



U.S. Food and Drug Administration

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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

MEMORANDUM

DATE: July 21, 2010

FROM: Bob A. Rappaport, MD
Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Arthritis Advisory Committee (AAC)

RE: Overview of the August 20, 2010, AAC Meeting to Discuss
NDA 22-531 for Sodium Oxybate for the Treatment of Fibromyalgia

At this meeting of the AAC, we will be discussing the New Drug Application for sodium oxybate for the treatment of fibromyalgia, submitted by Jazz Pharmaceuticals, Inc. Sodium oxybate, also known as gamma-hydroxybutyrate (GHB), is a Schedule III central nervous system depressant with hypnotic properties that has well recognized abuse potential.

Sodium oxybate was approved in 2002, as Xyrem, for the reduction of daytime sleepiness and cataplexy in patients with narcolepsy, and it is also approved in the European Union and Canada for the treatment of various symptoms associated with narcolepsy. The FDA approval included a restricted distribution program called the Xyrem Success Program, as well as a Risk Management Plan. Prior to approval, a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee was held in order to discuss the efficacy and safety of the product, given its history as a drug of abuse.

The Applicant states that the proposed mechanism of action for the treatment of pain in fibromyalgia is inhibition of central pain through stimulation of the B-subtype of the GABA receptor, which may inhibit spinal neurons and/or excitatory neurotransmitter release in the spinal cord. Actions at supraspinal sites may also contribute to the effects of sodium oxybate on pain. The Applicant also maintains that sodium oxybate improves the disruption of the sleep architecture that is associated with fibromyalgia and, as a consequence, decreases the widespread pain associated with fibromyalgia. If approved, sodium oxybate will be the fourth

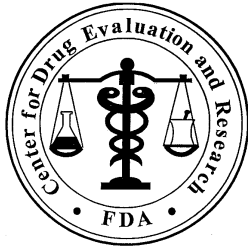
product approved for the treatment of fibromyalgia, joining duloxetine (Cymbalta), milnacipran (Savella), and pregabalin (Lyrica).

The safety profile for sodium oxybate as reflected in the product label includes a boxed warning for abuse potential, and important central nervous system adverse events associated with abuse, including seizure, respiratory depression and profound decreases in level of consciousness, sometimes resulting in coma and death.

The results of the Applicant's efficacy and safety studies in patients with fibromyalgia will be presented during the meeting, along with postmarketing safety data and the Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS). You will be asked to discuss the study findings and whether the results support the efficacy claims proposed by the Applicant, whether the proposed REMS appears adequate to mitigate the risks of abuse and misuse associated with sodium oxybate, and whether the benefit-risk balance is in favor of approving this drug for the treatment of fibromyalgia.

Thank you in advance for participating in this meeting and providing us with your expertise and insights regarding this New Drug Application.

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

Date: July 21, 2010

To: FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee Members

Thru: Claudia B. Karwoski, PharmD
Director, Division of Risk Management (DRISK)
Office of Surveillance and Epidemiology (OSE)

From: Sodium Oxybate Risk Management Review Team

Subject: Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s)/Application Number: Sodium oxybate oral solution:
1. Xyrem; NDA 021196
2. Rekinla (proposed tradename); NDA 022531

Indications: For the treatment of:
1. Excessive daytime sleepiness and cataplexy in patients with narcolepsy (NDA 21-196)
2. *Proposed:* Treatment of Fibromyalgia (NDA 22-531)

Applicant/sponsor: Jazz Pharmaceuticals, Inc.

EXECUTIVE SUMMARY

This is a review of Jazz Pharmaceutical's proposed Risk Evaluation and Mitigation Strategy (REMS) for sodium oxybate for the proposed treatment of fibromyalgia. Sodium oxybate is currently approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy under the proprietary name Xyrem. Because of the risk of abuse and misuse, Xyrem was initially approved with a Risk Management Plan that consisted of mandatory enrollment of prescribers and patients, distribution through a single specialty distributor, education directed at healthcare providers and patients, and a post-marketing evaluation program.

The Sponsor submitted a New Drug Application (NDA 22-531) for sodium oxybate for the treatment of fibromyalgia in December 2009 and proposes to market the drug under a different proprietary name, Rekinla, and a different concentration. We have a concern that the use of two proprietary names (Xyrem and Rekinla) for sodium oxybate has the potential to cause errors as medication errors of this type have been reported with other products that share a common active ingredient, but use different proprietary names.

The Sponsor has proposed a REMS for sodium oxybate for the fibromyalgia indication that builds on the existing program for Xyrem. In order to address the risk of abuse, misuse, and overdose, the program includes enrollment of prescribers and distribution through 15 specialty pharmacy providers that would have to be certified. In order to address the risk of medication errors secondary to the use of different proprietary names and different concentrations, the Sponsor has proposed different but similar programs for each indication.

Additionally, we note the existence of two REMS programs for the same established name may create confusion among prescribers who treat patients for narcolepsy and fibromyalgia. The same established product with two enrollment forms and two pharmacy dispensing mechanisms based on treatment indication may be confusing for prescribers, pharmacies, and patients and may be burdensome to the healthcare system.

We ask that the Advisory Committee members discuss the safety concerns and the proposed REMS and its implementation in the fibromyalgia population with regard to the following critical issues:

- Whether the proposed REMS is sufficient to address the potential for misuse and abuse with expanded use
- Whether the proposal for two similar but separate programs (e.g., separate prescriber and patient enrollment, specialty pharmacies, and educational materials) for each indication is sufficient to address the potential for medication errors without increasing the burden to the healthcare system.

1 BACKGROUND

1.1 Introduction

Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB), an endogenous neurotransmitter synthesized from gamma aminobutyric acid (GABA) and found in the central nervous system (CNS). GHB binds to two receptors: the GHB receptor (GHR) and the B-subtype of the GABA receptor (GABA_BR) in the CNS. After oral administration, sodium oxybate is rapidly absorbed and has a half life of 0.5 to 1 hour.

Xyrem (sodium oxybate) oral solution formulation was approved by the FDA on July 17, 2002 for the treatment of cataplexy in patients with narcolepsy, and on November 18,

2005 for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. The Sponsor submitted a New Drug Application (NDA 22-531) for sodium oxybate for the treatment of fibromyalgia in December 2009. The precise mechanism of action of sodium oxybate in patients with narcolepsy is not known; in patients with fibromyalgia, sodium oxybate is believed to inhibit central pain through stimulation of the gamma aminobutyric acid receptors (specifically GABA_BR), which may inhibit central spinal neurons and/or excitatory neurotransmitter release in the spinal cord.

To date, there is no good information on the prevalence of narcolepsy in the U.S. population. According to the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institute of Health (NIH) “narcolepsy is estimated to affect about one in every 2000 Americans (or approx. 155,000 total), but the exact prevalence rate remains uncertain, and the disorder may affect a larger segment of the population.”¹ According to the Xyrem Periodic Safety Update Report #16, 12,182 patients were prescribed Xyrem in the U.S. during the one year period 7/17/2008 – 7/16/2009.

The estimated prevalence of fibromyalgia is 5.0 million in the U.S.^{2,3} Based on the estimated prevalence of fibromyalgia, we anticipate a substantial expansion in the number of patients who could use sodium oxybate if it were approved for that indication.

The Sponsor proposes a different name and strength for the fibromyalgia indication. The table below provides comparative characteristics of the two products.

	Approved	Proposed
Tradename	Xyrem	Rekinla
Indication	treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy	treatment of fibromyalgia
Potential User Population Size (rough approx.)	150,000	5,000,000
Concentration	500mg/mL	375mg/mL
Recommended starting dose	4.5 g/night	4.5 g/night
Dosing frequency	two equally divided doses	two equally divided doses
Maximum nightly dose	9 g	9 g
How supplied	180 mL bottle	360 and 480 mL bottles

1.2 Approved Risk Management Program

Sodium oxybate is a controlled substance classified as schedule III in its approved form and a schedule I for illicit use. Because of concerns about the risk of abuse and misuse, the Xyrem July 2002 approval was under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) and with a RiskMAP to assure safe use of the product.

¹ National Institute of Neurological Disorders and Stroke (NINDS) website www.ninds.nih.gov

² Lawrence R. et al Estimates of the Prevalence of Arthritis and Other Rheumatic Conditions in the United States, Part II. Arthritis and Rheumatism, Vol. 58, No. 1. 26-35. January 2008.

³ Wolfe F, Ross K, Anderson J, Russell J and Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis and Rheumatology, 38:19-28. 1995.

The RiskMAP, entitled the Xyrem Success Program, included the following major components:

- Restricted distribution program that requires that Xyrem be distributed and dispensed through a central pharmacy. The central pharmacy requirements include:
 - Verification that the physician is eligible to prescribe Xyrem®
 - Verification of all patient registry information
 - Filling of the initial prescription only after the prescriber and the patient have received and read the educational materials
 - First prescription limited to a one month's supply, no greater than 3 refills and no more than a 3 month supply with each shipment - *This requirement was modified in 2003 to allow up to 5 refills per prescription*
 - Arrange and verify shipment (shipment includes Drug Product Kit containing drug product, bottle adapter, measuring device, dosing cups, and Medication Guide)
- Education program - to educate physicians and patients about the risks and benefits of Xyrem, including support via ongoing contact with patients and a toll-free Helpline
 - Xyrem® Physician Success Program
 - Xyrem® Patient Success Program (video and printed materials)
- Mandatory registration of patients and prescribing physicians into a secure database
- Xyrem® Post-Marketing Evaluation Program - This was outlined in the approval letter under postmarketing commitment #3. The commitment was that the Sponsor assess the post marketing safety of Xyrem in a prospective cohort of the first 1,000 patients prescribed Xyrem. Physicians were urged to evaluate patients every 3 months for the first 6 months of therapy and report to the Sponsor via a questionnaire, all adverse events (including inappropriate use). The Sponsor reported difficulty in collecting physicians' responses and at the time of the approval of the expanded indication, the Sponsor was notified that they had fulfilled their Postmarketing Commitment #3 outlined in the original approval letter after nearly 700 patients did not show any new safety signals.

2 MATERIALS REVIEWED

- Materials reviewed for proposed REMS:
 - July 17, 2002 Initial Xyrem approval letter
 - November 18, 2005 Xyrem efficacy supplement approval letter
 - Proposed REMS for NDA 21-196, submitted on September 2, 2008, and amended November 14, 2008, August 26, 2009, August 31, 2009, September 1, 2009, and October 8, 2009 Xyrem Proposed REMS Amendment
 - Proposed REMS for NDA 22-531, submitted on December 11, 2009 and amended on April 9, 2010 and June 25, 2010
- Materials reviewed for abuse and misuse trends and medication errors
 - September 6, 2006 Xyrem (NDA 021196) Correspondence from Jazz Pharmaceuticals
 - September 15, 2009 Xyrem (NDA 021196) Periodic Safety Update Report (PSUR)
 - November 18, 2009 Estimates of use and abuse related to GHB or Xyrem (sodium oxybate) and deaths related to GHB (gamma hydroxybutyrate) use: Margie Goulding, PhD., Epidemiologist, Division of Epidemiology (DEPI) OSE

- December 14, 2009 Adverse Event Reporting System (AERS) overview including Misuse, Abuse, Overdose, and Drug-induced vulnerability: Charlene Flowers, R.Ph., Safety Evaluator, Division of Pharmacovigilance (DPV) I
- January 8, 2010 Information on Xyrem and GHB from the Drug Enforcement Agency (DEA) and the Committee on Drug Facilitated Sexual Assault of the Society of Forensic Toxicologists (SOFT): James M. Tolliver, PhD Pharmacologist, Controlled Substance Staff (CSS)
- March 24, 2010 Proprietary Name Review for Rekinla (Sodium Oxybate) Oral Solution: Raichell Brown, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)

