In reviewing each of these documents, I have edited them. Each of the edited documents is separate from this review.

Key changes to each of these documents are addressed below

11.1 Risk Management Program Proper

Key changes to the program have been to the following components and are acceptable to the reviewer.

- The names of the manufacturer and distributor have been deleted based on advice that the sponsor has received from law enforcement bodies. The central pharmacy distributing the drug has been referred to as such, rather than as
- The Risk Management Program summary that accompanied the Approvable Letter of 4/9/02 specifically stated that "all patient assignment of benefit forms and registry information would need to be signed and sent back to the central pharmacy before the first prescription is filled." The sponsor has altered this section to
  - Delete "assignment of benefits" forms from this statement. The sponsor justifies this deletion on the basis that these forms are a legal contract between the pharmacy and patient which will be mailed out as a separate step for insurance billing purposes, if needed, and that it is not necessary for the form to be returned in order for a prescription to be filled unless the central pharmacy deems it necessary
  - State that registry information will need only to be verified (and not signed and sent back to the pharmacy) before the first prescription is filled. The Xyrem® Patient Success Program materials do not contain any registry information.
- Under the "Drug Product Kit" heading the sponsor has deleted the following statement from the summary

11.2 Xyrem® Physician Success Program Elements

Only key changes are addressed below

11.2.1 Letter To Physician

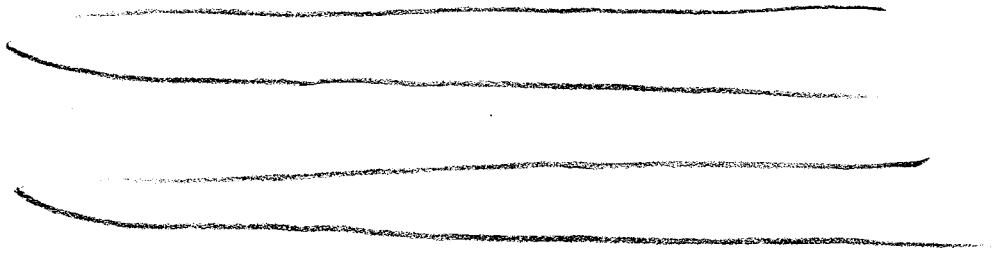
Changes to this letter made by the sponsor are minor and acceptable. I have not made any changes to the document submitted by the sponsor.

11.2.2 Physician Booklet ("Doctor Book")

The physician declaration that accompanied the Approvable Letter of 4/9/02 read as follows

Physician Declaration – Please initial each box	To be completed at initial prescription only
☐ I have read the materials in the Xyrem Physician Success Program	
☐ I verify that the patient has been educated with respect to Xyrem preparation, dosing and scheduling	
☐ I understand that Xyrem is approved for the treatment of cataplexy in patients with narcolepsy	
☐ I understand that Xyrem has not been shown to be effective or safe for any other indication. I also understand that there is not evidence that doses greater than 9 gm/day are safe.	

In this submission the sponsor has edited the declaration to read as follows:



These and other, more minor, changes to the label are acceptable. I have not made any changes to the document submitted by the sponsor.

11.3 Xyrem® Patient Success Program Elements

11.3.1 Letter To Patient

The sponsor has made only very minor changes to this document. I have not made any changes to the document submitted by the sponsor.

11.3.2 Patient Booklet ("Patient Book")

Key changes to this document as made by the sponsor are summarized below

- Under the heading "How soon might I see a change in my symptoms" the text that accompanied the Approvable Letter of 4/9/02 contained the following statement: "You can expect to see some improvement within the first weeks."

The sponsor has edited this statement to read as follows:

You can expect to see some improvement within the first weeks of Xyrem® therapy, however, may take up to 8 weeks.

I have further edited this statement so as to use language that might be understood by a lay person (see edited document for full details).

- Under the heading "What should I avoid while taking Xyrem®" the text that accompanied the Approvable Letter of 4/9/02 contained the following statement

What should I avoid while taking Xyrem?

11.3.3 Patient Video

The sponsor has submitted the script of a video that that is intended to instruct patients regarding the following

- Preparation and use of Xyrem®
- Precautions needed to ensure the in-home safety of Xyrem®
- Laws governing, and precautions to be taken against, the misuse of Xyrem®

I have read the script of the video and found it acceptable.

11.4 Post-Marketing Program Elements

This program consists of the post-marketing safety evaluation form and accompanying documents.

11.4.1 Instructions

- Changes made by the sponsor to the document that accompanied the Approvable letter of 4/9/02 are minor and do not warrant further comment
- I have not made any changes to the document submitted by the sponsor.

