CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-196

CORRESPONDENCE

ORPHAN MEDICAL

July 1, 2002

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products [HFD-120]
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike, Room 4025
Rockville, MD 20852
Phone: 301-594-2850

SUBJECT: Xyrem® (sodium oxybate) oral solution
NDA #21-196 Post-NDA Submission No. 99
USER FEE NUMBER 3,814, ORPHAN DESIGNATION NUMBER 94-858

Commitment to Timing of Anticipated Post-Approval Clinical Trials

Dear Dr. Katz:

Orphan Medical has previously indicated that we commit to conducting two additional clinical trials as post-approval commitments following FDA marketing authorization of this pending priority NDA. In a recent phone call, Ms. Anna Marie Homonnay-Weikel, requested that we document our anticipated timing for completion of those two clinical trials. We were asked to indicate three approximate dates that include the anticipated date of protocol submission to our IND, the date the study would be initiated; and the anticipated date of final report submission to FDA. We commit to the following timing on these two clinical trials with this letter.

Trial 1: Drug Interaction Study:

Description: Evaluation of the pharmacokinetics of oxybate when administered concomitantly with a proton pump inhibitor in normal human volunteers.

Protocol Submission: A protocol will be submitted to IND [redacted] within three months of market authorization of Xyrem NDA 21-196.

Protocol Initiation: This trial will be initiated, first patient, first visit, within three months of FDA approval of the protocol.

Final Report: A final report on this trial will be submitted to FDA NDA 21-196 within 6 months of study initiation.

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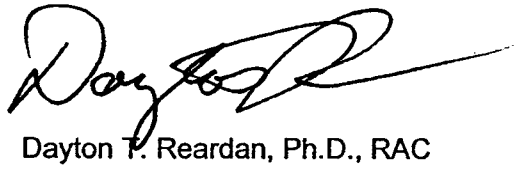
Trial 2: Xyrem Study in Respiratory Compromised Subjects

Protocol Submission: Orphan Medical anticipates making a written request for discussion of study design with the Division of Neuropharmacology within three months of FDA marketing authorization of Xyrem NDA 21-196. We then commit to submission of a protocol for FDA review within 3 months of a meeting with FDA to present the final trial design of this study.

Protocol Initiation: We commit to initiate the trial (first patient, first visit) within three months of FDA approval of the protocol.

Final Report: This trial is anticipated to take 12 months from initiation, with a final report 3 months following completion of the study (last patient, last visit).

Sincerely yours,



Dayton T. Reardan, Ph.D., RAC
Vice President of Regulatory Affairs
Phone: 952-513-6969
E-mail: dreardan@orphan.com

cc: Anna Marie Homonnay-Weikel RPh [Cover Letter - E-mail]

ORPHAN MEDICAL

January 8, 2002

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products [HFD-120]
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike, Room 4025
Rockville, MD 20852
Phone: 301-594-2850

SUBJECT: Xyrem® (sodium oxybate) oral solution
NDA #21-196 Post-NDA Submission No. 80
USER FEE NUMBER 3,814, ORPHAN DESIGNATION NUMBER 94-858

Product Label revision to comply with Medication Guide Regulation (21 CFR 208.24)

Dear Dr. Katz:

Thank you for the letter of notice provided in December regarding the requirement to amend our proposed product labeling for Xyrem in relation to the medication guide. A copy of that letter is included with this submission. Your letter was electronically signed on December 13, 2001.

The Medication Guide regulations promulgated in part 208 of Title 21, in particular 208.24(d) require that: "The label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided."

Orphan Medical proposed in our class 2 response dated October 5, 2001 to include a copy of the approved Medication Guide in each box of Xyrem. Each box is proposed to contain a 180 mL bottle of Xyrem, a PIBA, an oral syringe, two child resistant dosing cups, a professional insert with a Medication Guide attached via a tear off perforation. Therefore each box of Xyrem will contain a Medication Guide. Since the central pharmacy and each dispenser will be required to provide the full box of Xyrem each time Xyrem is dispensed, Orphan Medical proposes that only the carton (box) of Xyrem include language requiring dispensing of the Medication Guide.

