study.

Sodium oxybate

Means and standard deviations (SD) for plasma sodium oxybate PK parameters are presented in Table 5. The statistical analysis of sodium oxybate PK parameters is in Table 6. Mean sodium oxybate concentrations with and without diclofenac co-administration are plotted over time in Figure 3.

Table 5 Sodium Oxybate Plasma PK Parameters

PK Parameter	Units		Treatment A sodium oxybate + diclofenac placebo (reference)			Treatment B sodium oxybate + diclofenac		
			0-4 h	4-8 h	0-10 h	0-4 h	4-8 h	0-10 h
C_{max}	(µg/mL)	N	18	18	18	18	18	18
		Mean	91.7	83.0	94.8	98.8	77.0	99.9
		SD	25.32	27.41	26.98	25.15	25.24	25.85
		Geometric Mean	88.1	78.8	90.8	95.5	73.2	96.5
		Geometric SD	1.36	1.40	1.37	1.32	1.39	1.32
t_{max}	(h)	N	18	18	18	18	18	18
		Median	0.750	4.63	0.875	0.750	4.75	0.750
		Min, Max	0.50, 1.00	4.50, 4.75	0.50, 4.75	0.50, 0.75	4.50, 5.00	0.50, 4.75
AUC_{τ}	(µg*h/mL)	N	18	18	--	18	18	--
		Mean	135	144	--	136	144	--
		SD	54.0	68.2	--	52.1	71.6	--
		Geometric Mean	126	131	--	127	129	--
		Geometric SD	1.48	1.57	--	1.48	1.60	--
AUC_{0-t}	(µg*h/mL)	N	--	--	18	--	--	18
		Mean	--	--	284	--	--	286
		SD	--	--	128.1	--	--	131.3
		Geometric Mean	--	--	260	--	--	260
		Geometric SD	--	--	1.54	--	--	1.56
AUC_{0-inf}	(µg*h/mL)	N	–	–	18	–	–	18
		Mean	--	--	288	--	--	289
		SD	--	--	131.3	--	--	133.7
		Geometric Mean	--	--	262	--	--	263
		Geometric SD	--	--	1.55	--	--	1.56
λz	(1/h)	N	--	--	18	--	--	18
		Mean	--	--	1.20	--	--	1.18
		SD	--	--	0.392	--	--	0.349
$t_{1/2}$	(h)	N	–	–	18	--	--	18
		Mean	--	--	0.651	--	--	0.639
		SD	--	--	0.2531	--	--	0.1963

The percent mean ratio of the sodium oxybate plasma exposure (AUC 0-4 or AUC 4-8) for the co-administration of Xyrem + diclofenac versus Xyrem + diclofenac placebo were 100 % and the 90% confidence intervals (CIs) for these comparisons were within the 80-125% equivalence range (Table 6). Similarly, Cmax 0-4 and 4-8 had CI values within 80-125%. The median t_{max} of 0-4 and 4-8 hour interval data as shown in Table 5 all occurred

within one hour (0.75 hour) after each of the respective two doses of Xyrem (i.e., Xyrem doses administered at 0 h and at 4 h); further, Tmaxs also have very comparable ranges for Xyrem coadministration versus Xyrem alone.

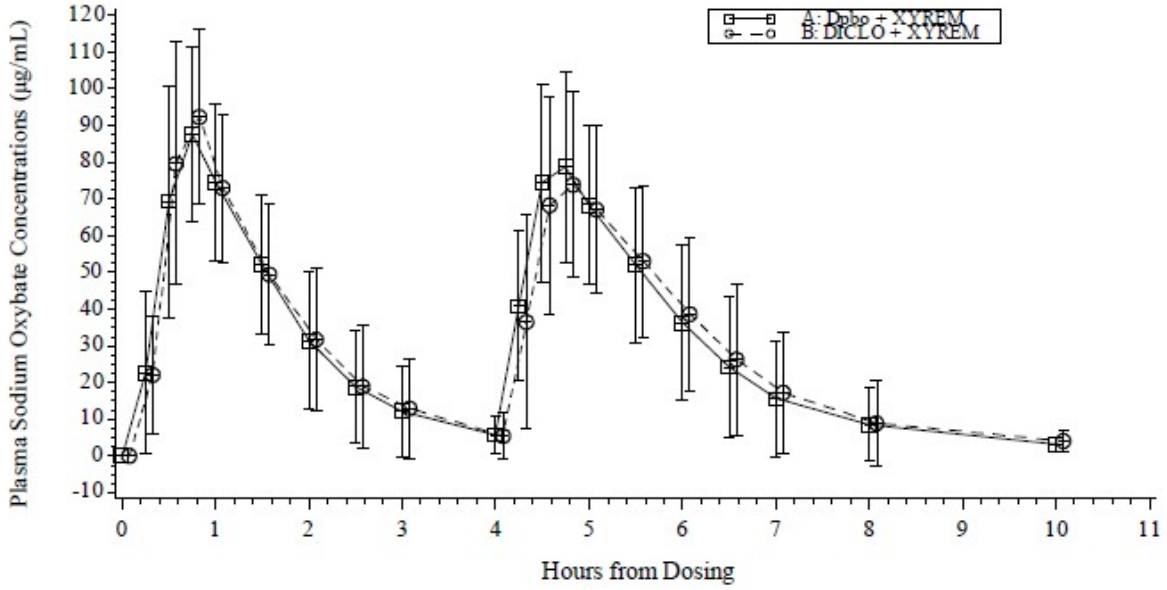
There is no effect of diclofenac on the pharmacokinetics of sodium oxybate.

Table 6 Statistical Comparisons of Plasma Sodium Oxybate PK Parameters: SXB + Diclo versus SXB + Dpbo

Parameter (Units)	Geometric LS Means[a]		% Mean Ratio Test/ Reference[b]	% Difference[c]	p-value	90% Confidence Interval
	Test SXB + DICLO N=18	Reference SXB + Dpbo N=18				
C_{max} 0-4 h (µg/mL)	90.6	83.5	109	8.54	0.0969	100, 118
C_{max} 4-8 h (µg/mL)	69.5	74.5	93.4	-6.63	0.0961	87.3, 99.9
C_{max} (µg/mL)	91.2	85.5	107	6.70	0.1528	98.9, 115
AUC_{τ} 0-4 h (µg*h/mL)	122	121	101	1.11	0.6607	96.8, 106
AUC_{τ} 4-8 h (µg*h/mL)	124	125	99.0	-0.98	0.6800	95.1, 103
$AUC_{0\text{-}t}$ (µg*h/mL)	250	249	101	0.60	0.6752	98.2, 103
$AUC_{0\text{-}inf}$ (µg*h/mL)	253	252	101	0.51	0.7347	98.0, 103

SXB=Sodium oxybate, DICLO=diclofenac, Dpbo=diclofenac placebo

Figure 3 Mean (+/-SD) Sodium Oxybate Concentration with and without Diclofenac Co-administration



Treatment A=Xyrem + diclofenac placebo (Dpbo)
Treatment B=Xyrem + diclofenac (DICLO)

Urinary excretion of sodium oxybate: The cumulative percent of dose excreted in urine was about 2.5 % of the dose for drug alone and was 2.3 % upon coadministration. Renal clearances were also comparable (498 ml/hr versus 466 ml/hr). Overall there are no differences in sodium oxybate renal excretion following the two treatments. Renal elimination of sodium oxybate is not a major route of elimination. The drug mainly undergoes conversion to a succinate by a dehydrogenase enzyme, and is then metabolized via the Krebs cycle and eliminated as carbon dioxide (CO_2) by the lungs, and as water.

Comments:

Comment 1: The 90% CIs for the relevant sodium oxybate PK parameter values of the dosing intervals of 0-4 hours, and 4-8 hours were within the accepted 80% to 125% equivalence range; Tmaxs between treatments were comparable.

There was no effect of diclofenac on the pharmacokinetics of Xyrem.

Comment 2:

The dosing strategy of administering diclofenac one hour earlier than Xyrem dosing was designed to obtain the maximal effect of diclofenac with its Tmax of about 1 hour on Xyrem which has a very short half life of about 0.5 hours.

Diclofenac

Means and standard deviations (SD) for plasma diclofenac PK parameters are presented in Table 7. The statistical analysis of diclofenac PK parameters is in Table 8. Mean diclofenac concentrations with and without Xyrem co-administration are plotted over time in Figure 4.