11.4.2 Letter

- Changes made to the document that accompanied the Approvable letter of 4/9/02 are acceptable and do not warrant further comment
- I have not made any changes to the document submitted by the sponsor.

11.4.3 Outline

The sponsor has not made any changes to the form that accompanied the Approvable letter of 4/9/02

11.4.4 Form

- Changes made to the document that accompanied the Approvable letter of 4/9/02 are acceptable and do not warrant further comment
- I have not made any changes to the document submitted by the sponsor.

11.4.5 Additional Item

In the cover letter, the sponsor has asked the following question

"It is our understanding from the language you placed in the letter to doctors that that safety information on 1000 patients followed for 6 months on Xyrem® therapy will fulfill our obligations for this program. Can you please confirm our agreement?"

The answer to this question is, I believe, that the sponsor's understanding is correct.

12. Proposed Labeling

This has been submitted in 3 separate formats: Microsoft Word, PDF (annotated) and PDF ("clean")

The key changes made to the label, that accompanied the Approvable action letter of 4/9/02, were to the following sections of the label. More minor changes are acceptable and are not reviewed below. I have edited the label submitted by the sponsor in a separate document.

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

14. Proposed Advertisement

This to be submitted separately to the Division of Drug Marketing, Advertising and Communications within about 2 weeks after the current submission.

15. Drug Stability And Expiration Dating

This section of the submission has been addressed by the Chemistry reviewer, Dr Thomas Oliver. He, and his Division, have recommended the following: "The requested tentative expiry of 36 months is acceptable."

16. Follow-Up Of Patients At Study Site #8

16.1 Background

- Dr Martha Hagaman is/has been a principal investigator for the following Orphan-sponsored clinical trials of Xyrem®: OMC-GHB-2, OMC-SXB-21, [redacted] OMC-GHB-3, OMC-SXB-6 and OMC-SXB-7. Only the OMC-SXB-7 and [redacted] studies are currently ongoing as part of Treatment IND # [redacted], and IND # [redacted] respectively.
- The St Thomas Hospital Institutional Review Board in Nashville, TN, had, in a letter dated 1/21/02, terminated the OMC-SXB-7 study at that hospital; Dr Hagaman was the Principal Investigator conducting the study at that site under the jurisdiction of that Institutional Review Board. The letter to Dr

Hagaman cited a number of deficiencies in the conduct of the study as the reason for the Institutional Review Board's action. Please refer to the text of that letter which was submitted to this Division under IND [redacted] (submission #056; correspondence date 1/24/02), and to the addendum (completed 3/29/02) to my review of the earlier Response To Approvable Letter (dated 10/5/01) for further details

- An inspection of the Hagaman study site was performed by Patricia Smith, Investigator, of the New Orleans District Office, and Ni Khin, MD, of the Division of Scientific Investigations, accompanied by John Feeney, MD, of this Division. The inspection was performed from March 11-14, 2002. Data from four studies were reviewed at the time of the inspection; these studies were OMC-GHB-2, OMC-GHB-3, OMC-SXB-7, and OMC-SXB-21.

  An FDA Form 483 was issued to Dr Hagaman at the end of the visit. The deficiencies listed in the form were in the following areas: record-keeping, Institutional Review Board reporting, informed consent, and oversight. Several of the deficiencies noted were considered serious enough to raise questions about the reliability of the data from that site.

16.2 Extent To Which Site # 8 (Martha Hagaman, MD) Participated In Orphan-Conducted Clinical Studies Included In NDA

A total of 46 unique patients have been enrolled at this site in clinical trials included under this NDA. A number of patients have participated in more than 1 study

The number of patients enrolled in each study, at Site #8 and in the entire study is listed in the following table. Note that [redacted] an ongoing study of the efficacy of Xyrem® for excessive daytime sleepiness in narcolepsy, is not included in the table (only limited safety data for this study have been included in the application).

Study #	Number Enrolled At Site #8	Number Enrolled In Entire Study
OMC-GHB-2	18	136
OMC-GHB-3	16	118
OMC-SXB-6	15	185
OMC-SXB-7 (Cohort 1*)	20	236
OMC-SXB-7 (Cohort 2**)	1	32
OMC-SXB-21	7	55

*Cohort #1 is composed of all patients enrolled in the OMC-SXB-7 study through 9/30/00, the cut-off date for the initial (120-Day) safety update included in this NDA.
** Cohort #2 is composed of all patients enrolled in the OMC-SXB-7 study from 9/30/00 through the cut-off date for the current safety update (6/30/01) included in this NDA

16.3 Additional Information Requested From Sponsor

The additional information request pertained largely to patients who discontinued from this study at Site #8 for reasons other than adverse events. The purpose of seeking this information was to confirm that these patients had not experienced any adverse events of concern, while participating in clinical trials of Xyrem® that were thus far unrecognized.