3 RESULTS OF REVIEW OF PROPOSED REMS

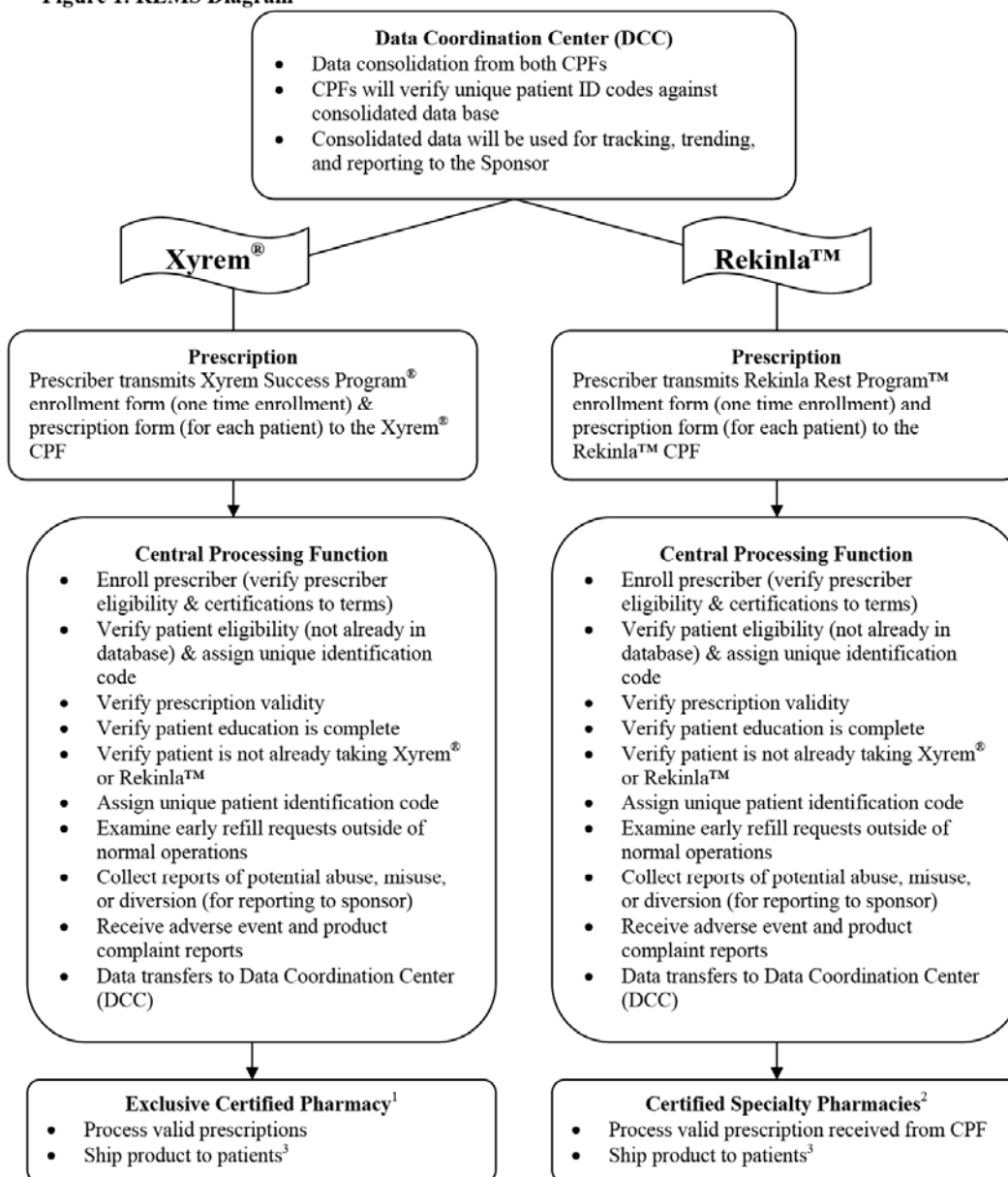
Xyrem was included on the list of products deemed to have in effect an approved Risk Evaluation and Mitigation Strategy (REMS) under section 505-1 of the Federal Food, Drug and Cosmetic Act at the time of the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007. The Sponsors of such listed products were required to submit a REMS proposal by September 21, 2008. Jazz Pharmaceutical submitted their proposed REMS for Xyrem in August of 2008 that was similar to the existing RiskMAP; this proposal has been amended several times and is currently under review. The Sponsor additionally submitted a proposed REMS for sodium oxybate for the new indication. Below is a summary of the latest REMS proposal for Xyrem and Rekinla:

- Patient and Healthcare Provider Education
 - Medication Guide – the Sponsor proposes product-specific Medication Guides for Rekinla and Xyrem
 - Physician Brochure – This brochure provides information to prescribers about the responsibilities of the Rekinla REST Program and guidelines for dosing and titrating Rekinla. It also includes a copy of the Physician Registration Form and the Patient Prescription Form.
 - Educational materials for pharmacies have not been submitted to date
- Mandatory Certification and Enrollment
 - Mandatory prescriber certification through enrollment – prescribers will be required to be enrolled into the Xyrem REMS (Success Program) and/or Rekinla REMS (REST Program). If prescribers treat both fibromyalgia patients and narcolepsy patients, they will be required to be enrolled in both programs.
 - Patient enrollment – prescribers complete a one-time patient enrollment using either the Rekinla Prescription Form or the Xyrem Prescription Form. Patients are provided educational materials and prescribers educate patients on the preparation, dosing, and scheduling of Rekinla or Xyrem. Patients can only be enrolled in one program.
 - Pharmacy certification
 - Rekinla will be dispensed (shipped) to the fibromyalgia patient by certified pharmacies (15 to begin with) after receiving prescription from CPF (see below)
 - Xyrem will be dispensed (shipped) to the narcolepsy patient only by an exclusive central pharmacy (single pharmacy) after receiving prescription from CPF (see below)

- Product distribution
 - Both products will not be dispensed or stocked at the same pharmacy.
 - A limited amount of Xyrem will be stocked at the exclusive central pharmacy
 - A limited amount of Rekinla will be stocked at some certified pharmacies
 - Neither product will be stocked at retail pharmacies
 - On rare occasions will a retail pharmacy receive the product for shipment to a patient
- Logistical/Implementation Components
 - Central Processing Function (CPF) – each program will have its own CPF with the following functions:
 - Enroll prescriber by verifying prescriber eligibility and certifications to the terms of the program
 - Verify patient eligibility (not already in database) and assign unique identification code
 - Verify prescription validity
 - Verify patient education is complete
 - Examine early refill requests
 - Collect reports of potential abuse, misuse, or diversion (for reporting to sponsor)
 - Receive adverse event and product complaints
 - Data transfers to Data Coordinating center
 - Data Coordinating Center
 - Consolidate data from both CPFs that is used to verify unique patient ID codes
 - Consolidated data will be used for tracking, trending, and reporting to the sponsor

The diagram below provided by the Sponsor shows the structure, function and procedures for the REMS for Rekinla and Xyrem.

Figure 1. REMS Diagram



1. No retail pharmacies. An exclusive central pharmacy completes the entire process

2. No retail pharmacies. Not more than 15 certified specialty pharmacies planned for Rekinla™ at this time.

3. Each shipment will include product-specific oral syringe and Medication Guide. Exceptions to direct patient shipments are made when required by patient's insurance or other valid reason

4 ABUSE, MISUSE, AND OVERDOSE

4.1 Abuse and Misuse Concerns

On February 18, 2000, President Clinton signed bill H.R. 2130 which made GHB a Schedule 1 drug. When Xyrem was approved in 2002 it was listed as Schedule III, while GHB including salts, isomers and salts of isomers of GHB, not found in approved products, are listed as Schedule I under the Controlled Substances Act (CSA).

GHB was scheduled due to its potential of abuse and misuse, dependency, and clandestine laboratories producing GHB. GHB is also known as a date-rape drug due to documented sexual assault case reports for persons under GHB's influence.

The current Xyrem label (approved in 2006) has the following boxed warning:

WARNING: Central nervous system depressant with abuse potential.
Should not be used with alcohol or other CNS depressants.

Sodium oxybate is GHB, a known drug of abuse. Abuse has been associated with some important central nervous system (CNS) adverse events (including death). Even at recommended doses, use has been associated with confusion, depression and other neuropsychiatric events. Reports of respiratory depression occurred in clinical trials. Almost all of the patients who received sodium oxybate during clinical trials were receiving CNS stimulants.

Important CNS adverse events associated with abuse of GHB include seizure, respiratory depression and profound decreases in level of consciousness, with instances of coma and death. For events that occurred outside of clinical trials, in people taking GHB for recreational purposes, the circumstances surrounding the events are often unclear (e.g., dose of GHB taken, the nature and amount of alcohol or any concomitant drugs).

Xyrem is available through the Xyrem Success Program, using a centralized pharmacy. 1-866-XYREM88 (1-866-997-3688). The Success Program provides educational materials to the prescriber and the patient explaining the risks and proper use of sodium oxybate, and the required prescription form. Once it is documented that the patient has read and/or understood the materials, the drug will be shipped to the patient. The Xyrem Success Program also recommends patient follow-up every 3 months. Physicians are expected to report all serious adverse events to the manufacturer. (see WARNINGS).

To address the potential for abuse and misuse of sodium oxybate, Xyrem was approved with a Risk Management Program that restricts the distribution of the drug to only enrolled prescribers and patients. The program also prohibits the drug from being dispensed by retail pharmacies. A description of the approved program is summarized below (see section 1.3).

With the approval of an expanded indication and use there is an increased concern of possible misuse or unintentional exposure to family members. Sodium oxybate dosing requires the patient to prepare both doses before bedtime; after taking the first dose the patient prepares the second dose which then is left on the patient's bedside for later use thus accidental overdose in children is a possibility. Furthermore, the Sponsor has proposed larger bottle sizes, thus making more available in a medicine cabinet for possible misuse by family members or exposing a child to an even a larger overdose if ingested accidentally.

During the Agency review of the proposed REMS for the currently approved product, the Sponsor provided information and literature references that they assert demonstrate that the background use of illicit GHB has declined sharply since scheduling and has remained low. The Sponsor also pointed out that their tracking of possible misuse, abuse, and diversion revealed that there have been only a small number of requests for early refills, a possible signal for diversion (18 of 30,050 patients).

Based upon the Sponsor's assertion, the Agency conducted an independent review of available data sources to determine if rates of abuse and misuse with sodium oxybate and GHB are declining.

4.2 Estimates of Use and Abuse of Xyrem (sodium oxybate) and Deaths Related to GHB (gamma hydroxybutyrate) Use

The Division of Epidemiology (DEPI) obtained data from Jazz Pharmaceuticals on: 1) number of patients prescribed Xyrem and 2) filled Xyrem prescriptions. To determine the estimates and evaluate trends related to abuse of Xyrem or GHB and related outcomes such as emergency department visits and death, DEPI searched the following data sources:

- The Monitoring the Future survey, an ongoing study of the behavior, attitudes, and values of American secondary school students, college students, and young adults.
- The Drug Abuse Warning Network (DAWN) of the Substance Abuse and Mental Health Services Administration (SAMHSA) a national database of drug-related visits to hospital emergency departments and mortality data from medical examiners
- The American Association of Poison Control Centers (AAPCC) a poisoning surveillance database

The number of patients prescribed Xyrem reported by the Sponsor increased from 458 in 2002 to 11,797 in 2008, and the number of prescriptions filled increased from 949 in 2002 to 74,145 in 2008.

In general the data sources on abuse that were searched provided limited data on GHB and even less information on Xyrem or sodium oxybate.

The Monitoring the Future survey showed some evidence of a decline in use of GHB among secondary school students over the 2000-2008 period; for a sample of 8th, 10th and 12th graders the annual prevalence of GHB use declined from 1.4% in 2000 to 0.9% in 2008. However, these results do not provide much reassurance for two reasons: 1) there is evidence in the literature of the tendency to underreport stigmatized behavior (e.g., illicit drug use) in surveys, and 2) 8th, 10th and 12th graders may not be representative of the true population of GHB users (who may be older). Therefore, these estimates are likely underestimates of the true magnitude of GHB use.

The AAPCC case mentions for GHB exposure point toward a decline⁴ over the 2003-2007 period (800 case mentions in 2003 to 518 in 2007), but these are just case mentions/counts, not national estimates, with no variation estimates with which to test for a statistically significant difference between the year 2003 and year 2007 case count numbers. Case mentions are not reliable estimates, and their significance should not be over interpreted.