Table 7 Diclofenac Plasma PK Parameters

Parameter	Units		Treatment B sodium oxybate + diclofenac			Treatment C sodium oxybate placebo + diclofenac (reference)		
			0-4[a] h	4-8[a] h	0-10[a] h	0-4[a] h	4-8[a] h	0-10[a] h
C_{max}	(ng/mL)	N	18	18	18	18	18	18
		Mean	993	671	1062	978	550	978
		SD	410.8	356.0	368.3	371.2	194.6	371.2
		Geometric Mean	913	578	1000	916	519	916
		Geometric SD	1.53	1.83	1.44	1.45	1.42	1.45
t_{max}[a]	(h)	N	18	18	18	18	18	18
		Median	1.00	6.00	1.00	1.00	6.00	1.00
		Min, Max	0.50, 3.00	4.50, 8.00	0.50, 8.00	0.50, 3.00	5.00, 8.00	0.50, 3.00
AUC_{τ}	(ng*h/mL)	N	18	18	--	18	18	--
		Mean	1050	806	--	1018	778	--
		SD	215.0	261.2	--	220.3	183.2	--
		Geometric Mean	1029	757	--	994	760	--
		Geometric SD	1.23	1.49	--	1.26	1.25	--
AUC_{0-t}	(ng*h/mL)	N	--	--	18	--	--	18
		Mean	--	--	2092	--	--	1968
		SD	--	--	437.2	--	--	358.8
		Geometric Mean	--	--	2054	--	--	1936
		Geometric SD	--	--	1.21	--	--	1.21
AUC_{0-inf}	(ng*h/mL)	N	--	--	12	--	--	12
		Mean	--	--	2138	--	--	2061
		SD	--	--	349.4	--	--	426.3
		Geometric Mean	--	--	2112	--	--	2018
		Geometric SD	--	--	1.17	--	--	1.24
λz	(1/h)	N	--	--	12	--	--	12
		Mean	--	--	0.536	--	--	0.555
		SD	--	--	0.0795	--	--	0.1274
$t_{1/2}$	(h)	N	--	--	12	--	--	12
		Mean	--	--	1.32	--	--	1.31
		SD	--	--	0.177	--	--	0.294

When diclofenac was co-administered with Xyrem compared with diclofenac with Xyrem placebo, the 90% confidence intervals for the comparisons of AUC 0-4, AUC 4-8, and Cmax 0-4 for diclofenac were within the 80-125% equivalence range; Cmax 4-8 h showed 90% CI of 87% - 157% (Table 8). The point estimate for AUC 0-4, and for AUC 4-8 were about 103 % indicating comparable exposures from both treatments. Mean Tmaxs were 1 hour with very comparable ranges from both treatments.

A check of the individual values for Cmax 4-8 hours showed that one subject had a high value of 1630 ng/ml upon coadministration relative to the values of the other subjects, and, in the coadministration arm only. Without this value the mean point estimate is 1.11 instead of 1.17. Also, this value of 1630 ng/ml is not unusual, as in the other interval of Cmax 0-4 hour higher values were also seen but they were seen for both the treatments.

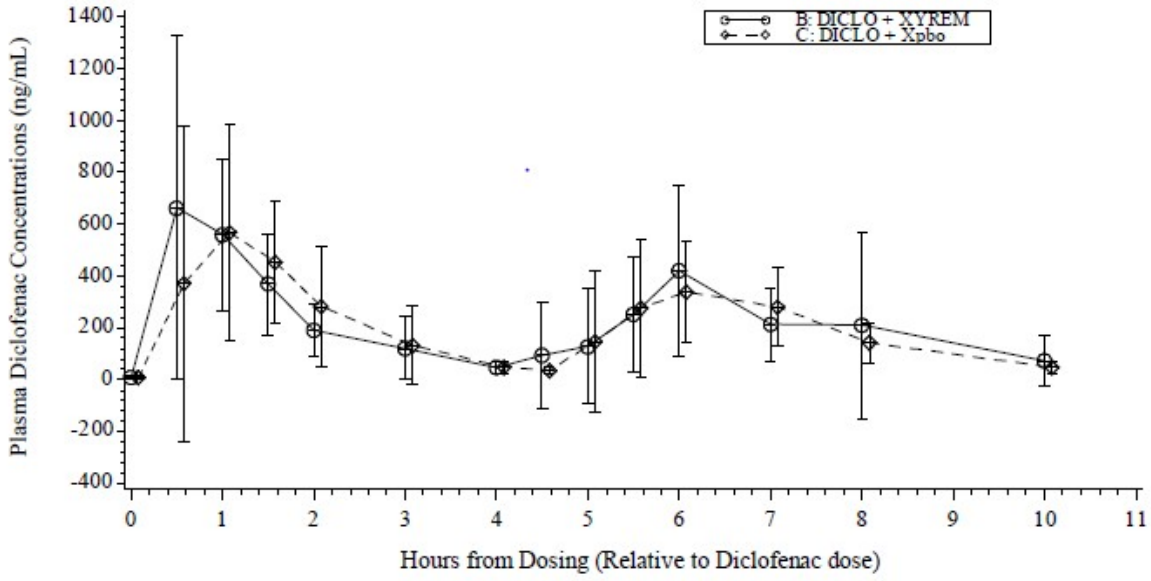
Co-administration of diclofenac with Xyrem did not appear to affect the PK of diclofenac.

Table 8 Statistical Comparisons of Plasma Diclofenac PK Parameters: SXB + DICLO versus Spbo + DICLO

Parameter (Units)	Geometric LS Means[a]		% Mean Ratio Test/ Reference[b]	% Difference[c]	p-value	90% Confidence Interval
	Test SXB + DICLO N=18	Reference Spbo + DICLO N=18				
C_{max} 0-4 h[d](ng/mL)	909	907	100	0.21	0.9855	82.0, 123
C_{max} 4-8[d] h(ng/mL)	592	506.2	117	17.0	0.3608	87.4, 157
C_{max} (ng/mL)	978	904	108	8.20	0.4622	90.1, 130
AUC_t 0-4[d] h(ng*h/mL)	1028	1002	103	2.57	0.6308	93.7, 112
AUC_t 4-8[d] h (ng*h/mL)	751	740	102	1.53	0.8785	85.6, 120
AUC_{0-t} (ng*h/mL)	2060	1933	107	6.55	0.1160	99.7, 114
AUC_{0-inf} (ng*h/mL)[c]	2130[e]	2019[e]	106	5.51	0.3967	94.1, 118

DICLO=Diclofenac; SXB=Sodium oxybate; Spbo=Sodium oxybate placebo.

Figure 4 Mean (SD) Diclofenac Concentration with and without Sodium Oxybate Co-administration



Treatment B=Xyrem + diclofenac (DICLO)
Treatment B=Xyrem placebo (Xpbo) + DICLO

Comments:

Comment 1: Diclofenac with its short half life of about 1.3 hours has almost reached zero level concentrations at the end of the dosing interval of four hours. Theoretically about 90% of the drug should have been eliminated (3 t1/2's), and the observed data also

showed that only about 8 % of the drug remained at the end of the dosing interval of 4 hours, i.e., that over 90 % of diclofenac had been eliminated. Further, the C4 hour or the C8 hour concentrations were ~ 8 % of the observed Cmax. So the relevant PK assessment is in looking at the AUC and Cmax values for both treatments over the 0-4, and 4-8 hour dosing intervals.

Co-administration of diclofenac with Xyrem did not appear to affect the PK of diclofenac.

Adverse Events: AEs were comparable in both treatments for both the number of reports and in the number of subjects who experienced them. Most of the adverse events seen in the study were somnolence, headache, nausea, mild vomiting, dizziness, euphoric mood, dry mouth, abdominal discomfort, and feeling hot. Most of the AEs were mild in severity and none were severe. No deaths or SAEs occurred during the study and no subject discontinued early because of an adverse event.

Overall Conclusion: Neither Xyrem nor diclofenac affected the pharmacokinetics of the other drug.

(3) Xyrem – Valproic acid -- Clinical Study Report Study 12-008

Study Title: A randomized, double-blind, placebo-controlled, five-period, crossover study to evaluate the Pharmacokinetics and Pharmacodynamics of Xyrem® (sodium oxybate) oral solution co-administered with Depakote® ER (divalproex sodium ER tablets) in healthy volunteers.