Each request and the sponsor's response is summarized below

16.3.1 Request #1

16.3.1.1 Request (4/30/02)

Patient #0810 discontinued from the OMC-SXB-7 study at Site #8. Please provide a detailed explanation as to why this patient discontinued from the study.

16.3.1.2 Response (5/8/02)

In summary, the submission indicates the following:

- This patient (DCH) participated in the following trials

Clinical Trial	Start Date
OMC-GHB-2 (Placebo arm)	4/4/97
OMC-GHB-3	6/5/97
OMC-SXB-7	4/29/99

- The patient received GHB for 2 years and 9 months with doses that ranged from 4.5 to 9 g/day
- The patient discontinued from the OMC-SXB-7 trial on 2/12/02 (at Visit 12, Month 33). The summary reason for discontinuation was "patient request." In the current submission, the sponsor indicates that the patient discontinued treatment at the time of transfer of OMC-SXB-7 study patients from Site #8 in Nashville to Atlanta (Site #8 was closed by the Institutional Review Board that had jurisdiction over that site).
- During a phone conversation between the investigator and patient on **5/4/02**, the patient indicated that she did discontinued from the study as she did not want to travel to Atlanta and felt that her narcolepsy was under control.
- The sponsor indicated that there was no evidence that the patient discontinued on account of an adverse event.

16.3.2 Request #2

16.3.2.1 Request (5/6/02)

A number of patients participating in clinical trials at this site discontinued for reasons other than adverse events; for these patients the reasons cited include "withdrawal of consent," "patient request," etc. A table listing these patients is below

Study #	Patient #	Reason For Discontinuation
OMC-GHB-3	0803	Withdrew consent
OMC-GHB-3	0811	Other
OMC-GHB-3	0815	Withdrew consent
OMC-GHB-3	0820	Other
OMC-SXB-6	0836	Patient request
OMC-SXB-6	0837	Patient request
OMC-SXB-6	0838	Patient non-compliance
OMC-SXB-7	0845	Protocol deviation

For each of these patients, please provide as full a description as possible of the reason for discontinuation. Please also ascertain the current health status of these patients.

16.3.2.2 Response (5/28/02)

I have summarized the sponsor's response in the following table

Study #	Patient # /Initials	Full reason for discontinuation*	Present-day follow-up
OMC-GHB-3	0803	"She (patient) does not feel like it's doing any good and she hates waking up to take the medication"	Unsuccessful (previous phone number disconnected)
OMC-GHB-3	0811	Patient felt "the trial was too much trouble to take it and wake up to take it again."	5/14/02: Being treated by a primary care physician and taking methylphenidate for narcolepsy
OMC-GHB-3	0815	Study coordinator noted that "patient dropped drug off and stated that she did want to continue in the study"	Unsuccessful (phone number changed; new phone number unpublished)
OMC-GHB-3	0820	Progress note states the following: "not sleeping well, grouchy, major cataplexy 2 –3 times a day." The Case Report Form records that the investigator felt that discontinuing study medication was "in the patient's best interests." Investigator recollected that "study medication did not seem to help so patient discontinued."	Unsuccessful despite numerous attempts
OMC-SXB-6	0836	Source documents and Case Report Form indicated that the reason for discontinuation was headaches. However, investigator, in a telephone conversation on 5/23/02, indicated that • Discontinuation was NOT because of headache since that symptom diminished • Patient had requested to discontinue because of the complexity of maintaining the visit schedule	Unsuccessful
OMC-SXB-6	0837	Case Report Form recorded that "patient states that she has been healed at church on 1/8/00. She has had no cataplexy since this time and has stopped taking medication and would like to come in for a termination visit."	5/11/02: Patient reported that her cataplexy symptoms remained much improved for 1 ½ months after discontinuing GHB. At present the patient is receiving Dexedrine 60 mg PO Q.D. and Prozac 20 mg PO Q.D. to control her symptoms of narcolepsy
OMC-SXB-6	0838	Patient stopped taking medication and missed 3 subsequent study visits. Source documents state that patient terminated participation in the study "due to shift work and schedule changes."	Unsuccessful: phone number disconnected
OMC-SXB-7	0845	Patient ended participation in the trial on account of pregnancy (considered a protocol violation). She then re-entered the trial with approval of the medical monitor, apparently after her pregnancy had ended	5/11/02: Patient continues to be enrolled in the OMC-SXB-7 trial and is "doing well" at 6 g/day

*based on source document and/or Case Report Form

16.3.3 Request #3

16.3.3.1 Request (5/16/02)

This request for information concerns Patient #0824.

