

Final Minutes

Peripheral and Central Nervous System Drugs Advisory Committee

June 6, 2001

Xyrem®, Orphan Medical Inc.

Consideration of (NDA) 21-196, Xyrem® (sodium oxybate, Orphan Medical, Inc.), proposed to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness for persons with narcolepsy. A main focus of the deliberations will be on risk management issues.

The meeting was held at the Holiday Inn, in Bethesda, Maryland. Prior to the meeting, the members, consultants and guests had reviewed background material from the FDA. In order for the public to be informed, the background material was also available on the Dockets page before the meeting. There were approximately 130 persons in attendance. The meeting started at 8 a.m. and ended at 6:00 p.m.

Attendance:

PCNS and Consultants Present: Claudia Kawas, M.D., Acting Chair ,
Gerald Van Belle, Ph.D., LeRoy Penix , M.D., Jerry Wolinsky, M.D., Richard Penn, M.D.,
Ella Lacey, Ph.D,

PCNS Consultants Absent: Howard Weiner, M.D, Michael Grundman, M.D.,

Substance Abuse Consultants: Pippa Simpson, Ph.D., Carol Falkowski, Ph.D., Christine Sannerud,
Ph.D. (non-voting)

Substance Abuse Guest Speakers (non-voting): Jerry Frankenheim, Ph.D., JoEllen Dyer, Ph.D.,

Neurology – Sleep Guest Speakers (non-voting) Christian Guilleminault, M.D., Ronald Chervin, M.D.
(Both receiving webcast and on direct phone link)

FDA Participants: Robert Temple, M.D., Russell Katz, M.D, Ranjit Mani, M.D., Deborah Leiderman, M.D.,
Sharon Yan, Ph.D.

Overview of FDA's Presentation:

Russell Katz, M.D., gave an overview of the FDA questions for the meeting.

Orphan Medical Presentations

Introduction

Dayton Reardan, Ph.D., Orphan Medical

Medical Need, Efficacy and Safety

Emanuel Mignot, M.D., Stanford University Sleep Clinic

Efficacy

William Houghton, M.D., Orphan Medical

Polysomnographic Effects of Xyrem

Jed Black, M.D., Stanford University Sleep Clinic

Safety and Summary of Risks versus Benefits

Bill Houghton, M.D., Orphan Medical

RISK MANAGEMENT PRESENTATIONS

FDA invited speakers:

Epidemiology of GHB Abuse Issues

Carol Falkowski, Hazelden Foundation, Minnesota

Adverse Medical Effects with GHB

Jo Ellen Dyer, Pharm.D. California Poison Control System -San Francisco, University of California San Francisco

Sponsor Presentations on Risk Management and Abuse Liability

Bob Balster, Ph.D., Medical College of Virginia

Risk Management

Patti Engel, RN, BSN, Orphan Medical

PUBLIC SPEAKERS:

All speakers had been asked to limit their comments to five minutes. All have also been asked to disclose any potential conflicts of interest before they begin their statement.

Sharon Fitzgerald, Littleton, Colorado

Abbey S. Meyers, President, National Organization for Rare Disorders, Inc®

Robert L. Cloud, Narcolepsy Network, Inc.

Cindy Pekarick, Pennsylvania

Eric Strain, M.D., College on Problems of Drug Dependence

Deborah Zvorsec, Ph.D., Hennepin County Medical Center, Minnesota

Trinka Porrata, California

Richard Gelula, Executive Director, National Sleep Foundation

Matt Speakman, West Virginia

Charles Cichon, President, National Association of Drug Diversion Investigators

Debbie Alumbaugh, Florida

Brian Hunter, Young Adults With Narcolepsy

Joe Spillane, Pharm.D., Florida

Mali Einen, California

Sandra Jones, California

Committee Discussion and Votes:

- 1. Has the sponsor demonstrated efficacy of Xyrem® for the proposed indication to treat cataplexy and excessive daytime sleepiness in patients with narcolepsy?**
 - a. If no, is there any reasonable claim for which the sponsor has presented substantial evidence of effectiveness?

The committee altered the question several times. The final vote on efficacy was changed when the committee started to discuss the safety data and decided that efficacy needed to be considered primarily in relationship to the data available to judge the safety data. Hence, this record only notes the final question which addressed efficacy and then safety in relationship to data available on 6-9 grams of Xyrem® :

Has the sponsor demonstrated efficacy (at 6 – 9 grams) of Xyrem® for the proposed indication of cataplexy?

Yes = 5 No= 4

Has the sponsor demonstrated efficacy (at 6 – 9 grams) of Xyrem® for the proposed indication of daytime sleepiness?

Yes=0 No = 9

- 2. Has the sponsor established the safety of Xyrem® when used for the proposed indication for which substantial evidence of effectiveness has been submitted?**

This was only voted on in terms of cataplexy and with a dose range of 6-9grams/day.