Study Dates: The study was initiated on 24 August 2012, and was completed on 14 October 2012

Sponsor: Jazz Pharmaceuticals, 3180 Porter Drive, Palo Alto, CA 94304

Clinical Research Organization: Celerion, 1930 Heck Ave, Neptune, NJ 07753

Bioanalytical Laboratories: (b) (4) (for sodium oxybate and valproic acid concentrations)

Objective of the Study: The primary objective of this study was to evaluate the PK and PD of Xyrem coadministered with divalproex sodium ER tablets. The secondary objective of this study was to evaluate and compare the safety and tolerability of Xyrem with and without co-administration of divalproex sodium ER tablets.

Formulations used:

Xyrem® (sodium oxybate) oral solution, 500 mg/mL, Lot No: 3100078, Expiry Date: 31 July 2017

Xyrem placebo (sodium citrate oral solution), Lot No: 3103243; Retest Date: 31 July 2014

Depakote ER (divalproex sodium ER tablets) 250 and 500 mg tablets;
for 250 mg tablets the Lot No is : 15340AA; Expiry Date: 13 August 2013, and
for the 500 mg tablets the Lot No is: 16396AA; Expiry Date: 28 January 2014

Rationale for the Doses Selected:

The therapeutic dose range established for Xyrem in clinical trials with narcolepsy patients is 6 to 9 grams (g) per day given in two equal, divided doses at bedtime and then again 2.5 to 4 hours later. Two 3 g doses of Xyrem, administered 4 hours apart, were evaluated, as this dose regimen was found to be the lowest effective nightly dose in patients with narcolepsy.
A 1250 mg dose of divalproex sodium ER tablets, which is equivalent to a 1000 mg daily dose of valproic acid was assessed because a 500 mg bid dosing regimen has been used in clinical studies with healthy subjects to evaluate safety and drug interactions with valproic acid.

Study Design:

This was a Phase 1, randomized, double-blind, placebo-controlled, five-period, crossover study in 20 healthy male subjects who completed the study. Subjects met the inclusion and exclusion criteria. Following screening and baseline procedures, eligible subjects were entered into the study to receive one of the following treatments per period, in randomized order:

Periods 1 and 2:

Subjects were randomized to receive two 3 g doses of Xyrem or Xyrem placebo 4 hours apart in a crossover fashion at approximately 9 AM (first dose) and 1 PM (second dose) on Days 1 and 3.

Period 3:

All subjects received divalproex sodium ER tablets 1250 mg once a day at 8 AM on Days 5 through 14.

Periods 4 and 5:

Subjects continued taking 1250 mg divalproex sodium ER tablets once a day at 8 AM on Days 15 through 18. Subjects were also randomized to receive either two 3 g doses of Xyrem or of Xyrem placebo with the first dose at 9 AM and the second dose 4 hours later at 1 PM on Days 15, and then received the alternate Xyrem treatment for crossover purposes on Day 18. The first dose of Xyrem or Xyrem placebo was taken 1 hour after

dosing with divalproex sodium ER tablets, and the second dose of Xyrem or Xyrem placebo was taken 4 hours after the first Xyrem/Xyrem placebo dose.

Study Schema

<table>
<tr><td colspan="2"></td><td colspan="7">Treatment Periods
Treatment Days
Randomized Treatments</td><td></td><td></td></tr>
<tr><td>Screening</td><td>Baseline</td><td>Period 1</td><td>Period 2</td><td>Period 3</td><td colspan="2">Period 4</td><td colspan="2">Period 5</td><td>Washout</td><td>Final Day</td></tr>
<tr><td>Days -21 through -2</td><td>Day -1</td><td>Days 1 & 2</td><td>Days 3 & 4</td><td>Days 5-□14</td><td colspan="2">Days 15-□17</td><td colspan="2">Day 18</td><td>Days 19 & 20</td><td>Day 21</td></tr>
<tr><td colspan="2"></td><td>A or B Day 1</td><td>A or B Day 3</td><td>C Days 5□-14</td><td>A or B Day 15</td><td>C Days 15□-</td><td>A or B Day 18</td><td>C Day 18</td><td></td><td></td></tr>
</table>

A = Xyrem, two 3 g doses, 4 hours apart at approximately 9 AM (1st dose) and 1 PM (2nd dose)
B = Xyrem placebo, two doses, 4 hours apart
C = Divalproex sodium 1250 mg, once a day at approximately 8 AM
(A washout period followed each of the treatment periods (Days 2, 4, and 19-20)

Subjects took divalproex sodium ER tablets with 240 mL of water and Xyrem or Xyrem placebo (each dose diluted with 60 mL of water) with 180 mL of water. On non-Xyrem/Xyrem placebo dosing days, standard meals were provided, and there were no food or fluid restrictions.

On Days 1, 3, 15, and 18, subjects received a light breakfast 2 hours before dosing with divalproex sodium, a standardized low-fat meal (lunch) 2 hours after the first Xyrem/Xyrem placebo dose, and another standardized meal (dinner) 8 hours after the first Xyrem/Xyrem placebo dose. After the last sodium oxybate PK sample was collected, subjects were allowed food and fluid ad libitum, and a standardized snack was provided.

The light breakfast consisted of cornflakes cereal with one cup of skim milk, 200 mL of orange juice, and 200 mL of water (or equivalent meal <300 calories and <1 g fat). The standardized low-fat lunch was typically <500 calories and contained about 20% to 30% fat content (i.e., calories derived from fat).

Sampling Schema:

Sodium Oxybate

Blood samples (4 mL) to measure plasma sodium oxybate concentrations were collected on Days 1, 3, 15, and 18 before the Xyrem/Xyrem placebo dose and at 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 4.25 h, 4.5 h, 4.75 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 8 h,

10 h, and 12 h after the first Xyrem or Xyrem placebo dose. These blood samples were dispensed into labeled sodium heparin tubes.

Urine to measure sodium oxybate concentrations was collected on Days 1, 3, 15, and 18, before dosing (-4 to 0 hours), and during 0 to 4, 4 to 8, and 8 to 12 hour intervals after the first Xyrem or Xyrem placebo dose.

Valproic acid

Blood samples (4 mL) for valproic acid concentrations were collected on Days 13 and 14 before the dose of divalproex sodium (to determine trough concentrations for the assessment of the attainment of steady state). On Days 15 and 18, blood samples (4 mL) to measure plasma valproic acid concentrations were collected at -1 h (before the divalproex sodium dose), 0 h, 1 h, 2 h, 3 h, 7 h, 11 h, 15 h, and 23 h relative to the first dose of Xyrem/Xyrem placebo. These blood samples were dispensed into labeled potassium oxalate ethylenediaminetetraacetic acid (K2 EDTA) tubes.

Analytical Method:

The PK analyses were performed by a central bioanalytical laboratory. Bioanalytical assays for plasma and urine samples were conducted at (b) (4) using validated methods that consisted of extraction and then analysis using liquid chromatography-tandem mass spectrometry. The method was specific for the moieties of sodium oxybate and valproic acid.

Sodium oxybate

The validation aspects of the assay are that the method for plasma is linear over the range of 1.00 - 160 mcg/mL with a lower limit of quantitation (LLOQ) of 1.0 µg/mL. The internal standard used was sodium oxybate – d6 (deuterated). The freeze thaw cycle covered 4 cycles of freeze (-20^0C) and thaw (37^0 C) and showed that the compound is stable. Accuracy was close to 100 % and precision was within 5 %.

Sodium oxybate was linear from 5.0 to 480 mcg/mL in human urine. The lower limit of quantitation (LLOQ) for analysis in urine was 5.0 µg/mL. Accuracy was 100 +/- 2%, and precision was within 3 %.

Valproic acid

The lower limit of quantitation (LLOQ) for analysis of valproic acid in plasma was 4.0 ug/mL. The method is linear over 4.0 – 384 ug/ml. The internal standard used was the deuterated form of valproic acid (d6). Accuracy was near 100 % (96 -100%) and precision was within 3.5 %. VPA was stable in human plasma over 4 cycles of freeze (-70°C) and thaw (room temperature or 37 ± 3 °C).