DAWN national estimates of emergency department (ED) visits involving GHB fell and then rose nominally (but both not statistically significantly) over the 2004-2007 period; 1,789 visits in 2004, 1,036 visits in 2005, 1,084 visits in 2006 and 2,207 visits in 2007. DAWN ED data were the only source with information on Xyrem, but the Xyrem-related ED visit case counts were not large enough to make reliable national estimates. Thus

⁴ But these are just case mentions (i.e. counts), not national estimates, and there are no variation estimates with which to test for a statistically significant difference between the year 2003 and year 2007 case count numbers.

neither the magnitude of, nor a potential trend in, Xyrem abuse nationwide could be evaluated. Still in each year examined (2004-2007), there were patients who had taken Xyrem who ended up in an emergency department. The Xyrem-related ED visit cases included cases categorized as overmedication, adverse reaction, “other” (i.e. abuse), and suicide attempt.

Thus, the DAWN, AAPCC, and Monitoring the Future results are mixed and have several limitations (as mentioned above). The strongest data is the DAWN ED data, which does not show a decline in GHB abuse. Thus, the combined results from these available data sources do not substantiate the sponsor’s claim that there has been a decline in GHB use, and the DAWN ED data on Xyrem does not support a conclusion of a decline in Xyrem abuse/misuse.

The DAWN mortality data ranged from 11 to 18 GHB-related deaths each year for calendar years 2004-2007. These are counts of GHB-related deaths provided by DAWN-participating medical examiners nationwide (although the data are not nationally representative, the number of medical examiner/coroner jurisdictions (counties) participating in DAWN increased from 150 in year 2004 to 246 in year 2007). DEPI only looked for deaths labeled GHB-related since once in the bloodstream, sodium oxybate and GHB become indistinguishable. Florida State Medical Examiner data reported 1 to 2 GHB-related deaths (where GHB was believed to have a causal role in the death) each year between 2006 and 2009. DEPI noted that the DAWN Medical Examiner data, and Florida State Medical Examiner data did not report national estimates of GHB-related deaths because of the small numbers reported (less than 20/year), and thus while there is evidence that deaths due to GHB have occurred in recent years, trends in GHB-related deaths over time could not be evaluated.

4.3 Postmarketing Safety Data: AERS Overview including Misuse, Abuse, Overdose, and Drug-induced Vulnerability (Xyrem)

The Division of Pharmacovigilance (DPV) I completed a high-level evaluation of FDA’s AERS data (crude counts). The AERS search criteria included the time from product approval July 17, 2002, until September 15, 2009 for all adverse events reported for sodium oxybate (Xyrem). The AERS search identified 755 adverse events reported for Xyrem, including 681 U.S. reports.

A hands-on review was conducted for unique cases of diversion, misuse, abuse, overdose, and drug-induced vulnerability. The reviewer identified five relevant cases of misuse (1), overdose (1), and patient vulnerability (3). There was one case each of which the patient’s prescription was seized and misused for recreational purposes; one patient also experienced a non-fatal overdose. There were three cases of drug induced vulnerability; the three patients were vulnerable to sexual assault because their family member or acquaintance recognized the patient was incapacitated from the effects of Xyrem.

4.4 Information on Xyrem and GHB from the DEA and the Committee on Drug Facilitated Sexual Assault of the Society of Forensic Toxicologists

The Controlled Substance Staff (CSS) in FDA obtained information about Xyrem and GHB from the following sources:

- The National Forensic Laboratory Information System (NFLIS) NFLIS is a program of the DEA, Office of Diversion Control that collects information from drug exhibits analyzed by federal, state and local forensic laboratories located across the United States. NFLIS does not provide product specific information. As of April 2008,

NFLIS represents 276 individual laboratories and handles over 88% of the nation's annual state and local drug analysis cases.

The NFLIS data provided by DEA demonstrate that GHB, as well as its physiological precursors, GBL (gamma-butyrolactone) and 1,4-butanediol, continue to be diverted and abused. Because of a growing number of laboratories, trends cannot be analyzed, but data from the period of 2003-2008 suggest that diversion and abuse of GHB and GBL have declined. Over the period of 2003 through 2008, the annual number of GHB seizures recorded in the NFLIS system continuously decreased from 339 (in 2003) to 189 (in 2008). An examination of the Annual Reports of the NFLIS show that over the period of May 2003 to April 2008 there was a progressive increase in the number of forensic drug laboratories participating in the NFLIS system. The progression of the number of participating laboratories was as follows; 189 (reported May 2003), 232 (July 2004), 244 (March 2005), 263 (April, 2006), 274 (June 2007), 276 (April, 2008), and 278 (April 2009). The substantial reduction in number of GHB seizures recorded in NFLIS over the period of 2003 to 2008, coupled with the substantial increase in number of participating laboratories in NFLIS over the same period suggest a true reduction in the number of GHB seizures over the time period. This would be consistent with the effects produced by the scheduling of GHB in March of 2000. Unfortunately, NFLIS data do not allow a distinction between exhibits involving Xyrem and exhibits involving clandestinely produced GHB.

- The Committee on Drug Facilitated Sexual Assault (DFSA) associated with the Society of Forensic Toxicologists (SOFT) monitors drugs confirmed in laboratory analysis to be used to facilitate sexual assault.

The Committee on DFSA associated with the SOFT is aware of two sexual assault cases (one in 2003 and the other in 2005) involving Xyrem. Although some cases of drug facilitated sexual assault involving GHB have been documented in the scientific literature, no cases of sexual assault have been reported to the DFSA committee over the last seven years (2002-2009).

The CSS reviewer concluded that the possible reasons for the decline of GHB and GBL diversion and abuse include:

- Scheduling of GHB (Farias-Reid Date Rape Prohibition Act of 2000)
- Designation of GBL as a List I chemical (Farias-Reid Date Rape Prohibition Act of 2000)
- Diversion and abuse of 1,4-butanediol
- Changes of law enforcement priorities.

4.5 Xyrem-related Deaths from July 17, 2008 through July 16, 2009

The Division of Risk Management (DRISK) reviewed the section on Xyrem-related deaths from the Periodic Safety Update Report (PSUR) for NDA 21-196 dated September 15, 2009: During this reporting period (July 17, 2008 to July 16, 2009), 28 (20 females/8 males) fatalities were reported with Xyrem use. In 14 of the 28 cases cause of death was determined and of those, 3 were possible abuse or misuse cases: two cases where of overdose (multiple drugs including Xyrem), and one was a case of acute intoxication

(GHB + other CNS depressants). The remaining 8 of the 14 cases where the cause of death was determined were unrelated to abuse, misuse, and overdose of Xyrem.⁵

4.6 Results of ORA Inspection of Jazz Pharmaceuticals

FDA's Office of Regulatory Affairs (ORA) inspected the Xyrem RiskMAP at Jazz Pharmaceuticals headquarters in September 2007 at the request of CDER. Review of the written procedures collected at that time revealed that some of the written procedures and criteria for decision-making were incomplete. ORA inspected the Xyrem RiskMAP at Express Scripts Specialty Distribution Services (SDS), the contractor responsible for the distribution of the drug, in September 2008 and found that written procedures related to potential abuse and misuse were unclear and case notes related to safe handling and potential abuse and misuse were incomplete. The inspector also noted that there were no clear cut procedures in place to handle situations of loss of product and early refills. SDS stated at the end of the inspection that they would improve their procedures and documentation.

CDER Office of Compliance and ORA re-inspected the Express Scripts Specialty Pharmacy Distributor (SDS) in November 2009, and obtained all written procedures used to implement the RiskMAP. The investigators found that the pharmacy had amended and improved their procedures, case notes were thorough and complete, and distribution appeared to be tightly controlled.

During the inspection it was noted that, in the 13 month period, 10/1/2008 to 11/1/2009, 273 Risk Management Reports were filed with Jazz by SDS. Risk Management Reports are reports of events related to Xyrem dispensing and usage, and include the following, among other things:

1. Patient's loss/misuse of the product
2. Patient did not receive and carrier shows receipt of delivery
3. Lost/stolen package or bottle
4. Delivered to incorrect address and not returned
5. Patient request for early refills that are unsubstantiated by the prescribing physician
6. Invalid physicians

The FDA investigators selected 34 Risk Management Reports of a variety of issues for detailed review. Cases included those where physicians contacted the SDS to discontinue patients who were believed to be abusing or misusing the drug, and cases where requests for early refills were denied by physicians. A few examples of these scenarios are below:

- Control Number 173
Prescriber's office called to discontinue patient from program 2/11/09. He had been notified by a family member that the patient has misused her last two bottles of Xyrem. She drank the whole bottle one night and ended up in the emergency

⁵ The causes of death were as follows: 2 lung cancer, 1 leukemia, 1 bronchopneumonia, 1 myocardial infarction secondary to respiratory failure, 1 suicide, 1 internal bleeding, and 1 possible cerebral vascular accident due to the obesity associated with hypertension (patient died suddenly at night).

room on Dec. 31, 2008. Per prescriber's office patient has also been taking pain medication and abusing other drugs. Patient is currently in rehab for drug abuse.

- **Control Number 205:**
A prescriber had seen a specific patient between 2005 and 2008. During that time, the patient had frequently requested early refills, which were usually denied. The prescriber told SDS he felt the patient was abusing Xyrem and needed drug rehab. The original prescriber was informed when the patient received prescriptions from three subsequent prescribers and talked to each of the new prescribers. The patient eventually received a prescription along with other treatment from a sleep specialist.
- **Control Number 212:**
Prescriber called SDS to place a hold on refills for a patient on 4/10/09 because husband had called and reported patient was taking more Xyrem than she was supposed to. Patient had gotten 4 days early refill in March 09 with prescribers approval, attempted to get an early refill on 4/9/09, but did not want SDS to get approval from prescriber and insurance, so declined refill. Patient again requested early refill (6 days early) on 4/15/09. SDS left message at prescriber's office, and on 4/20/09, nurse at prescriber's office called to keep the prescription discontinued until the patient could be seen in the office.
- **Control Number 277**
Prescriber called and stated he had just found out patient was a drug addict, known to sell his prescription drugs. Prescriber requested patient enrollment be discontinued and prescription terminated.

The proposed REMS for Xyrem includes a provision to ship Xyrem to an alternate pharmacy on rare occasions. The records reviewed at SDS show that prior to 11/1/2009, there had been 32 shipments to 13 alternate pharmacies. These included a psychiatric in-patient facility, 7 Veterans Administration pharmacies, a pharmacy provider for an Adult Correctional Facility, and four local in-network pharmacies. The written procedures showed that the utilization of an alternate pharmacy must be reviewed and approved by the Operations Director, the Pharmacist-in-Charge, and the Manager-in-Charge. Before shipping Xyrem, SDS educates the alternate pharmacy contact about Xyrem. After delivery, SDS verifies receipt through the carrier's tracking service, and calls the pharmacy and the patient to confirm the date the patient received the order. They also confirm the lot number and volume dispensed to the patient.

4.7 Summary of Abuse, Misuse, and Overdose Trends

The review team could find no direct evidence that disputed the Sponsor's assertion that the background use of illicit GHB has declined sharply since scheduling and has remained low. We did find the numbers of reported cases of abuse and misuse for Xyrem has been small in recent years.

Any decline in illicit GHB since 2000 use is likely the result of the scheduling of GHB, designation of GBL as a List I chemical, diversion and abuse of 1,4-butanediol and changes of law enforcement priorities. It is also very possible the observed low counts of abuse and misuse with Xyrem are as a result of an effective implementation of the REMS program that has been in place for Xyrem since its approval.

It is important to note two additional issues that seriously limit our ability to evaluate the level of sodium oxybate abuse. There is difficulty identifying cases of abuse and misuse.

For most of the data sources reviewed, there is an inability to distinguish GHB from sodium oxybate or Xyrem, which means there may be misclassification of sodium oxybate abuse cases, i.e. sodium oxybate cases being counted as GHB cases, and vice versa. There is very likely underreporting of cases of abuse and misuse and sexual assault also may play a part in the observed low rate of sodium oxybate abuse, so the small case count numbers (from DAWN ED data) for suspected sodium oxybate abuse and misuse do not allow us to make reliable national estimates. Thus, we have very little data with which to judge the level of abuse and misuse of sodium oxybate in the U.S.