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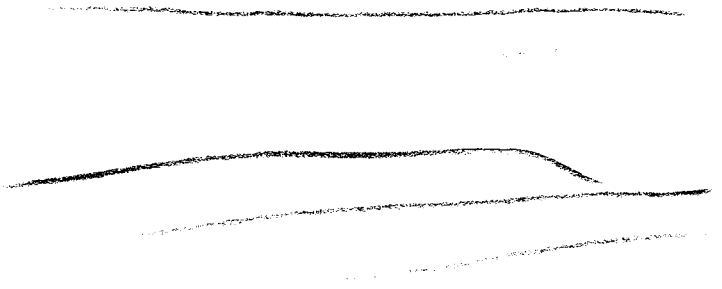
The regulation as restated above, allows for the container **OR** the package to instruct the authorized dispenser regarding the Medication Guide. In addition, since virtually all Xyrem will be dispensed by a central pharmacy, training and instruction can be assured so that each patient will receive the Medication Guide each time Xyrem is dispensed. Since all cartons (boxes, kits) of Xyrem must be dispensed to ensure that each patient receives all components, it is certainly justified to include the instructions to the pharmacist prominently on the outer carton.



This item has a production lead-time of about 5-6 weeks, and in fact was already printed at substantial cost to the company in order to be prepared for distribution upon FDA approval. Feedback was obtained from the chemistry review group at FDA in about February or March of last year that the bottle label and carton label appeared to meet all requirements at that time. The original proposal of a patient package insert was modified when FDA requested a Medication Guide in place of our proposed patient package insert last August 2001. Orphan Medical will therefore have to reprint this component with the proposed change in advance to ensure timely supply of Xyrem upon FDA approval. We would like to request feedback that what we have proposed is acceptable to FDA at this time. We recognize that FDA reserves the right to make changes up to and after approval, however, we request some assurance that what we have proposed is acceptable at this time.

Please find attached the following documents:

1. The letter from Dr. Katz requiring medication guide instructions on the product label.
2. Our proposed language for the Xyrem carton to meet this requirement.
3. A copy of the current proposed bottle label which remains unchanged.

If you have any suggestions or modifications, please communicate those to us at your earliest opportunity. We remain, as always, available to answer any questions you may have regarding this submission.

Sincerely yours,

Dayton T. Reardan, Ph.D., RAC
Vice President of Regulatory Affairs
Phone: 952-513-6969
E-mail: DReardan@Orphan.com

cc: Anna Marie Homonnay-Weikel RPh [E-mail]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Orphan Medical
Attention: Dayton Reardan, Ph.D., RAC
Vice President of Regulatory Affairs
13911 Ridgedale Drive
Suite 250
Minnetonka, MN 55305

Dear Dr. Reardan:

Please refer to your September 30, 2000, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xyrem® (sodium oxybate) Oral Solution.

On March 26, 2001, we received your March 23, 2001, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 2, 2001.

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/

Russell Katz
3/30/01 09:43:24 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-196

Orphan Medical Inc.
Attention: Dayton Reardan, Ph.D.
Vice President, Regulatory Affairs
13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305

Dear Dr. Reardan:

Please refer to your new drug application (NDA) dated September 30, 2000, received October 2, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xyrem® (sodium oxybate) Oral Solution.

FDA is notifying Orphan Medical Inc. that we have determined that Xyrem® Oral Solution poses a serious and significant public health concern requiring distribution of a Medication Guide pursuant to 21 CFR Part 208. Distribution of a Medication Guide would be necessary to help prevent serious adverse effects [21 CFR 208 (c) (1)].

Therefore, in accordance with 21 CFR 208, you are responsible for ensuring that a Medication Guide for Xyrem® is available for every patient who is dispensed a prescription for Xyrem®. In addition, you are responsible for ensuring that the label of each container of Xyrem® includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is to be provided.

If you would like to discuss this issue with the division, please call Ms.Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz
12/13/01 01:03:31 PM

3 page(s) of revised draft labeling has been redacted from this portion of the review.