Overall the method is specific for the moieties of sodium oxybate and valproic acid, and is validated.

Results:

Sodium oxybate

Pharmacokinetics:

Means and standard deviations (SD) for plasma sodium oxybate PK parameters with and without divalproex sodium are presented in Table 9. The statistical analysis of sodium oxybate PK parameters is in Table 10. Mean sodium oxybate concentrations with and without divalproex sodium co-administration are plotted over time in Figure 5.

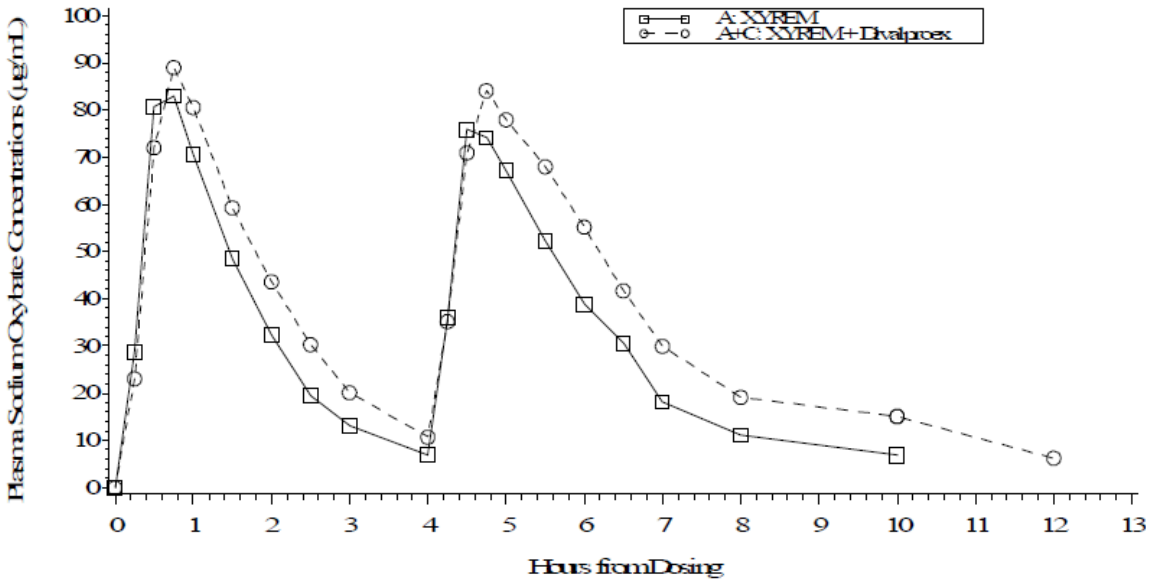
Table 9 Sodium Oxybate Plasma PK Parameters With and Without Divalproex Sodium

PK Parameter	Units		Treatment A + C SXB + DVP (test)			Treatment A SXB (reference)		
			0-4 h	4-8 h	0-12 h	0-4 h	4-8 h	0-12 h
C_{max}	(µg/mL)	N	18	18	18	18	18	18
		Mean	92.9	90.7	99.6	95.0	84.6	97.5
		SD	12.69	17.82	15.21	22.48	12.30	21.53
		Geometric Mean	92.2	89.2	98.6	93.0	83.8	95.7
		Geometric SD	1.138	1.211	1.161	1.217	1.154	1.201
t_{max}	(h)	N	18	18	18	18	18	18
		Median	0.750	4.75	2.75	0.625	4.50	0.875
		Min, Max	0.50, 1.0	4.5, 6.0	0.50, 6.0	0.50, 1.0	4.3, 6.5	0.50, 5.5
AUC_{τ} AUC_{0-t}	(µg*h/mL)	N	18	18	18	18	18	18
		Mean	162	190	378	139	149	297
		SD	51.36	82.17	176.4	42.75	62.82	118.8
		Geometric Mean	155	175	346	133	138	277
		Geometric SD	1.352	1.505	1.521	1.333	1.483	1.444
AUC_{0-inf}	(µg*h/mL)	N	–	–	18	–	–	17
		Mean	--	--	383	--	--	297
		SD	--	--	182.4	--	--	126.5
		Geometric Mean	--	--	350	--	--	276
		Geometric SD	--	--	1.529	--	--	1.463
λz	(1/h)	N	–	–	18	–	–	17
		Mean	--	--	1.14	--	--	1.26
		SD	--	--	0.4321	--	--	0.5026
$t_{1/2}$	(h)	N	–	–	18	–	–	17
		Mean	--	--	0.722	--	--	0.655
		SD	--	--	0.3438	--	--	0.2964

Table 10 Statistical Comparisons of Sodium Oxybate Plasma PK Parameters: Xyrem + Divalproex Sodium versus Xyrem

Parameter (Units)	Geometric LS Means[a]		% Mean Ratio Test/ Reference[b]	% Difference[c]	90% Confidence Interval	p-value
	Test SXB+DVP (N=18)	Reference SXB (N=18)				
C_{max} 0-4 h (ug/mL)	91.8	92.6	99.1	-0.92	92.7, 106	0.8135
C_{max} 4-8 h (ug/mL)	89.6	84.2	106	6.45	99.7, 114	0.1168
C_{max} (ug/mL)	98.5	95.7	103	2.93	96.5, 110	0.4482
AUC_{τ} 0-4 h (ug*h/mL)	155	133	116	16.2	110, 123	0.0002
AUC_{τ} 4-8 h (ug*h/mL)	175	139	126	26.5	119, 135	<0.0001
AUC_{0-t} (ug*h/mL)	345	277	125	24.6	117, 132	<0.0001
AUC_{0-inf} (ug*h/mL)	350	276[d]	127	26.9	120, 134	<0.0001

Figure 5 Mean (+/-SD) Sodium Oxybate Concentration with and without Divalproex Sodium



After administration of Xyrem with divalproex sodium and Xyrem alone, mean concentration-time profiles indicated higher sodium oxybate exposure for the Xyrem + divalproex sodium treatment compared to Xyrem alone (Figure 5).

The 90 % CI for AUC 0-4 was within range (110 -123 %) with a point estimate of 116% (Table 10). The upper bound of the 90% CI was higher than the 125% limit for equivalence for AUC 4-8 (90 % CI was 119 – 135% with a point estimate of 126% (Table 10). The overall increase in exposure accounting for the two four-hour intervals is about 20 %). The coefficient of variation (% cv) for AUCs was between 31-43% and for Cmaxs it was 13-23%. The Cmax's were comparable between treatments and the 90 % CIs were within the limits for equivalence. Tmaxs seen were around 0.75 hours.

A check of AUC ratios of individual subjects for coadministration : Xyrem alone for the 0-4 hour interval shows that 5 subjects had ratios of 1. 0 or below 1.0, 7 subjects had ratios between 1.0 and 1.2, and 8 subjects had ratios > 1.2 including a subject who had a value of 1.47 (Figure 7). Similarly, for the 4-8 hour interval, there were 4 subjects with ratios of 1.0 or below 1.0, 3 subjects with ratios between 1.0 and 1.2, and 13 subjects with ratios above 1.2 including 4 subjects with values > 1.4; the highest ratio seen was 1.7 (Figure 8). The high ratios observed in both the intervals cannot be explained on the basis of gender (as all the subjects in the study were males), or age (comparable ages of healthy adults between 26 – 44 years), or body mass index (17 % difference between subjects).

Urinary excretion of sodium oxybate: The cumulative percent of dose excreted in urine was about 2.5 % of the dose for drug alone and was 4.3 % upon coadministration. Renal clearance increased by approximately 30% when Xyrem was co-administered with divalproex sodium (676 mL/h) compared with Xyrem administered alone (537 mL/h). Urinary excretion is not the main route of elimination for Xyrem.

Pharmacodynamics (PD):

Twelve PD tests were conducted for the assessment of cognitive function. PD results focus on the comparison of Xyrem + divalproex sodium (Treatment A+C) versus Xyrem alone (Treatment A) and are as follows:

Power of Attention: No significant differences were seen between treatments.

Continuity of Attention (which is a measure of impairment in sustained attention): Co-administration resulted in statistically significant greater impairment at 8 h than Xyrem alone.

Karolinska Sleepiness Scale: No significant difference amongst treatments.