5 MEDICATION ERRORS

5.1 Risk of Medication Errors

Sodium oxybate is associated with medication errors involving incorrect dosing of the drug. Incorrect dosing errors generally consist of overdoses in which the incorrect dose of sodium oxybate is prescribed, or patients accidentally administer the wrong quantity of sodium oxybate. Such events have been reported post-marketing with the Xyrem product, and patient administration errors were reported in controlled clinical studies.

Sodium Oxybate is a CNS depressant that when taken in excessive doses, or in combination with other CNS depressants, can cause CNS adverse events including seizure, respiratory depression, and decreased consciousness that may lead to coma and death (see boxed warning for Xyrem). Some of the medication error reports described serious adverse events that occurred due to the incorrect dosing of sodium oxybate, and in many of these cases the adverse events required hospitalization of the patient.

A noteworthy medication error trend occurred between October 2005 and July 2006, shortly after the indication for use was expanded to include treatment of excessive daytime sleepiness in patients with narcolepsy. In this ten-month period, there were a total of 4,590 medication errors that were reported to Jazz Pharmaceuticals (correspondence from Jazz Pharmaceuticals submitted September 6, 2006). These medication errors were described by Jazz Pharmaceuticals as dosing errors in which the dose of Xyrem was miscalculated into milliliters and the total daily dose was mistakenly used as the divided nightly dose. According to Jazz Pharmaceuticals, these errors occurred when prescribing the drug, and “nearly all prescription errors” were corrected and therefore not translated into administration of the incorrect dose to the patient.

On November 13, 2006, Supplement-012 for NDA 021196 was approved to address these errors. This supplement included changes to the prescription form to prevent potential dosing errors caused by confusion in the units of measure (grams and milliliters) as well as the required conversion factor from a total nightly dose to the divided doses that must be taken by the patient. Jazz Pharmaceuticals has not requested any further changes to the Xyrem prescription form since this supplement was approved, so we assume that the revised form has adequately addressed these prescribing errors. However, given the serious CNS depressant effects of Sodium Oxybate and the large number of medication errors cases reported with the currently marketed product, Xyrem, we have concern that the new proposed product is prone to the similar types of errors. These concerns are intensified by the spike in medication errors that occurred between 2005 and 2006, and the fact that the proposed fibromyalgia indication is more prevalent than narcolepsy. The approval of the fibromyalgia indication is likely to greatly expand the number and types of physicians who prescribe sodium oxybate along with the number of patients who use sodium oxybate, thereby increasing the risk of medication errors for those healthcare providers and patients who are inexperienced with prescribing and using sodium oxybate.

Jazz Pharmaceuticals proposes several Elements to Assure Safe Use (ETASUs) in the proposed REMS for Rekinla. However, many of these elements were in place with the Xyrem REMS when the 4,590 medication errors occurred which indicates to us that the elements may not adequately manage the medication error risk. We are reassured that the elements have some impact on the risk by the fact that the prescribing errors were largely remedied prior to patient administration by the Central Pharmacy prescription review process. However, the prescription review process for Rekinla differs slightly (15 certified pharmacies as opposed to one central pharmacy for Xyrem) and it is unclear to us how this modification impacts the safe use of sodium oxybate.

In addition, we also have concern that the introduction of Rekinla has the risk of introducing new types of medication errors due to changes that Jazz Pharmaceutical proposes for the commercial product. Specifically, Jazz Pharmaceuticals proposes to market sodium oxybate for the fibromyalgia indication under the proprietary name, Rekinla, rather than use the existing proprietary name Xyrem. Also, Jazz Pharmaceuticals proposed to market sodium oxybate for the fibromyalgia indication in a new concentration of 375 milligrams per milliliter. Xyrem is currently marketed in a concentration of 500 milligrams per milliliter. These changes to the commercial product introduce variables that potentially complicate practitioner and patient use of sodium oxybate, perhaps leading to medication errors. These risks are described in further detail below.

5.2 Use of Different Proprietary Names

We have concern that the use of a two proprietary names (Xyrem and Rekinla) for sodium oxybate has the potential to cause medication errors. Patients diagnosed with fibromyalgia and narcolepsy may be mistakenly prescribed both Rekinla and Xyrem by prescribers that fail to recognize that the commercial products each contain sodium oxybate. If undetected prior to dispensing or administration, such errors would lead to ingestion of excessive amounts of sodium oxybate with potential risk for serious adverse events or death. To counter FDA's concern and support the use of the Rekinla proprietary name, Jazz Pharmaceuticals contends that "*the narcolepsy and fibromyalgia patient populations do not overlap.*" However, Jazz Pharmaceuticals provides no data to support this contention and we remain unconvinced that the narcolepsy patient population and fibromyalgia patient population are mutually exclusive since some patients might be diagnosed with both narcolepsy and fibromyalgia.

The basis of our medication error concern with respect to the use of two proprietary names for sodium oxybate is that medication errors of this type have been reported with other products that share a common active ingredient, but use different proprietary names. However, we are unaware of any such errors that have occurred with products that are marketed under a restricted distribution program which monitors patients closely, which lessens our concern to some extent. For this proposed product, Jazz Pharmaceutical believes that the elements within the Rekinla and Xyrem REMS programs mitigate this risk, specifically, prescriber enrollment, restricted distribution program, along with labeling and educational materials. However, it is unclear from our evaluation of these proposed elements whether the elements in the Xyrem and Rekinla REMS programs will fully mitigate this risk. It appears that the success of these strategies relies on the timely communication between the various distribution parties and a fully integrated database of patients and prescribers. At the time of this review, it is not clear to us from the information provided by Jazz Pharmaceuticals whether the two REMS programs are able to achieve these goals.

Additionally, we note that the use of two different proprietary names appears to complicate the development and distribution of educational materials and will likely require that separate and distinct materials be developed for each commercial product, even if the risks that are communicated are the same.

5.3 Dosing Errors

We have concern that the commercialization of the 375 milligram per milliliter concentration is a source of error because the number is cumbersome for Rekinla's dose calculations and when converting the dose from milligrams to the corresponding volume in milliliters. According to Jazz the concentration of 375 mg/mL was selected "for patient dosing convenience and manufacturing efficiency" and to "minimizes bottles and components to be dispensed each month." Jazz Pharmaceuticals does not provide detail in the Application to substantiate either of these reasons. Moreover, we note that recommended dosing for the narcolepsy indications of Xyrem recommends dosing of 4.5 grams to 9 grams per night (in divided doses), which is virtually the same as the recommended doses for Rekinla (4.5 to 6 grams per night, in divided doses). We question if 375 mg/mL is more convenient and less wasteful, why this concentration was not similarly pursued for Xyrem.

Also, when considering this risk of dose calculation errors, we believe that the numerical value '375' is cumbersome when calculating the doses. Neither patients nor practitioners are likely to accurately calculate, for example, the volume of Rekinla 375 mg/mL oral solution that will deliver a 2.25 gram dose without the aid of a calculator. Even with aid of a calculator, the multi-step calculation is more complex than what would be required for the 500 mg/mL concentration of sodium oxybate and therefore more prone to error. Jazz Pharmaceuticals contends that this risk is minimized by the use of separate prescription forms for each commercial product, and by the fact that each prescription form only specifies the intended dose in grams thereby circumventing the need for prescribers to reference the concentration to calculate the dose of Rekinla in milliliters.

Because Rekinla is formulated as an oral solution, the conversion of dose from milligrams to a corresponding volume will need to occur when dispensing and administering a product. During dispensing, pharmacists will have to calculate the total volume of sodium oxybate to dispense based on dose, and referencing the wrong concentration of sodium oxybate could lead to the incorrect volume to be dispensed. This risk is somewhat reduced by the use of restricted distribution of each product by separate certified pharmacies which will likely provide extensive pharmacist education on each product. Additionally, when administering the product, patients may use a device that measures in milliliters or teaspoonfuls thus requiring conversion of dose from milligrams to a volume.

Jazz Pharmaceutical intends to distribute product-specific measuring devices that markings specifying the dose in grams with each prescription of Rekinla and Xyrem. However, circumstances may arise when such devices are not available at the time of use or patients may elect not to use the manufacturer's device thereby introducing some potential for error. Additionally, we have some concern that the dosing device itself could be a source of error due to the fact that oral dosing syringes are conventionally calibrated by volume. Because the Rekinla and Xyrem oral dosing device use an unconventional dosing calibration (milligrams), healthcare providers, patients, and caregivers may overlook or become confused by the milligram calibration which may lead to dosing errors. Post-marketing experience with similarly calibrated dosage devices

(e.g. Tamiflu) has demonstrated that this is a source of error. For this product, the provision of an unconventionally calibrated dosage device may be justified to reduce the risk of dose calculation errors that can be associated with converting a milligram dose of sodium oxybate to a volume. However, we will have to evaluate and consider these risks carefully.

In addition to the risks posed by the cumbersome concentration Jazz Pharmaceuticals proposes, we also have concern that marketing a concentration of the sodium oxybate oral solution that differs from the currently marketed product creates risks for dosing errors. Some prescribers may prescribe Rekinla and Xyrem. Depending on their familiarity with one or the other concentration, or the sodium oxybate labeling materials they reference, the presence of two different concentrations may predispose them to using the incorrect concentration when calculating a patient dose. Jazz Pharmaceuticals contends that this risk is minimized by the use of separate prescription forms for each commercial product, and by the fact that each prescription form only specifies the intended dose in grams thereby circumventing the need for prescribers to reference the concentration to calculate the dose in milliliters. We agree that these measures are likely to reduce the risk, but perhaps not fully eliminate, prescribing errors of this nature.

Overall, we believe there is a higher risk of dosing errors if the 375 mg/mL concentration is commercialized for Rekinla. Jazz Pharmaceuticals believes that the REMS program, minimizes such risks. However, we believe that such risks could be further reduced if the 500mg/mL concentration was selected for commercialization for the fibromyalgia indication.

6 SUMMARY

The Sponsor has proposed a REMS for sodium oxybate for the fibromyalgia indication that builds on their existing program for Xyrem. In order to address the risk of abuse, misuse, and overdose, the program includes enrollment of prescribers and distribution through specialty pharmacy providers. The drug can only be dispensed to patients that have been enrolled by the prescriber into the REMS program. Based upon the data sources reviewed by the Agency, the sponsor appears to have reasonably accomplished this goal for Xyrem, however use in general has been low (approximately 10,000-12,000 patients per year for the past 3 years⁶) and for reasons described in this review, there are limitations in our ability to confidently evaluate sodium oxybate abuse and misuse trends in the U.S. Approval of sodium oxybate for the treatment of fibromyalgia will almost assuredly increase the likelihood of abuse and misuse or unintentional exposure of sodium oxybate to other members in the household. While neither the existing REMS for Xyrem, nor the proposed REMS for Rekinla guarantee protection of household members from accidental or unintentional misuse, any proposed REMS would need to put greater emphasis on educating healthcare providers and patients about the safe use and appropriate storage of this product given the ease with which this product can be misused or unintentionally consumed, and should include a robust postmarketing surveillance/evaluation program.

In order to address the risk of medication errors secondary to the use of different proprietary names and different concentrations, the Sponsor has proposed different but similar programs for each indication. As mentioned above, each program will require enrollment of prescribers and patients into the REMS and distribution of the drug by

⁶ Source: NDA 21-196; Post-Approval Submission 080, Jazz Pharmaceuticals, October 7, 2009.

specialty pharmacies. Each program will have a separate enrollment process for prescribers and separate educational materials for both prescribers and patients. The biggest difference between the two programs is the use of multiple specialty pharmacy providers for Rekinla (15 to start) versus a single pharmacy provider for Xyrem. The use of multiple specialty pharmacies for Rekinla is likely to accommodate the substantially higher use that is anticipated in this population. The Sponsor proposes a Data Coordinating Center that would cross check patient enrollment across the two programs to ensure that patients (identified by a unique enrollment number) are only enrolled in one program. Furthermore, each program will enroll separate specialty pharmacies and therefore no pharmacy will stock both products.