Yes=4 No=4 Abstain=1

- 3. Is the adoption of a risk management plan necessary for the safe use of Xyrem®?**

Yes=8 No=1

(The no vote was cast because it is a complicated issue and can't resolve all the issues for control. If it is limited a patient population may not be served – which was equated to pain management limitations. "The devil is in the details.")

Please evaluate the following components of the Risk Management Program:

4. Safe Use in Home

- a. Should there be a requirement for additional safeguards in patient's homes, e.g., keeping drugs in a locked storage space?

Yes=1 No=8 (because all drugs should be in a safe place)

- b. Should there be additional warnings on the labeling of the dose cups and/or bottle of GHB?

Unanimous that labels on bottles and dose cups should indicate what the substance is and the dose in the container. (Thus if someone overdosed and went to and ER the staff would know what they had ingested.)

- c. Is there any special concern or advice regarding limitations on the quantity of Xyrem[®] supplied at any one time?

No consensus ; perhaps it might be extended to 3 months

- d. What special concerns should be communicated in the product label and other printed materials?

Not specifically discussed but answered in other questions.

5. Safe Use by Patient

- a. Should patients sign an informed consent form before receiving the initial shipment of the drug?

Yes=5 No=4

The dissenter's thought that without details it was hard to vote on. What would be in the informed consent? One person suggested that contract might be better choice of words where the patient could acknowledge the dispensing of the drug and the risks.

- b. Should patients be required to return a registry form before receiving the first shipment?

Yes=2 No=1 Abstain = 6

The consensus was that maybe they won't take this seriously and how was this going to be different from consent.

6. Appropriate Prescribing

- a. Should physicians document that they read the materials sent to them before the pharmacy fills the initial prescription?

Yes=7 No=2

The members cautioned that a sleep center physician should only have to sign this once. MD needs to know that it is GHB and should be definitely informed of this information.

- b. Should physicians be required to demonstrate safe use and appropriate dosage preparation to patients before the first prescription and be required to document that it has been accomplished?

The word physician staff was added to the sentence:

Yes = 1 No=7 Abstain =1

- c. Should there be restricted prescribing for the product? (e.g., only to those who have a diagnosis of cataplexy)

This was discussed at great length. There are two concerns to consider: The patient's interests and protecting the public from abuse/misuse. Many felt that there was a definite need to protect the public. Since it can be miss diagnosed, a member felt that someone needs to monitor who is treated. There was concern that PK studies should be done on children before prescribed. There was also sensitivity to the fact that not all patients will be at sleep centers . One of the sleep specialists indicated that in his opinion one couldn't confirm cataplexy.

Yes=7 No=1 Abstain =1

- d. Does the Risk Management Program assure appropriate prescribing or sufficiently reduce the risks of misuse or overdose from Xyrem?

The patient needs to know that the substance is GHB and that there is the potential for abuse/legal consequences.

- e. Should certification of physicians for prescribing Xyrem be required?

Yes=0 No=8 Abstain=1

7. Central Pharmacy

- a. Is the institution of the sponsor's central pharmacy adequate?

Not discussed

- b. Should the central pharmacy be described in the product labeling, as well as educational and promotional material?

Not discussed

8. Post Market Surveillance

- a. Should there be a requirement for post-marketing reporting of cases of misuse, abuse, overdose, dependence, and diversion?

Not discussed

- b. Should the role of the central pharmacy include providing post-marketing and surveillance reports to the Agency in addition to the sponsor?

Not discussed

- c. Should these reports be provided on a regular basis and include monitoring prescribing and dispensing patterns?

Not discussed

9. Other recommendations

- a. Any other recommendations on how to protect the family of the patient, on the handling, storage, and disposal of GHB, on labeling and on post market follow-up for misuse and overdose?

The fact that Xyrem is GHB is not in the patient educational material. Although the sponsor indicated that they had intentionally not used the word GHB on advice of abuse experts, members of the committee felt that the patient definitely needed to know this information.

Since the sponsor has an investment in making a profit, members questioned if it was realistic to expect that the sponsor serve as the reporter of adverse events, abuses etc. "Who will police the police."

The committee and guests discussed the issues and their views are recorded in the transcript. A verbatim transcript of this meeting will be available on the FDA's Dockets Management Branch Website approximately 30 days after the meeting. The address is [HTTP://www.fda.gov/ohrms/dockets/ac/acmenu.htm](http://www.fda.gov/ohrms/dockets/ac/acmenu.htm).

I certify that I attended the June 6, 2001 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and that these minutes accurately reflect what transpired.

Sandra Titus 6/25/01
Sandra Titus, Ph.D. Date
Executive Secretary, PCNS

Claudia Kawas M.D. 6/19/01
Claudia Kawas, M.D. Date
Acting Chair, PCNS

Prepared on June 6, 2001
Sandra Titus