Simple Reaction Time Mean (impairment in attention focus): Greater impairment was seen with the combination treatment at 4 hours.

Digit Vigilance Accuracy (impairment in sustained attention): A significantly greater impairment with the combination treatment at 4 h.

Digit Vigilance Mean Reaction Time: No differences between treatments at any time point.

Digit Vigilance False Alarms: No significant differences between treatments at any time point.

Choice Reaction Time Mean. No significant differences between treatments at any time point.

Choice Reaction Time Accuracy (impairment means worsened accuracy). There was significantly greater impairment with Xyrem alone at 6.5 h.

Tracking Distance from Target (impairment in motor control, skilled coordination and sustained attention): There was significantly greater impairment with the combination treatment at the 8 h time point.

Numeric Working Memory Sensitivity Index: There were no significant differences between treatments at any time point.

Numeric Working Memory Mean Reaction Time (impairment in speed with which information can be retrieved from memory): Significantly greater impairment was observed for the combination treatment at 2.5, 5, and 8 h.

Of the twelve tests conducted, *5* showed that greater impairment was seen with coadministration treatment than with Xyrem alone treatment, 1 test showed greater impairment with Xyrem alone versus coadministration; there were six tests where impairments were comparable.

In summary, co-administration of Xyrem and divalproex sodium produced statistically significantly greater deficits than Xyrem alone in Numeric Working Memory Mean Reaction Time at 2.5, 5, and 8 h; in Simple Reaction Time Mean, and in Digit Vigilance Accuracy at 4 h; and in Continuity of Attention, and Tracking Distance from Target at 8 h. The study showed that co-administration of Xyrem and divalproex sodium produced greater impairments to attention than were seen with either drug alone. There was no difference amongst the two treatments in sleepiness.

Safety:

In terms of Adverse Events (AEs) a total of 146 treatment-emergent AEs were reported by 20 of the 20 (100%) subjects treated, with 59 AEs in 19 subjects during treatment with Xyrem, and 61 AEs in 20 subjects during treatment with Xyrem + divalproex sodium. The most frequently reported AEs (reported in 2 or more subjects during any treatment) were somnolence, euphoric mood, dizziness, nausea, and vomiting. All AEs were reported as resolved at the end of the study. There were no deaths, other serious adverse events, or early discontinuations due to AEs occurred during the study.

Somnolence was reported by 18 (90%) subjects receiving Xyrem + divalproex sodium, and 16 (80%) subjects receiving Xyrem alone. Somnolence was of moderate severity in 10 subjects receiving Xyrem + divalproex sodium, and in 6 subjects receiving Xyrem alone. The remaining somnolence events were considered to be of mild severity. The investigator considered all somnolence events to be related to study drug or procedure.

Euphoric mood 10 (50%) subjects receiving Xyrem + divalproex sodium and 8 (40%) subjects receiving Xyrem alone. For all events, the investigator considered euphoric mood to be of mild severity and related to study drug or procedure.

Dizziness was comparable with 7 (35%) subjects each receiving the Xyrem + divalproex sodium and Xyrem alone treatments. For all events, the investigator considered dizziness to be of mild severity and related to study drug or procedure.

Nausea was reported by 4 (20%) subjects receiving Xyrem + divalproex sodium, 3 (15%) subjects receiving Xyrem alone. Nausea was considered to be of moderate severity in 1 subject receiving divalproex sodium, and was of mild severity in the remaining cases. For all events, the investigator considered nausea to be related to study drug or procedure.

Vomiting was seen in 2 (10%) subjects receiving Xyrem alone and 1 (5%) subject receiving Xyrem + divalproex sodium. It was considered to be of mild severity and related to study drug or procedure. The sponsor excluded the two subjects who vomited from descriptive statistics.

The observed AEs in the healthy subjects were comparable between coadministration treatment and Xyrem alone treatment in terms of the number of AEs reported as well as in the types of AEs.

PD and Safety:

Regarding dose response, the Clinical Trials Section of labeling mentions that a dose-response relationship has been observed for nausea, vomiting, paresthesia, disorientation, irritability, disturbance in attention, feeling drunk, sleepwalking, and enuresis, and that the incidence of these reactions was notably higher at 9 g per night. It further states that discontinuations of treatment due to adverse reactions were greater at higher doses of Xyrem. In this study the observed AEs with healthy subjects were consistent with the approved product labeling for Xyrem and divalproex sodium.

Respiratory Depression: An issue of concern with Xyrem is that clinically significant respiratory depression has occurred in Xyrem-treated patients and this is mentioned as a black box Warning in the Full Prescribing Information of labeling. The concurrent use of Xyrem with other CNS depressants, including as for example opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs (AEDs), general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death (as per label). 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. As per the Depakote ER prescribing information, divalproex sodium may produce CNS depression, especially when combined with another CNS depressant (and Xyrem is a CNS depressant). There is concern for respiratory depression in narcolepsy patients which could potentially be a safety concern particularly when Xyrem, a CNS depressant, is coadministered with divalproex sodium which may also produce CNS depression.

There is no PK/PD relationship known or established between Xyrem levels and PD of respiratory depression and it is therefore unknown if respiratory depression is related to AUC or Cmax.

Conclusion: From a PK standpoint the overall increase in exposure of Xyrem is about 25 % (AUC ratio range of 0.83 to 1.71). The first interval of AUC (0-4) showed that the two treatments were comparable as the 90 % CIs were within the 80 -125 % range (110 -123 %). The % coefficient of variation (% cv) for AUCs was between 31-43% which relative to the mean increase in exposure of 25%, shows that there is considerable inter-subject variability in both treatments. Co-administration of Xyrem and divalproex sodium showed greater impairments to attention than were seen with either drug alone. There was no difference amongst the two treatments in sleepiness. The number of AEs reported as well as the types of AEs in this study in healthy subjects were similar between coadministration treatment and Xyrem alone treatment. There is no PK/PD relationship known or established between Xyrem levels and PD of CNS depression (e.g., respiratory depression) and it is therefore unknown if CNS (respiratory) depression is related to AUC or Cmax.

It is recognized that CNS depression is a concern when Xyrem either alone or in combination with valproic acid is administered and that its dose adjustment upon coadministration should be considered from a safety standpoint. However, specific dosing recommendation cannot be provided as, from a PK standpoint intersubject variability of 31- 43 % for AUC is considerable and PD endpoint, like sleepiness, was comparable between treatments in this study in healthy subjects. Further, both the number of AEs as well as the types of AEs in this study were similar. However, safety concern does remain for narcolepsy *patients* for CNS depression.

Comment 3: Valproic acid increased the mean exposure of Xyrem by about 25 %. This is being mentioned in Labeling.

Valproic acid

Means and standard deviations (SD) for plasma valproic acid PK parameters are presented in Table 11. The statistical analysis of valproic acid PK parameters is in Table

12. Mean valproic acid concentrations with and without Xyrem co-administration are plotted over time in Figure 6.

Table 11 Valproic Acid Plasma PK Parameters

PK Parameter	Units		SXB+DVP (test) (N=18)	SPBO+DVP (reference) (N=18)
C_{maxss}	(ug/mL)	Mean SD Geometric Mean Geometric SD	97.8 19.93 95.8 1.240	97.0 20.19 95.0 1.242
t_{maxss}	(h)	Median Min, Max	12.0 2.0, 16	12.0 2.0, 24
C_{minss}	(ug/mL)	Mean SD	69.3 25.60	69.2 20.71
t_{minss}	(h)	Median Min, Max	24.0 1.0, 24	24.0 1.0, 24
AUC_{tau}	(ug*h/mL)	Mean SD Geometric Mean Geometric SD	2055 507.7 1994 1.293	2056 467.7 2003 1.272