The basis of our medication error concern with respect to the use of two proprietary names for sodium oxybate is that medication errors of this type have been reported with other products that share a common active ingredient, but use different proprietary names. However, we are unaware of any such errors that have occurred with products that are marketed under a restricted distribution program which monitors patients closely, which lessens our concern to some extent. For this proposed product, Jazz Pharmaceutical believes that the elements within the Rekinla and Xyrem REMS programs mitigate this risk. However, it is unclear from our evaluation of these proposed elements whether the elements in the Xyrem and Rekinla REMS programs will fully mitigate this risk. It appears that the success of these strategies relies on the timely communication between the various distribution parties and a fully integrated database of patients and prescribers. At the time of this review, it is not clear to us from the information provided by Jazz Pharmaceuticals whether the two REMS programs are able to achieve these goals.

Additionally, we note the existence of two REMS programs for the same established name may create confusion among prescribers who treat patients for narcolepsy and fibromyalgia. The same established product with two enrollment forms and two pharmacy dispensing mechanisms based on treatment indication may be confusing for prescribers, pharmacies, and patients and burdensome to the healthcare system.

We ask that the Advisory Committee members discuss the safety concerns and the proposed REMS and its implementation in the fibromyalgia population with regard to the following critical issues:

- Whether the proposed REMS is sufficient to address the potential for misuse and abuse with expanded use
- Whether the proposal for two similar but separate programs (e.g., separate prescriber and patient enrollment, specialty pharmacies, and educational materials) for each indication is sufficient to address the potential for medication errors without increasing the burden to the healthcare system

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Efficacy and Safety Background for the Advisory Committee
Sodium Oxybate
NDA 22-531

Executive Summary

Sodium oxybate, the sodium salt of gamma-hydroxybutyrate (GHB), is a central nervous system depressant with hypnotic properties. The proposed indication is for the management of fibromyalgia.

The drug is currently approved as Xyrem for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. The Applicant's fibromyalgia development goal was to show that sodium oxybate is safe and effective across multiple symptom domains in the fibromyalgia population.

The Applicant has provided substantial evidence of effectiveness in two Phase 3, adequate and well-controlled (AWC) trials which demonstrated that Xyrem reduced pain in patients diagnosed with fibromyalgia. The Applicant is seeking claims based on an objective measurement of sleep in the Phase 2 study. The Division determined that the analyses of the data do not support these sleep claims.

The safety profile of sodium oxybate for fibromyalgia was demonstrated in over 1,060 treated subjects/patients in doses up to 9 g per night. The adverse event profile appears acceptable across the to-be-marketed dose range and is generally consistent with that seen in the currently approved Xyrem for narcolepsy.

In the fibromyalgia development program, 96% of the patients who received sodium oxybate were less than 65 years of age. In the Phase 2/3 controlled studies, the mean age was 46.8 years for Xyrem-treated patients, the majority were Caucasian (>91%), and 63.9% of patients had a BMI < 30 kg/m². An adverse event analysis by subgroup of age, gender, race, BMI category, dose/body weight ratio, Beck Depression Inventory (BDI-II) total score, and geographic region of United States (US) or European Union (EU), showed AEs of headache and nausea occurred slightly more frequently in patients ≥ 65 years but otherwise, no statistically or clinically significant pattern was seen in types or numbers of AEs by subgroup.

The Applicant's submitted safety data adequately evaluated adverse events (AEs) relevant to the drug's central mechanism of action, AEs of the known safety profile of Xyrem use in the narcolepsy population through submission of postmarketing data, and risk mitigation through the submission of a Risk Evaluation and Mitigation Strategy (REMS) which is currently under review.

Background of NDA 22-531 (Sodium Oxybate)

Introduction and Background

Sodium oxybate, the sodium salt of gamma-hydroxybutyrate (GHB), is a central nervous system (CNS) depressant with hypnotic properties. Sodium oxybate is an odorless, white crystalline powder which is highly soluble and fully dissolved in water. It has been approved as Xyrem in the US since 2002 (NDA 21-196) for the *treatment of cataplexy in narcolepsy*, with an efficacy supplement to expand the indication to *treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy* approved in 2005. It is also approved in the European Union (EU) and Canada for various symptoms associated with narcolepsy.

The currently approved Xyrem for narcolepsy, a Schedule 3 controlled substance, was approved as an Orphan drug under Subpart H and includes restricted distribution through a centralized pharmacy as well as a Risk Evaluation and Mitigation Strategy (REMS). The Xyrem label includes a boxed warning for abuse potential, and lists important central nervous system adverse events including seizure, respiratory depression and profound decreases in level of consciousness, with instances of coma and death. Prior to approval, a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee was held in order to discuss the efficacy, safety, and the risk/benefit balance of its use in patients with narcolepsy.

The Applicant submitted NDA 22-531 for sodium oxybate for a new indication of treatment of fibromyalgia. The active moiety of the currently approved Xyrem product, sodium oxybate, for narcolepsy is identical to the active moiety of the proposed product for fibromyalgia, with the only difference being that the approved product is formulated as a 500 mg/mL oral solution concentration whereas the proposed product for fibromyalgia is 375 mg/mL concentration. The labeled dosages of 4.5 g, 6 g, 7.5 g or 9 g are the same for both products. The mechanism of action of sodium oxybate for the treatment of pain in fibromyalgia is unknown, as is the mechanism of action for its use in treatment of narcolepsy. Sodium oxybate has an absolute bioavailability of 88% (although absorption is delayed and decreased by food) with a half-life of approximately 0.5 to 1 hours.

The dosing instructions for the treatment of fibromyalgia and narcolepsy are the same, that is, to administer the drug twice nightly as two equally divided doses diluted with ¼ cup water and taken while lying down, with the first dose taken at bedtime and the second taken 2.5 to 4 hours later.

FDA-Approved Products for the Treatment of Fibromyalgia

There are currently three FDA-approved drugs used to treat fibromyalgia. Lyrica (pregabalin), approved in 2007 for the treatment of fibromyalgia, was the first of the three drugs to be approved, followed by Cymbalta (duloxetine) in 2008, and Savella (milnacipran) in 2009. The indication for all three drugs is “*the management of fibromyalgia*.” Lyrica and Cymbalta have other approved indications in addition to fibromyalgia, whereas Savella is currently indicated only for the management of

fibromyalgia. Labeled efficacy claims for all three relied on pain as the primary endpoint, and the effects on patient function and patient global as secondary endpoints. Labeled assessments for secondary endpoint claims include the Patient Global Impression of Change (PGI-C), Fibromyalgia Impact Questionnaire (FIQ), and Physical Component Summary (PCS) of SF-36.

Table 1, below, summarizes relevant features regarding scheduling and abuse potential of the fibromyalgia-approved drugs as found in the product labels.

Table 1 Currently Approved Fibromyalgia Drugs

Drug Trade Name	Drug Class	Schedule	Labeled Abuse Potential
Lyrica	Pregabalin	Controlled Substance (Schedule V)	Active at receptor sites associated with drugs of abuse.
Cymbalta	SNRI	Not controlled	Has not been systematically studied in humans for its potential for abuse. In animal studies, it did not demonstrate barbiturate-like (depressant) abuse potential.
Savella	SNRI	Not controlled	Did not produce behavioral signs indicative of abuse potential in animal or human studies.

SNRI=Selective serotonin and norepinephrine reuptake inhibitor

Applicant's Rationale for Product Development

The two major diagnostic criteria for classifying fibromyalgia (FM) in adults, as defined in 1990 by the American College of Rheumatology (ACR), are a history of widespread pain for at least 3 months and patient report of tenderness in at least 11 of 18 defined tender points when digitally palpated^{1,2}. The etiology of fibromyalgia is unknown. A 2004 article published in the Journal of the American Medical Association (JAMA)³ has reported a fibromyalgia prevalence of approximately 2% in the adult US population, including 3.4% of women and 0.5% of men. At any one time, 10% to 12% of the general population report chronic generalized musculoskeletal pain that cannot be traced to a specific structural or inflammatory cause.⁴

Although chronic widespread pain is the defining feature of fibromyalgia, patients often also exhibit a range of other symptoms to include sleep disturbance, fatigue, irritable bowel syndrome, headache, and mood disorders.⁵ The Applicant referenced studies

¹ Mease, P. Fibromyalgia Syndrome: Review of Clinical Presentation, Pathogenesis, Outcome Measures, and Treatment. The Journal of Rheumatology 2005, Volume 32 Supplement 75:6-21.

² <http://www.rheumatology.org/practice/clinical/classification/fibromyalgia/fibro.asp>

³ Goldenberg, DL, et al. Management of Fibromyalgia Syndrome. JAMA, November 17, 2004;292(19):2388-2395

⁴ Croft P., et al. The prevalence of chronic widespread pain in the general population. J. Rheumatology. 1993;20:710-713.

⁵ Mease, P. Fibromyalgia Syndrome: Review of Clinical Presentation, Pathogenesis, Outcome Measures, and Treatment. The Journal of Rheumatology 2005, Volume 32 Supplement 75:6-21.

performed by Scharf^{6,7} and colleagues who demonstrated sleep architecture changes relevant to daytime symptom relief, as well as subjective improvement in pain and fatigue, when sodium oxybate was used in fibromyalgia treatment.

The Applicant reports that although sodium oxybate's exact mechanism of action for pain reduction in fibromyalgia is unknown, it is postulated that it inhibits central pain through stimulation of the gamma aminobutyric acid (GABA) subtype B GHB receptor (GABA_BR) which may inhibit spinal neurons and/or excitatory neurotransmitter release in the spinal cord. There may also be actions at supraspinal sites. GHB reportedly does not have activity at mu, delta, or kappa central opioid receptors.

Fibromyalgia Clinical Development

The Applicant has conducted seven clinical trials to assess safety and efficacy of sodium oxybate for the treatment of fibromyalgia. This backgrounder will focus on the two Phase 3, double-blind, placebo-controlled, 14-week studies (06-008 and 06-009) which served as the key studies to support efficacy and the Phase 2, placebo-controlled, double-blind 8-week study (OMC-SXB-26) on which the Applicant plans to rely to support proposed sleep claims.

All Phase 2 and 3 placebo-controlled completed studies, as well as the ongoing, open-label Phase 3 study were conducted in fibromyalgia patients. Three Phase 1 drug-drug interaction studies were conducted in healthy volunteers.

A brief description of the trials is provided in Table 2 below.

⁶ Scharf MB, Hauck M, Stover R, McDannold M, Berkowitz D. Effect of gamma-hydroxybutyrate on pain, fatigue, and the alpha sleep anomaly in patients with fibromyalgia: preliminary report. J Rheumatol 1998a;25(10):1986–90.

⁷ Scharf, MB, Baumann M, and Berkowitz DV. The effects of sodium oxybate on clinical symptoms and sleep patterns in patients with fibromyalgia. J Rheumatol 2003; 30(5): 1070-4.

Table 2: Description of Clinical Trials in Fibromyalgia Development

Trial	Design	Treatments/Number Subjects
06-008 (US) Completed	Phase 3, randomized, double-blind, placebo-controlled, parallel group	Fixed dose SXB (sodium oxybate) 4.5 g or 6g or Placebo nightly x 14 weeks. Randomized: 548 Treated: 547 Completed: 334
06-009 (US & EU) Completed	Phase 3, randomized, double-blind, placebo-controlled, parallel group	Fixed dose SXB 4.5 g or 6g or Placebo nightly x 14 weeks. Randomized: 573 Treated: 571 Completed : 376
OMC-SXB-26 (US) Completed	Phase 2, randomized, double-blind, placebo-controlled, parallel group	Fixed dose SXB 4.5 g or 6g or Placebo nightly x 8 weeks. Randomized: 195 Treated: 192 Completed: 151
06-010 (US & EU) Ongoing	Phase 3, open-label, extension study (Studies 06-008 or 06-009)	Flexible dose SXB 4.5 g, 6 g, 7.5 g, up to 9 g x 38 weeks. Enrolled: 561 Treated: 560 Completed: 228 (interim cut off)
07-005 07-007 07-008 (US) Completed	Phase 1, PK, drug-drug interaction studies	Fixed single dose SXB 2.25 g x 1 day with Duloxetine, Lorazepam or Tramadol. Enrolled: 61 (total all 3 studies combined) Completed: 60 (total all 3 studies combined)

(Source: Table prepared by reviewer from Applicant's submitted data)

REVIEW OF EFFICACY

Xyrem was evaluated for the treatment of fibromyalgia in one Phase 2 and two Phase 3 studies.

- OMC-SXB-26
- 06-008
- 06-009

Brief descriptions of these studies follow.

Study OMC-SXB-26

This was randomized, double-blind, placebo-controlled, parallel group, multi-center, Phase 2 study that examined the efficacy and safety of Xyrem for the treatment of fibromyalgia. Eligible patients that were diagnosed with fibromyalgia according to the American College of Rheumatology (ACR) entered a washout phase in which prohibited medications were withdrawn. Subjects then entered a 1-week baseline period for assessment of fibromyalgia symptoms. Those that continued to meet the enrollment criteria and reported a pain score greater than 4 on an 11-point visual analog scale (VAS) entered an 8-week, double-blind treatment period. Subjects were randomized (1:1:1) to Xyrem 4.5 g/night, Xyrem 6.0 g/night, or placebo. The primary measure of efficacy was

a composite response based on pain severity, functionality (FIQ), and patient global impression of change (PGIc). A patient was considered a responder if they met the following criteria at Week 8: at least a 20% reduction in baseline pain and FIQ scores and a score of “much better” or “very much better” on the PGIc. This study also included an objective measurement of sleep using polysomnography (PSG).

Statistical Methods and Results

The proportions of responders in each treatment were compared with a Chi-square test. This analysis was conducted on the intent-to-treat (ITT) population which included all randomized patients that received at least one dose of study drug. If an overall treatment effect was observed, then pair-wise comparisons between the Xyrem dose groups and placebo were conducted to identify effective doses. Missing values were imputed using the last observation carried forward (LOCF) and baseline observation carried forward (BOCF) imputation strategies.

Table 1: Primary Efficacy Results (Study OMC-SXB-26)

Analysis	Placebo (n=66)	Xyrem		Overall <i>P</i> value ^a
		4.5 g/night (n=62)	6 g/night (n=67)	
ITT Population				
LOCF Analysis	62	57	64	
Responders, n (%)	8 (12.9)	17 (29.8)	18 (28.1)	0.052
Comparison to placebo <i>P</i> value ^a		0.024	0.035	
BOCF Analysis	66	62	67	
Responders, n (%)	8 (12.1)	16 (25.8)	16 (23.9)	0.112
Comparison to placebo <i>P</i> value ^a		0.047	0.078	
Observed Data	54	52	49	
Responders, n (%)	8 (14.8)	17 (32.7)	17 (34.7)	0.041
Comparison to placebo <i>P</i> value ^a		0.030	0.019	

Note: Responder = a subject who achieved a PGIc response (‘very much better’ or ‘much better’), $\geq 20\%$ reduction in pain VAS from baseline, and $\geq 20\%$ reduction in FIQ total score from baseline

^a Chi-square test

Source: Table 5 from Applicant’s Study Report

A higher percentage of patients receiving Xyrem were responders compared to patients receiving placebo. The LOCF analysis resulted in a marginally significant p-value; however, the LOCF imputation strategy potentially assigned good scores to patients withdrawing because of bad outcomes. The more conservative analysis employing a BOCF imputation strategy failed to demonstrate a statistically significant overall treatment effect.

Since Study OMC-SXB-26 was the only study that utilized objective sleep parameters and the sleep parameters are proposed in the label, the Agency conducted exploratory analyses of the primary efficacy outcome defined in the Phase 3 studies, proportion of patients achieving at least a 30% reduction in baseline pain at the end of the study, and the individual components of the PSG. The Applicant analyzed the individual components of the PSG as the mean changes from baseline at Week 8 using observed data only and no adjustments for multiplicity. The Agency conducted these analyses

using the ITT population and the Holm's procedure to maintain the overall type I error at 0.05.

Table 2: Responder defined as $\geq 30\%$ reduction in baseline pain (Study OMC-SXB-26)

Treatment	n	Responders, n (%)	p-value (Chi-square test)
Placebo	65	12 (18)	-
Xyrem 4.5g	60	25 (42)	0.005
Xyrem 6.0g	67	27 (40)	0.006

Table 3: ITT Analysis of PSG parameters (Study OMC-SXB-26)

PSG measurement	Mean Change (stdev)			Adjusted p-value	
	Placebo (n=63)	Xyrem 4.5 (n=59)	Xyrem 6.0 (n=64)		
Stage 1 Sleep (min)	3 (21)	5 (19)	6 (23)	0.7	
Sleep Onset Latency (min):	1 st 4 hrs	-1 (43)	-2 (20)	3 (29)	1.0
	2 nd 4 hrs	-2 (29)	-5 (20)	-1 (13)	1.0
Stage 3/4 Sleep (min)	1 (31)	-10 (43)	-14 (40)	0.28	
Stage 2 Sleep (min)	-16 (55)	-4 (52)	-30 (69)	0.25	
Total Sleep Time (min)	-8 (70)	9 (46)	-25 (75)	0.12	
NREM Sleep (min)	-11 (56)	-9 (49)	-37 (71)	0.07	
REM Sleep (min)	2 (30)	18 (30)	13 (32)	0.056	
Sleep Efficiency (%)	-3 (15)	2 (10)	-5 (13)	0.045	
Wake after sleep (min)	14 (42)	-5 (42)	24 (52)	0.02	

As there was suggestive evidence of an overall treatment effect for sleep efficiency and wake after sleep onset, pair-wise comparisons of the individual Xyrem doses and placebo were conducted.

Table 4: Pair-wise comparisons of endpoints of significant endpoints (Study OMC-SXB-26)

PSG measurement	Mean Change from start of study		
	Placebo	Xyrem 4.5	Xyrem 6.0
Sleep Efficiency (%)	-3 (15)	2 (10)	-5 (13)
Comparison to placebo, p-value		0.04	0.2
Wake after Sleep	14 (42)	-5 (42)	24 (52)
Comparison to placebo, p-value		0.03	0.2

The comparison of Xyrem 4.5 to placebo suggests a possible treatment effect on wake after sleep onset. The result for sleep efficiency was actually in the wrong direction, efficacy was higher at the start of the study than at the end. Overall, these results are inconclusive and do not provide substantial evidence that Xyrem is better than placebo on the individual PSG parameters.

Studies 06-008 and 06-009

These were randomized, double-blind, placebo-controlled, multi-center, Phase 3, parallel-group, repeat-dose clinical trials. Study 06-008 was conducted at 74 centers in the United States. Study 06-009 was conducted at 67 centers in the United States and 41 centers in Europe. Subjects that were diagnosed with fibromyalgia according to the ACR and met enrollment criteria underwent a 2-week baseline assessment period. Patients were gradually withdrawn from any medication being used to alleviate pain or for treatment of fibromyalgia. Patients that maintained an average pain score greater than 50 mm on a 100 mm VAS pain scale were randomized 1:1:1 to placebo, Xyrem 4.5 g, or Xyrem 6.0 g.

The primary measure of efficacy was the proportion of subjects who achieved at least a 30% reduction in overall pain from baseline to Week 14. Five secondary endpoints were tested sequentially if there was a significant overall treatment effect observed with the primary endpoint. These are listed in order as follows:

1. Functionality Response (FIQ): The proportion of subjects who had at least a 30% reduction in FIQ total score from baseline at Week 14.
2. Fatigue VAS 100 mm: The mean change from baseline and Week 14.
3. PGIC: The proportion of subjects who had a response of “much better” or “very much better”
4. SF-36 Physical Component Summary (PCS): The mean change from baseline and Week 14.
5. Jenkins Sleep Scale: The mean change from baseline and Week 14 in Jenkins Scale (JS).

Statistical Methods and Results

The primary efficacy endpoint was analyzed using a Chi-square test. If there was an overall treatment effect, the individual Xyrem doses were compared to placebo. Analysis of sequentially tested secondary endpoints depended on the type of data. Proportions were compared using a Chi-square test, and continuous endpoints were analyzed using

analysis of variance (ANOVA) methods. The ANOVA model included terms for treatment and pooled center. To maintain the overall type I error at 5%, the Applicant sequentially tested the five secondary endpoints. If there was an overall treatment effect observed for the primary endpoint, the first key secondary was tested, if it showed a significant overall treatment effect, the next endpoint was tested, and so forth. The Applicant's method for handling missing data was BOCF.

Table 4: Primary Efficacy Results of Phase 3 Studies (06-008 and 06-009)

Study	Treatment	n	Responders, n (%)	p-value (Chi-square test)
06-008	Placebo	183	50 (27)	-
	Xyrem 4.5g	182	84 (46)	<0.001
	Xyrem 6.0g	182	72 (40)	0.01
06-009	Placebo	188	38 (20)	-
	Xyrem 4.5g	194	69 (36)	<0.001
	Xyrem 6.0g	189	68* (36)	<0.001

Analyses of the primary endpoint demonstrated a significant treatment effect in both studies regardless of dose. The Applicant proposed to sequentially test the five secondary endpoints. If there was an overall treatment effect observed in the analysis of the primary endpoint, the first secondary endpoint would be tested. If the analysis of the first secondary demonstrated an overall treatment effect, the next secondary endpoint would be tested, and so forth. This approach could be problematic since the requirement of an overall treatment effect to test sequential endpoints does not account for the comparisons of individual doses to placebo for each endpoint. To alleviate this concern, the Agency conducted sequential testing within each dose.

Table 5: Primary Efficacy Results Phase 3 Studies (06-008 and 06-009)

Study	Sequentially tested endpoints	p-value for comparison to placebo	
		Xyrem 4.5 g	Xyrem 6.0 g
06-008	1. FIQ	0.002	0.06
	2. Fatigue VAS	< 0.001	0.02
	3. PGlc	0.001	0.02
	4. PCS	0.001	< 0.001
	5. Jenkins	< 0.001	< 0.001
06-009	1. FIQ	<0.001	<0.001
	2. Fatigue VAS	<0.001	<0.001
	3. PGlc	0.002	<0.001
	4. PCS	0.002	0.003
	5. Jenkins	0.008	<0.001

For both studies, comparison of Xyrem 4.5 to placebo demonstrated a significant treatment effect for the five sequentially tested secondary endpoints. In Study 06-008, Xyrem 6.0 failed to show a significant treatment effect for the first sequentially tested endpoint. In Study 06-009, Xyrem 6.0 was highly significant for all endpoints.

REVIEW OF SAFETY

The Tradename for sodium oxybate for the proposed fibromyalgia indication has not been established. In this safety review, the term sodium oxybate (SXB) is used to refer to the study drug and Xyrem is used to denote the already approved product.

The Applicant's submission included pooled safety data from a total of 1,060 fibromyalgia patients who received sodium oxybate during Phase 2/3 fibromyalgia clinical trials (including 397 patients treated for at least 26 weeks and 160 patients treated for at least 52 weeks). Non-pooled data from integrated narcolepsy clinical development, summarized postmarketing data, and other published information pertinent to sodium oxybate's safety were also included in the Applicant's submission and reviewed.

Major Safety Results

Fibromyalgia Clinical Trials

Deaths: There were no deaths in the Phase 1, 2 or 3 studies.

Serious Adverse Events (SAEs): In the Phase 2/3 studies (controlled and uncontrolled, all-treated), there were 26 of 1,060 sodium oxybate-treated subjects (2.5%) who experienced at least one treatment-emergent serious adverse event (SAE). In the Phase 2/3 placebo-controlled studies, more subjects experienced SAEs in the sodium oxybate-treated (1%) than in the placebo (0.9%) groups. There were more sodium oxybate-treated subjects who experienced SAEs in the uncontrolled Phase 3 study (19 total) than sodium oxybate-treated subjects in the controlled studies (9 total) or Placebo (4 total). There was no clear dose-related effect.

Only the preferred terms chest pain, diverticulitis, and cholelithiasis were reported in more than one subject in any dose group.

AEs Leading to Discontinuation: Treatment-emergent adverse events (TEAEs) leading to discontinuation in the Phase 3, placebo-controlled studies occurred in 19% of All-sodium oxybate-treated compared to 8% of placebo-treated patients. Nervous system disorders was the SOC with the most TEAEs leading to discontinuation (7%) followed by Psychiatric disorders (6%) and GI disorders (6%). The MedDRA System Organ Class and Preferred Term of TEAEs leading to discontinuation occurring in $\geq 2\%$ of subjects at any sodium oxybate dosage or All-sodium oxybate-treated groups in Phase 3 placebo-controlled studies are shown in Table 3 below.