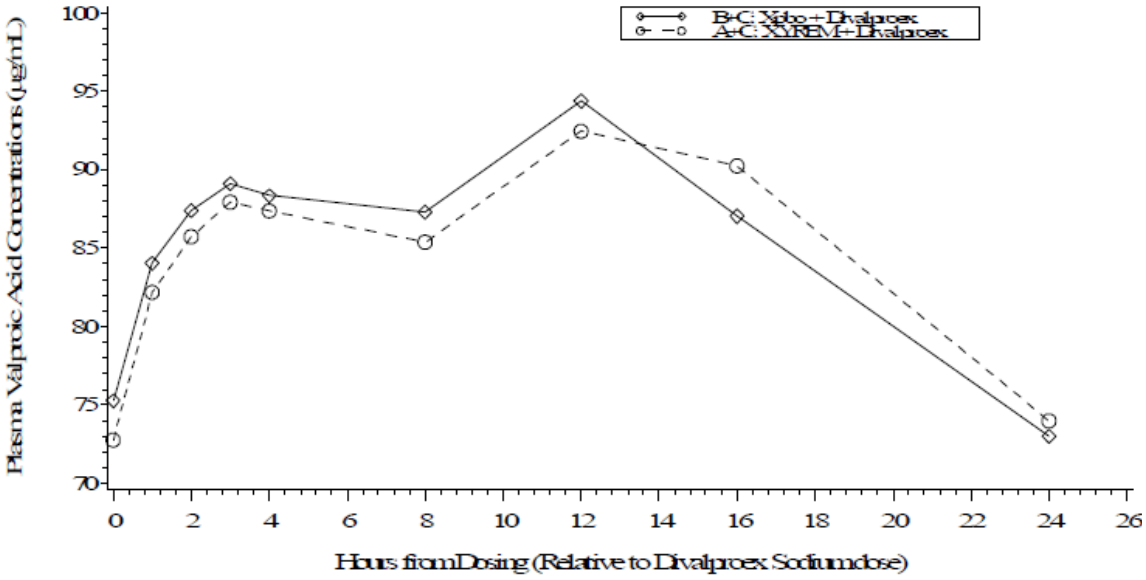
SPBO + DVP = Xyrem placebo two doses 4 hours apart + divalproex sodium 1250 mg ER tablet
SXB + DVP = Xyrem two 3 g doses 4 hours apart + divalproex sodium 1250 mg ER tablet

Table 12 Statistical Comparisons of Valproic Acid PK Parameters: Xyrem + Divalproex Sodium versus Xyrem Placebo + Divalproex Sodium

Parameter (Units)	Geometric LS Means[a]		% Mean Ratio Test/ Reference[b]	% Difference[c]	90% Confidence Interval	p-value
	Test SXB+DVP (N=18)	Reference SPBO+DVP (N=18)				
C_{maxss} (ug/mL)	95.7	94.8	101	0.90	95.9, 106	0.7626
C_{minss} (ug/mL)	65.0	66.0	98.6	-1.42	91.8, 106	0.7305
AUC_{tau} (ug*h/mL)	1994	2004	99.5	-0.48	95.8, 103	0.8274

SPBO + DVP = sodium oxybate placebo two doses 4 hours apart + divalproex sodium 1250 mg ER tablet
SXB + DVP = sodium oxybate two 3 g doses 4 hours apart + divalproex sodium 1250 mg ER tablet

Figure 6 Mean Plasma Valproic Acid Concentrations With and Without Xyrem Co-administration



Valproic acid has a half life of 9 hours and with 10 days of daily dosing it had reached steady state. The mean valproic acid concentration-time profiles were similar after administration of divalproex sodium with Xyrem placebo and after administration of divalproex sodium with Xyrem (Figure 6). Valproic acid as measured by the ratio between treatments (of coadministration : drug alone) for the PK parameters of AUCtau (24 hours), Cmaxss, and Cminss were all close to 1.00. The 90% CIs for these comparisons were contained within 80% to 125%. Tmaxss were about 12.0 hours for both treatments.

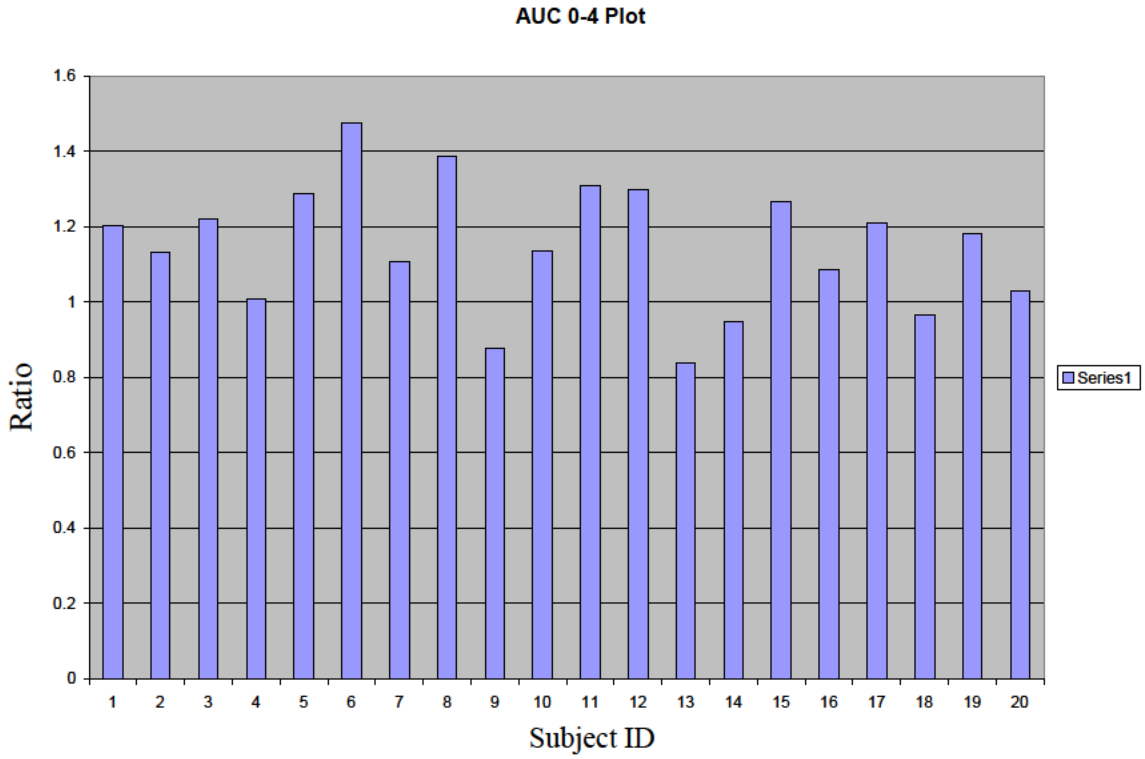
Co-administration of valproic acid with Xyrem did not affect the PK of valproic acid.

Comment:

Comment 1: Co-administration of valproic acid with Xyrem did not affect the PK of valproic acid.

Overall Conclusion: Valproic acid increased the exposure of Xyrem by about 25 %. In turn, the co-administration of valproic acid with Xyrem did not affect the PK of valproic acid.