Table 3 . TEAEs Leading to Study Discontinuation Occurring in $\geq 2\%$ by System Organ Class (SOC) or Preferred Term Phase 3, Placebo-Controlled Studies

MedDRA SOC/Preferred Term	Placebo N (%)	SXB 4.5 g N (%)	SXB 6 g N (%)	All SXB N (%)
Number of Subjects	N=371	N=376	N=371	N=747
Subjects with any AE Leading to Study Discontinuation	30 (8)	64 (17)	81 (22)	145 (19)
Nervous system disorders	7 (2)	17 (4)	32 (9)	50 (7)
Headache	0	5 (1)	16 (4)	21 (3)
Dizziness	0	6 (2)	10 (3)	16 (2)
Somnolence	3 (1)	1 (<1)	6 (2)	7 (1)
Psychiatric disorders	9 (2)	17 (4)	29 (8)	46 (6)
Anxiety	2 (<1)	4 (1)	10 (3)	14 (2)
Insomnia	2 (<1)	6 (2)	5 (1)	11 (2)
Depression	4 (1)	1 (<1)	6 (2)	7 (1)
Gastrointestinal disorders	7 (2)	18 (5)	25 (7)	43 (6)
Nausea	2 (<1)	11 (3)	14 (4)	25 (3)
Vomiting	1 (<1)	5 (1)	13 (3)	18 (2)
Diarrhea	0	2 (<1)	8 (2)	10 (1)
General disorders and administration site conditions	6 (2)	8 (2)	19 (5)	27 (4)
Fatigue	1 (<1)	3 (1)	6 (2)	9 (1)

(Source: Table prepared by reviewer, modified from Applicant's table in ISS; percentages approximated)

Common AEs: In the Phase 2/3 placebo-controlled studies, AEs occurred more frequently in the All-sodium oxybate treated (~79%) than placebo (~62%). Most AEs in the All-sodium oxybate-treated group were mild (30%) or moderate (~37%). In the Phase 2/3 placebo-controlled studies, severe AEs occurred with more frequency in the All-sodium oxybate-treated (11.3%) compared to placebo (4.6%). The most common AEs in the fibromyalgia controlled clinical trials were headache, nausea and dizziness as shown in Table 4, below.

Table 4. AEs Occurring in $\geq 5\%$ All-Sodium Oxybate-Treated (Preferred Term) Phase 2/3 Controlled Studies

Treatment Groups	Placebo N (%)	SXB 4.5 g N (%)	SXB 6 g N (%)	All SXB N (%)
Number of Subjects	N=436	N=436	N=438	N=874
MedDRA SOC/Preferred Term				
Nervous system disorders				
Headache	60 (14)	77 (18)	96 (22)	173 (20)
Dizziness	10 (2)	52 (12)	68 (15)	120 (14)
Gastrointestinal disorders				
Nausea	32 (7)	74 (17)	98 (22)	172 (20)
Diarrhea	24 (5)	28 (6)	36 (8)	64 (7)
Vomiting	13 (3)	23 (5)	39 (9)	62 (7)
Infections and Infestations				
Nasopharyngitis	17 (4)	23 (5)	30 (7)	53 (6)
Psychiatric disorders				
Anxiety	5 (1)	25 (6)	26 (6)	51 (6)

(Source: Table prepared by reviewer, modified from Applicant's submitted table in ISS; percentages approximated)

AEs of Special Interest: The following AEs were of special interest either due to the known safety profile of sodium oxybate or identified during the review:

- Depression: In the Phase 3 fibromyalgia studies, subjects were excluded for a current diagnosis or current treatment of major depressive disorder. The incidence of depression in the Phase 2/3 controlled studies was 2.3% in all-sodium oxybate treated compared to 1.1% placebo. The incidence was slightly higher in the sodium oxybate 6 g group (2.7%) compared to sodium oxybate 4.5 g (1.8%). There was one report of depression with suicidal ideation in the fibromyalgia trials.
- Respiratory depression: In the fibromyalgia clinical trials, patients were excluded if they had known obstructive sleep apnea syndrome (OSAS) and were not receiving continuous positive airway pressure (CPAP). Unresponsiveness was reported in one patient who experienced an SAE of sleep paralysis and was unresponsive to stimuli. The most frequently reported MedDRA preferred term respiratory-related AE was dyspnea (1.5%) in all-sodium oxybate-treated, compared to 0.9% in placebo.
- Overdose: In the fibromyalgia clinical trials, there were no reported cases of intentional overdose. There were four reported cases of dosing >9 g/night. One of these subjects experienced AEs of nausea and feeling jittery; another experienced an SAE of encephalopathy; the other two had no reported AEs.

Comparison of Fibromyalgia and Narcolepsy Safety Data

The Applicant provided summarized safety data from a total of 10 integrated narcolepsy clinical efficacy and safety studies in 781 patients.

Headache, dizziness and nausea were the most frequently occurring AEs in both fibromyalgia and narcolepsy trials in the all-treated Xyrem or sodium oxybate groups. Depression, somnolence and enuresis were AEs of interest which occurred with higher frequency in the narcolepsy trials than in the fibromyalgia trials. Adverse events which occurred more frequently in fibromyalgia trials than narcolepsy trials included anxiety (8%), insomnia (7%), and muscle spasms (6%). Frequently occurring TEAEs in the narcolepsy and fibromyalgia trials are summarized in Table 5.

Table 5. AEs Occurring in >5% All –Treated TEAEs by MedDRA Preferred Term in Narcolepsy and Fibromyalgia Trials

	Narcolepsy Trials	Fibromyalgia Trials
Treatment Group	All Xyrem N= 781	All sodium oxybate N=1060
% Experiencing Any AE	86	86
MedDRA preferred term		
Nausea	24	25
Headache	24	23
Dizziness	18	17
Nasopharyngitis	14	9
Somnolence	10	6
Influenza	9	5
Vomiting	9	10
Arthralgia	9	2
Upper respiratory tract infection	8	5
Diarrhea	8	10
Sinusitis	8	8
Back pain	8	4
Enuresis	8	<1
Depression	7	4
Fatigue	5	5
Pain in extremity	5	4
Sleep walking	5	<1
Anxiety	*	8
Insomnia	*	7
Muscle spasms	*	6

*Data not provided (Source: Narcolepsy trial data from Applicant's submission, referenced Table 15 in the Xyrem ISS for narcolepsy, submitted to NDA 21-196 in 2006)

The Applicant reported that there appeared to be a dose effect in the narcolepsy trials but no definite dose effect was seen in the fibromyalgia trials.

Caution should be used when comparing safety results between the fibromyalgia and narcolepsy trials due to the difference in patient populations, inclusion/exclusion criteria, permitted concomitant medications, and study designs.

Post Marketing Safety of Currently Approved Xyrem: The Applicant reports that an estimated 26,000 patients in the US, EU and Canada have received treatment with

commercial sodium oxybate at various doses during the period from product introduction in 2002 through March, 2008. Since the drug's approval, a pre-approval labeling supplement which contains the addition of the term, *anxiety*, has been submitted to the Agency and is pending action.

The following AEs were of special interest either due to the known safety profile of sodium oxybate or identified during the review:

- **Drug-induced vulnerability:** Four (4) cases were identified of sexual assault in which sodium oxybate was involved. Three of the four cases were postmarketing cases involving sexual assault and of those three cases, the use of sodium oxybate was confirmed in two. The fourth case occurred during a narcolepsy clinical trial (2002) in which an individual participating in the trial reported being sexually assaulted while enrolled in the study.
- **Abuse/Misuse:** Worldwide, there have been five confirmed reports of drug diversion.
- **Suicide:** There was one reported completed suicide with polydrug use (including sodium oxybate). Seven reported suicide attempts involving sodium oxybate overdose (with or without the involvement of other drugs or substances) were identified.
- **Deaths:** There were 21 reported deaths through 2008. Six were determined not due to sodium oxybate, seven were unknown cause, three were drug overdose with more than one drug involved and one case each of accidental drowning, suicide, renal failure, cardiac arrest and metastatic lung cancer. There were 51 deaths through November, 2009 (approximately 32,000 exposures). Causality was not assigned by the Applicant.

Safety Summary: The overall safety profile in fibromyalgia patients is similar to the established safety profile for that found in the currently-approved Xyrem label.

Conclusions:

- The Applicant has provided sufficient evidence to support the efficacy of sodium oxybate for the treatment of fibromyalgia.
- The Division determined that the efficacy analyses of the data do not support the Applicant's proposed labeling claims of improved sleep.
- The general safety profile in fibromyalgia is consistent with the currently approved Xyrem in narcolepsy.

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MEMORANDUM

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

**Division of Neurology Products (HFD – 120)
Center for Drug Evaluation and Research**

Date: July 12, 2010

**From: Russell G. Katz, M.D.
Division Director**

**Subject: NDA 22531
Xyrem®
Fibromyalgia**

**To: Director
Division of Anesthesia and Analgesia Products**

Document Type: Consult (Summary Only)

Review and Evaluation of Clinical Data

NDA (Serial Number)	22531 (000)
Sponsor:	Jazz Pharmaceuticals
Drug:	Sodium Oxybate
Proposed Indication:	Fibromyalgia
Material Submitted:	Original NDA/Consult
Correspondence Date:	12/11/09
Date Received By Reviewer:	4/16/10
Date Review Completed:	7/12/10
Reviewer:	Ranjit B. Mani, M.D.

SUMMARY

Background

The Division of Neurology Products has been consulted regarding this original New Drug Application (NDA) which seeks the approval of sodium oxybate oral solution 375 mg/mL for the treatment of fibromyalgia.

In the consultation request, the Division of Anesthesia and Analgesia Products, the primary reviewing division for this application, refers to text describing a beneficial effect of sodium oxybate on measures of sleep, in patients with fibromyalgia, in the proposed product labeling accompanying this application, and asks if those claims are substantiated by the submitted data.

Statements regarding the beneficial effects of sodium oxybate on sleep in patients with fibromyalgia are made in descriptions of the results of 3 controlled clinical studies that are contained in Section 14 ("Clinical Studies") of the proposed product label. These studies are OMC-SXB-26, 06-008, and 06-009.

Sodium oxybate oral solution (500 mg/mL) is currently approved by this Agency under the proprietary name "Xyrem®" for the treatment of excessive daytime sleepiness and cataplexy in narcolepsy.

Summary Of Pertinent Clinical Data

As already noted, the results of three efficacy studies of sodium oxybate in fibromyalgia (Studies OMC-SXB-26, 06-008, and 06-009) are the basis for the statements in proposed product labeling that describe a beneficial effect of sodium oxybate on measures of sleep. The results of each study that are pertinent to this consultation are further summarized below.

Study OMC-SXB-26

This was a randomized, double-blind, placebo-controlled, parallel-arm study whose objective was to evaluate the efficacy and safety of sodium oxybate oral solution as a treatment for fibromyalgia.

195 patients aged over 18 years who were diagnosed to have fibromyalgia using the American College of Rheumatology criteria were randomized in about equal proportions to 3 treatment groups for the 8-week parallel-arm duration of the trial. The 3 treatment groups were as follows.

- Sodium oxybate 4.5 g/night (in 2 equally divided doses)
- Sodium oxybate 6.0 g/night (in 2 equally divided doses)
- Placebo

The primary efficacy measure was the Fibromyalgia Syndrome Composite response, consisting of the proportion of subjects who met all three of the following response criteria:

- A reduction in average pain of 20% or greater on the visual analog scale from baseline to Week 8
- A reduction of 20% or greater in Fibromyalgia Impact Questionnaire score (considered a measure of functionality) from baseline to Week 8
- "Very much better" or "much better" on the Patient Global Impression of Change rated at the end of the study.

The primary efficacy analysis revealed a higher proportion of responders in each of the sodium oxybate groups as compared with the placebo group. While the overall p-value for that analysis was borderline statistically significant ($p = 0.052$), the subsequent comparison of each sodium oxybate dose group with placebo yielded p-values that were more clearly statistically significant.