Figure 7 Xyrem AUC (0-4) ratios of individual subjects



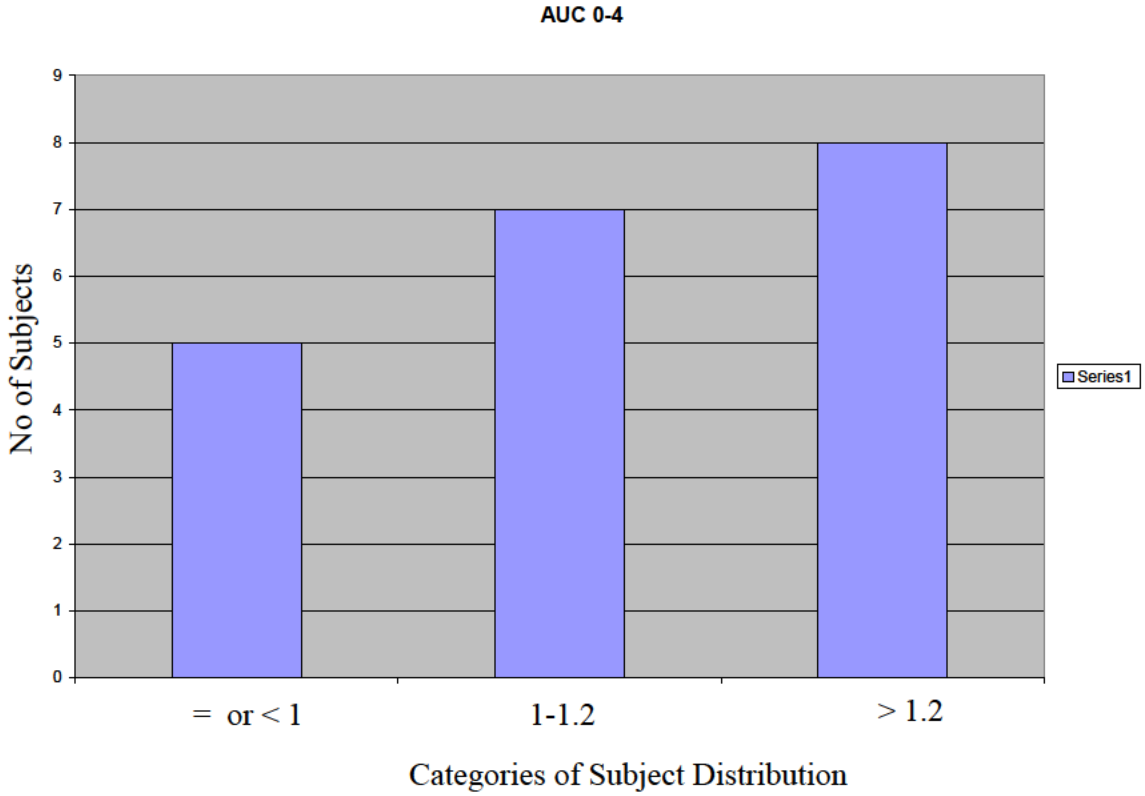
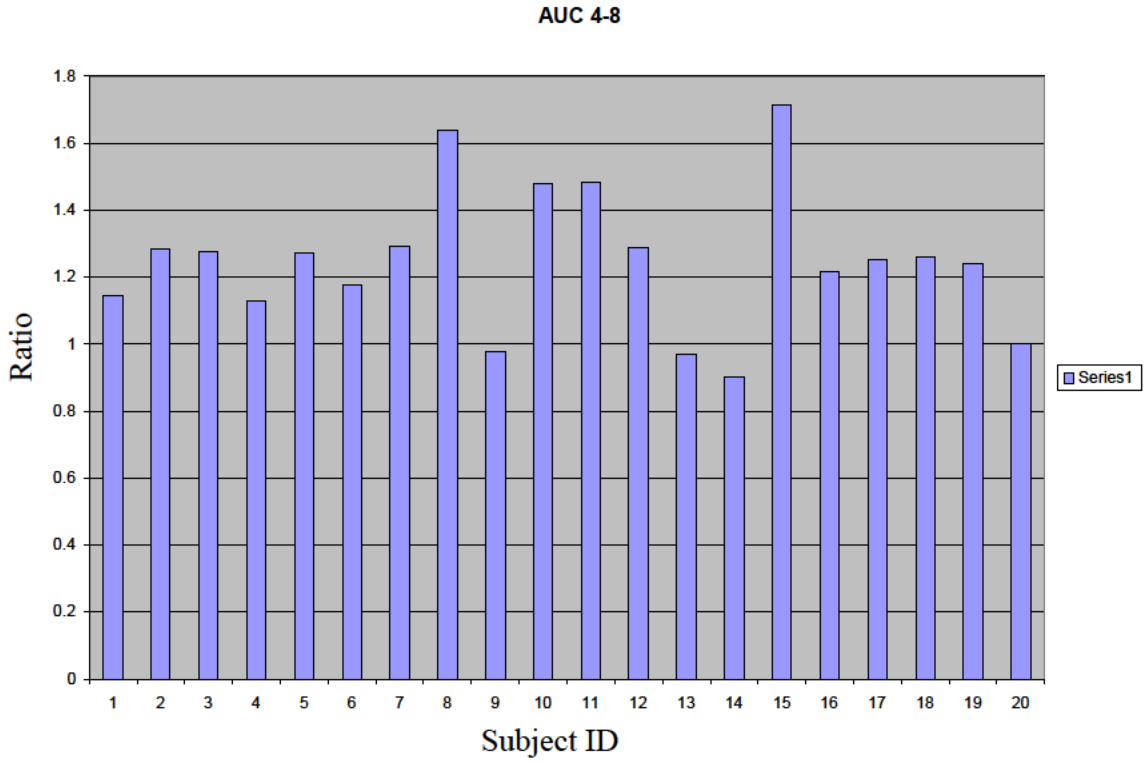
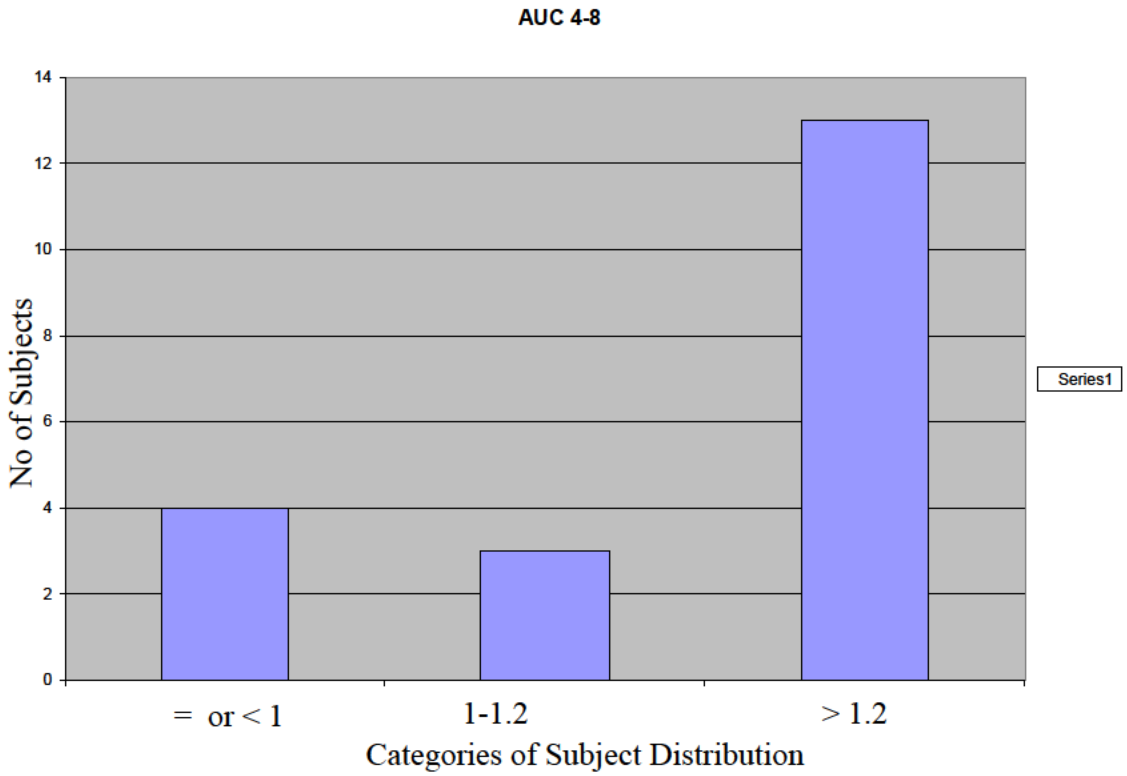


Figure 8 Xyrem AUC (4-8) ratios of individual subjects





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

/s/

RAMAN K BAWEJA
03/10/2014

RAMANA S UPPOOR
03/11/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-196/S-019

OTHER REVIEW(S)

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

Product Title[1]	**Xyrem® (sodium oxybate) oral solution CIII**
Applicant	**Jazz Pharmaceuticals**
Application/Supplement Number	NDA 21196/S-019
Type of Application	Efficacy Supplement
Indication(s)	Treatment of: Cataplexy in narcolepsy and Excessive daytime sleepiness (EDS) in narcolepsy
Office/Division	ODE I /DNP
Division Project Manager	Susan Daugherty
Date FDA Received Application	June 20, 2013
Goal Date	April 20, 2014
Date PI Received by SEALD	April 9, 2014
SEALD Review Date	April 10, 2014
SEALD Labeling Reviewer	Elizabeth Donohoe
Acting SEALD Division Director	Sandra Kweder

1 Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word "must" denotes that the item is a regulatory requirement, while the word "should" denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **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**: This item does not apply to the specific PI under review (**not applicable**).

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

NO 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *The margin between the columns is less than 1/2 inch at the Boxed Warning and at RMC.*

NO 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, 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 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" 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:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: *HL is greater than 1/2 page (excluding the length of the Boxed Warning); unless a waiver is granted, this does not meet the 1/2 page regulatory requirement.*

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *Recommend horizontal line extend the full width of the page for improved readability; see Appendix A for sample tool illustrating the horizontal line.*

NO 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *The headings for RMCs and D&A are not centered.*

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

Selected Requirements of Prescribing Information

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **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:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S.**

Approval:" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW 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 and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

NO 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment: *The listing for Contraindications precedes D&A; D&A should come first.*

NO 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(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, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment: *[See SRPI item #18 regarding improper inclusion of RMC for Contraindications] The RMC for D&A states ".. (b) (4) and should include the specific subsection heading ("Dosage and Administration, Dose Adjustment with Co-administration of Divalproex Sodium (2.4) ----- (b) (4). Also, the RMC related to Contraindications includes the specific contraindication; t presentation would be: "Contraindications (4) ----- 12/2012".*

NO 18. The RMC 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: *The listing for Contraindications is dated "12/2012"; this should be removed as it has been greater than one year since it was listed.*

Indications and Usage in Highlights

YES

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

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment: *The FPI Contraindications states: "Patients should not drink alcohol when using Xyrem"; according to the W&P, Contraindications, and BW guidance, the recommended specific language for contraindications: "is contraindicated in". The HL Contraindications states "In combination with sedative hypnotics or alcohol"; recommend clarifying in FPI if use of alcohol is contraindicatd when using Xyrem.*

Adverse Reactions in Highlights

YES 22. 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:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

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

If a product **has** FDA-approved patient labeling:

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

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

NO 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment: *The BW in FPI does not have "(CNS)" following "CENTRAL NERVOUS SYSTEM"; it is present in HL and TOC. Recommend adding "(CNS)" to BW in FPI or removal of "(CNS)" from headings in HL and TOC. If "CNS" is removed from the BW heading, include it with the first use of "Central Nervous System" in the text.*

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *Proposed headings for subsections 7.1 and 7.2 are not in title case; they should read: "7.1 Alcohol, Sedative Hypnotics, and CNS Depressants" and "7.2 Divalproex Sodium".*

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: *The following are italicized in the FPI and should not be: "5.3", the "7." in subsection 7.2 and the entire heading for subsection 12.3 (see SRPI item # 32).*

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. 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)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

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
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: *The heading for subsection "12.3 Pharmacokinetics" in the FPI is italicized and should not be.*

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or "[*see Warnings and Precautions (5.2)*]".

Comment: *For consistency, recommend that outer brackets are either italicized or not italicized throughout the PI. In the last cross-reference in the BW, they are italicized. Also recommend that the word "see"is consistently either italicized or not italicized; it is italicized in all the cross-references in the BW and in 12.3 under Specific Populations.*

NO 34. 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: *There are multiple vertical lines on the left edge throughout the PI because the version I have is in track changes; when I look at "Final" mark-up the vertical line corresponding to subsection 2.4 is removed.*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW 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 and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are 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 practice."

Comment:

YES 40. When postmarketing adverse reaction data are 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: *This statement has been modified but is acceptable if agreed to by the review division.*

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. 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 FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- **[text]**
- **[text]**

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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

/s/

ELIZABETH A DONOHOE
04/10/2014

ERIC R BRODSKY
04/10/2014
I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, Acting SEALD Director.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-196/S-019

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 021196 SUPPL # 019 HFD # 120

Trade Name Xyrem

Generic Name sodium oxybate

Applicant Name Jazz Pharmaceuticals

Approval Date, If Known April 11, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) – SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

The supplement provides for addition of information about drug reactions with ibuprofen, diclofenac, and extended-release valproate to the “Dosage and Administration”, “Drug Interactions”, and “Clinical Pharmacology” sections of the labeling.

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21196 Xyrem

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

1. Study 12-006, a randomized, double-blind, placebo-controlled, three-period crossover study whose primary objective was to evaluate the pharmacokinetics and pharmacodynamics of Xyrem® co-administered with ibuprofen; a secondary objective was to evaluate the safety and tolerability of Xyrem® with and without the co-administration of ibuprofen.
2. Study 12-007, a randomized, double-blind, placebo-controlled, three-period crossover study whose primary objective was to evaluate the pharmacokinetics and pharmacodynamics of Xyrem® co-administered with diclofenac; a secondary objective was to evaluate the safety and tolerability of Xyrem® with and without the co-administration of diclofenac.
3. Study 12-008, a randomized, double-blind, placebo-controlled, five-period crossover study whose primary objective was to evaluate the pharmacokinetics and pharmacodynamics of Xyrem® co-administered with divalproex sodium extended-release tablets; a secondary objective was to evaluate the safety and tolerability of Xyrem® with and without the co-administration of divalproex sodium extended-release tablets.

The pharmacodynamic portion of the review included:

• The use of the following tests for assessing the pharmacodynamic effects of the drugs investigated: Karolinska Sleepiness Scale; Simple Reaction Time Task; Digit Vigilance Task; Choice Reaction Time Task; Tracking Task; and Numeric Working Memory Task.

• The use of the following safety outcome measures: adverse events, vital signs, safety laboratory tests (hematology, clinical chemistry, and urinalysis), 12-lead electrocardiograms, and pulse oximetry. (The Columbia-Suicide Severity Rating Scale was used as a safety outcome measure in Study 12-008 only).

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the

agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒
Investigation #3	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒
Investigation #3	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1. Study 12-006, a randomized, double-blind, placebo-controlled, three-period crossover study whose primary objective was to evaluate the pharmacokinetics and pharmacodynamics of Xyrem co-administered with ibuprofen; a secondary objective was to evaluate the safety and tolerability of Xyrem with and without the co-administration of ibuprofen.

2. Study 12-007, a randomized, double-blind, placebo-controlled, three-period crossover study whose primary objective was to evaluate the pharmacokinetics and pharmacodynamics of Xyrem co-administered with diclofenac; a secondary objective was

to evaluate the safety and tolerability of Xyrem with and without the co-administration of diclofenac.

3. Study 12-008, a randomized, double-blind, placebo-controlled, five-period crossover study whose primary objective was to evaluate the pharmacokinetics and pharmacodynamics of Xyrem co-administered with divalproex sodium extended-release tablets; a secondary objective was to evaluate the safety and tolerability of Xyrem with and without the co-administration of divalproex sodium extended-release tablets.

The pharmacodynamic portion of the review included:

• The use of the following tests for assessing the pharmacodynamic effects of the drugs investigated: Karolinska Sleepiness Scale; Simple Reaction Time Task; Digit Vigilance Task; Choice Reaction Time Task; Tracking Task; and Numeric Working Memory Task.

• The use of the following safety outcome measures: adverse events, vital signs, safety laboratory tests (hematology, clinical chemistry, and urinalysis), 12-lead electrocardiograms, and pulse oximetry. (The Columbia-Suicide Severity Rating Scale was used as a safety outcome measure in Study 12-008 only).

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 049641	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 049641	YES ☒	! NO ☐
		! Explain:

Investigation #3		
IND # 049641	YES ☒	! NO ☐

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Susan Daugherty
Title: RPM
Date: 5/14/14

Name of Office/Deputy Division Director signing form: Eric Bastings, MD
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12;

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

/s/

SUSAN B DAUGHERTY
05/15/2014

ERIC P BASTINGS
05/15/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21196/S-019

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Jazz Pharmaceuticals
Attention: Joel Selcher, PhD
Senior Director, Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Dr. Selcher:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b)of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21196

SUPPLEMENT NUMBER: S-019

PRODUCT NAME: Xyrem (sodium oxybate) oral solution

DATE OF SUBMISSION: June 18, 2013

DATE OF RECEIPT: June 20, 2013

This supplemental application proposes to add information about drug reactions with ibuprofen, diclofenac, and extended-release valproate to the Dosage and Administration, Drug Interactions, and Clinical Pharmacology sections of the labeling.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 19, 2013 in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be April 20, 2014.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, please contact me via e-mail at heather.bullock@fda.hhs.gov or via telephone at (301) 796-1126.

Sincerely,

{See appended electronic signature page}

Heather M. Bullock, RN, BSN, MSHS
Lieutenant Commander,
United States Public Health Service
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

HEATHER M BULLOCK
07/17/2013