This study had numerous secondary efficacy measures, and the pre-specified statistical analysis plan had no provision for preserving the overall Type 1 error during the analysis of those parameters. However, at least nominally statistically significant treatment differences favoring each dose of sodium oxybate over placebo were seen for the change from baseline in each of the following subjective secondary efficacy measures of sleep: Epworth Sleepiness Scale (total score); Jenkins Sleep Scale (total score); and the Functional Outcomes of Sleep Questionnaire (total score). The sodium oxybate dose group that received 6 g/night also showed a nominally statistically significant superiority to placebo on some, but not all, parameters derived from clinical polysomnography: these included changes from baseline in the following: duration awake after sleep onset (decrease); duration of REM sleep (decrease); duration of NREM sleep (increase); duration of Stage 2 sleep (increase); and duration of Stage 3-4 sleep (increase). A nominally statistically significant decrease in the duration of REM sleep was also seen at the 4.5 g/night dose.

Studies 06-008 and 06-009

These studies were similar in their design and results and are therefore described together.

Each was a randomized, double-blind, placebo-controlled, parallel-arm study whose objective was to evaluate the efficacy and safety of sodium oxybate oral solution as a treatment for fibromyalgia.

In each study, patients aged over 18 years who were diagnosed to have fibromyalgia using the American College of Rheumatology criteria were randomized in about equal proportions to 3 treatment groups for the 14-week parallel-arm duration of the trial. The 3 treatment groups were as follows.

- Sodium oxybate 4.5 g/night (in 2 equally divided doses)
- Sodium oxybate 6.0 g/night (in 2 equally divided doses)
- Placebo

A total of 548 patients was randomized in Study 06-008 and a total of 573 patients in Study 06-009.

In each study, the primary efficacy measure was the Pain Severity Response consisting of the proportion of subjects who had at least a 30% reduction in overall pain from baseline to Week 14. In each study, if an overall statistically significant treatment difference was demonstrated on the primary efficacy analysis, a set of 5 selected secondary efficacy measures was then to be sequentially analyzed (at a level of significance of 0.05 at each step, but ceasing if statistical significance failed to be reached at any level) if the analysis of the primary efficacy measure showed an overall statistically significant difference ($p < 0.05$). Those secondary measures, in the sequence in they were to be analyzed, were as follows: Functionality Response (derived from the Fibromyalgia Impact Questionnaire); fatigue score from the visual analog scale; proportion of subjects with ratings of “very much better” or “much better” on the Patient Global Impression of Change; Physical Component Summary score from the Short Form-36 questionnaire; and, finally, the total score from the Jenkins Sleep Scale. For each secondary efficacy measure, the change from baseline to Week 14 was to be analyzed. At each level where the overall p-value was statistically significant, pairwise comparisons of each sodium oxybate treatment group with placebo were then to be performed at the same level of significance.

The results of the above efficacy analyses showed similar results for both studies: a statistically significant superiority of both doses of sodium oxybate over placebo on each of the 6 measures sequentially analyzed, beginning with the analysis of the primary efficacy measure; these included the analysis of change from baseline to Week 14 in the Jenkins Sleep Scale total score for both studies.

Proposed Statements (In Product Labeling) Regarding Beneficial Effects Of Sodium Oxybate On Sleep In Fibromyalgia

In the description of Studies 06-008 and 06-009, referred to, respectively, as Trials 1 and 2 in the draft product label, it is stated that patients in both trials treated with sodium oxybate showed an improvement in sleep based on Jenkins Sleep Scale scores, an effect which is displayed in an accompanying table in the draft label.

In the description of Study OMC-SXB-26, referred to as Trial 3 in the draft product label, the sponsor states that improvements in sleep were similar to those seen in Trials 1 and 2. It is also stated that there were improvements in a number of clinical polysomnography-derived parameters (which are listed) in those treated with either the 6 g/night dose alone, or both doses, of sodium oxybate.

Comments On Proposed Labeling Text Describing Effects Of Sodium Oxybate On Sleep In Fibromyalgia

The effects of sodium oxybate on sleep in fibromyalgia that are proposed for description in the product label are all based on the analysis of secondary efficacy measures.

In deciding what analyses based on secondary efficacy measures should be described in product labeling, our Division has generally applied the following criteria.

- The secondary efficacy measures whose analyses are intended for description in the product label should have been prospectively specified
- The prospectively-specified statistical analysis plan for those secondary efficacy measures should have included methods for preserving the Type 1 error.
- The results of the analyses of the secondary efficacy measures that are prospectively specified for inclusion in labeling should have been replicated.
- The secondary efficacy measures whose analyses are intended for description in the product label should address domains other than those covered by the primary efficacy measure (or measures).

We have also preferred that agreement be reached a priori between the sponsor and our Division as to which secondary efficacy measures are appropriate for inclusion in the product label.

Applying the above criteria, the inclusion of a description of the effects of sodium oxybate on sleep as seen on the change from baseline to Week 14 in the Jenkins Sleep Scale total score in Studies 06-008 and 06-009 may have at least some justification. While that instrument may not be as widely used in clinical trials as other measures such as the Epworth Sleepiness Scale, there is both face validity and relevant prior clinical trial experience with the Jenkins Scale. Furthermore, the beneficial effects of that instrument in Studies 06-008 and 06-009 have been

seen using a prospectively-designated method of analysis that included provision for preserving the overall Type 1 error, and have been replicated to a similar degree in both studies; a beneficial effect on that instrument at at least a nominally statistically significant level has also been seen at the same doses of sodium oxybate in Study OMC-SXB-26.

Nevertheless, it is difficult to determine to what extent the beneficial effect of sodium oxybate on sleep in Studies 06-008 and 06-009, as described above is distinct from its effects on the primary efficacy measure, the Pain Severity Response. For example, could the apparent beneficial effects of sodium oxybate on sleep have been primarily responsible for an improvement in pain, as also postulated by the sponsor, or could a reduction in pain have been responsible for improved sleep? In either circumstance, a description of the effects of sodium oxybate on sleep might be redundant, if not misleading, given that the effect of that compound on pain in fibromyalgia has already been described under the results of the primary efficacy analysis.

Thus, a description of the effects of sodium oxybate on measures of sleep in Studies 06-008 and 06-008 may not be quite justified by the available data and additional considerations above.

There may be an even less substantial basis for including a description of the effects of sodium oxybate on measures of sleep in Study OMC-SXB-26 in product labeling, even if those effects were at least nominally statistically significant, and were seen at very low p-values in a number of instances, as well as on many measures in that category. Here, there was no plan for preserving the overall Type 1 error during the analysis of even some of those measures. Furthermore, in this study too, it is also unclear to what degree the apparently beneficial effects of sodium oxybate on sleep are distinct from the effects of that compound on the composite primary efficacy measure which is intended to assess a combination of pain, functionality, and the patient's global assessment of significant improvement.

Should the sponsor wish to include one or more statements in product labeling asserting that sodium oxybate has a beneficial effect specifically on sleep (in fibromyalgia), and should the primary reviewing division judge that a beneficial effect on sleep is sufficiently distinct from an overall effect on fibromyalgia (as measured by outcomes such as the primary efficacy measures for Studies OMC-SXB-26, 06-008, and 66-009) and therefore warrants its own description in product labeling, a separate randomized, controlled clinical study of sodium oxybate should be conducted specifically for that purpose. Such a study should have as co-primary efficacy measures an objective instrument such as the Wake After Sleep Onset (WASO) measurement derived from clinical polysomnography and a subjective measure such as the subjective WASO derived from patient diaries; the latter measure will be needed so as to confirm that the effect on

the objective WASO is clinically meaningful. Under those circumstances, it will also be important that any beneficial effects that are seen on the objective and subjective WASO not be accompanied by a worsening in other measures such as sleep latency.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 7/12/10
cc:
HFD-120
NDA 22531 (000)

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MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 21, 2010

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (CSS)

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff (CSS)

Subject: NDA 22-531 - Rekinla (proposed tradename) (Sodium Oxybate)

Indication: Treatment of Fibromyalgia

Company: Jazz Pharmaceuticals

Submission: NDA 22-531 is located in the EDR.

Summary

Jazz Pharmaceuticals filed NDA 22-531 for approval of sodium oxybate (375 mg/ml) oral solution for the treatment of fibromyalgia for patients 18 years of age and older. On August 20, 2010, a joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee to consider the safety and efficacy findings and REMS proposal for sodium oxybate under consideration for treatment of fibromyalgia (NDA 22-531). We provide below some background information with our conclusions and recommendations concerning NDA 22-531.

Background

Sodium oxybate is a central nervous system depressant currently approved under the trade name of Xyrem for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. According to estimates from the National Institute of Neurological Disorders and Stroke, National Institute of Health (NIH), approximately 1 in every 2,000 individuals in the United States (approximately 154,000) suffers from narcolepsy.

Sodium oxybate is currently under review for possible approval to treat fibromyalgia. Although information on the prevalence of fibromyalgia is limited, it is estimated by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH) that approximately 5 million individuals in the United States suffer from fibromyalgia. Approval of sodium oxybate for treatment of fibromyalgia could potentially increase the number of individuals exposed to the drug.

As a central nervous system depressant, sodium oxybate has the potential to cause adverse events as a single agent or in combination with concomitant medications such as opioids and sedative/hypnotics. Such adverse events may be seen in fibromyalgia patients being treated with drugs along with sodium oxybate.

Sodium oxybate (as GHB) is known to be a drug that is abused and misused. It is most often abused in an illicit, nonpharmaceutical form. Since placement of sodium oxybate into Schedule I of the Controlled Substances Act in 2000, abuse and trafficking of nonpharmaceutical sodium oxybate has declined, but has not been eliminated. Xyrem, the pharmaceutical product containing sodium oxybate, also has the potential to be abused and is currently in Schedule III of the Controlled Substances Act. Since the introduction of Xyrem on the United States market in 2002, the number of documented cases involving abuse, misuse, or diversion of Xyrem is very low. This could be due in part to the controls placed on the distribution of Xyrem and the difficulty of detecting cases specifically involving Xyrem.

Proposed REMS for the sodium oxybate product intended for treatment of fibromyalgia calls for distribution from multiple, registered pharmacies with a hard stop available to prevent inappropriate prescribing and access. This contrasts with the current REMS for Xyrem, in which restrictive distribution of the product comes from a single, centralized pharmacy. The proposed REMS also calls for the certification of prescribers of the sodium oxybate product as well as enrollment of patients in a database maintained by Jazz Pharmaceuticals. Certification, patient enrollment, prescription verification and monitoring will be tracked by a "central processing function." Education regarding potential adverse events of sodium oxybate as well as appropriate safe use and handling of the product will be provided and required of certified prescribers and pharmacies as well as enrolled patients. The Sponsor also provided a proposed plan to evaluate the effectiveness of the education material.

Conclusions

1. In contrast to the number of sodium oxybate treated narcolepsy patients, a much larger population of fibromyalgia patients is likely to be exposed to sodium oxybate.
2. The distribution restrictions of sodium oxybate containing products for its various approved indications has to take into consideration patient access and the possible

increases in rates of abuse, misuse (including drug facilitated sexual assault) and diversion.

3. Approval of sodium oxybate for treatment of fibromyalgia may also result in increased reporting rates of adverse reactions due to interactions of sodium oxybate with other central nervous system depressants used in the fibromyalgia patient population.
4. In addition, sodium oxybate is a drug of abuse and misuse. The illicit, nonpharmaceutical form is a Schedule I controlled substance. Pharmaceutical products (Xyrem) containing sodium oxybate are currently in Schedule III. Any product containing sodium oxybate and approved for fibromyalgia will be similarly scheduled.

Recommendations

1. A detailed postmarketing surveillance and monitoring program is needed in order to positively identify and document cases of abuse, misuse (including facilitated sexual assault) diversion and overdoses involving approved products containing sodium oxybate. This program should include provisions for reporting of these cases to the FDA on a regular basis.
2. Continued assessment of any changes in rates of abuse, misuse, diversion, and malicious use needs to be conducted in order to provide assurance that the product continues to be appropriately scheduled in the CSA.