This patient discontinued from both Studies OMC-GHB-2 and OMC-GHB-3 on account of difficulty breathing.

- Could you supply us with a clinical description of the episodes of difficulty breathing, and how they were evaluated?

- Please ascertain this patient's current status. If an adequate description of the episodes of difficulty breathing is not available from source documents, perhaps the patient could now be asked to supply as much information about them, as possible, from memory.

16.3.3.2 Response (5/28/02)

The sponsor's response consists of a summary and a full narrative

16.3.3.2.1 Summary

The sponsor states the following

- The response was based on source documents obtained from the investigator
- The episodes of difficulty breathing were described by the patient as a "smothering feeling."
- The events began 15-20 minutes after dosing and lasted 3-4 minutes during which period the patient was unable to move
- The source documents also include an opinion from a pulmonologist (David Hagaman, MD) who felt that the events represented sleep paralysis
- Recent attempts (through 5/23/02) by the investigator to contact the patient have been unsuccessful

16.3.3.2.2 Full Narrative

This patient (initials: ——) was a 30 year old woman weighing 108 lbs. In addition to narcolepsy she had a past history of (unspecified) cardiac surgery (8/96) and hysterectomy (5/95).

She entered the OMC-GHB-2 trial on 11/24/97, completing the withdrawal and washout phases on 11/24/97 and 12/2/97, respectively. She began double-blind treatment (later confirmed to be GHB in a dose of 9 g nightly) on 12/19/97.

On the evening of 12/21/97, the third evening of dosing in the OMC-GHB-2 trial, she experienced a "smothering feeling" lasting 4 minutes. Study medication was discontinued on 12/21/97. Two days later, on 12/23/97, the patient experienced a second episode of a "smothering feeling" at 2.45 AM lasting 5 minutes, without having taken any study medication since 12/21/97. These events were recorded by the investigator as being severe; the patient was reported to have recovered fully from the event

She entered the OMC-GHB-3 open-label trial on 12/30/97 and while participating in that trial received the following doses of GHB

Date	Dose of GHB
12/30/97 through 1/3/98	3 g each evening
1/4/98	None
1/5/98 through 1/10/98	3 g each evening
1/11/98 through 1/16/98	1.5 g each evening
After 1/16/98	None (study medication completely discontinued)

The patient was recorded as reporting experiencing a "smothering feeling" from 1/12/98 through 1/16/98; the investigator recorded this event as being moderate in intensity, continuous, and associated with full recovering.

All the events that were described by the patient as a "smothering feeling" were recorded by the investigator in the Case Report Form as "difficulty breathing." One of these events was described by the investigator in a source document as follows: "patient reports awakening approximately 15 minutes after dosing on 1/16/98 with a feeling that she could not breathe, patient reports it lasted 3-4 minutes, states she could move during this episode, patient stopped drug at that time."

A pulmonologist [redacted] saw the patient on 1/12/98 and stated the following: "last night had episode of sleep paralysis 15-20 minutes after dose, she had fallen asleep then waking, inability to move arms and legs, didn't feel that she could breathe , lasted 2-3 minutes then she fell

asleep, contacted Dr ——— (medical monitor) will decrease dose to 1.5 g each night. This is sleep paralysis in my opinion."

16.4 Reviewer's Comments

- Despite the limited extent to which present-day follow-up was possible for a number of the patients for whom additional information was sought, it appears unlikely that any of the patients described in this section experienced adverse events of major concern (that we had previously been unaware of) while participating in clinical trials of Xyrem®
- It appears likely that the "difficulty breathing" experienced by Patient #0824 was a symptom of sleep paralysis.

17. Audit of Study Site #5

As a result of the serious deficiencies noted during the Agency inspection of Study Site #8, and in order to determine if there were more widespread faults in the conduct of the Orphan-sponsored long-term safety studies (especially Study OMC-SXB-7), it was decided to perform an inspection of Site #5 (Martin Scharf, PhD) since the latter enrolled the largest number of patients of any site participating in Study OMC-SXB-7.

The inspection of Study Site #5 was conducted over several days, beginning 4/22/02. The preliminary results of that inspection indicate that there were NO serious deficiencies at that site.

18. Additional Information About A Patient At Site #41

18.1 Background

Dr Mortimer Mamelak is the Principal Investigator at Site #41, which is located in Toronto, Ontario, Canada.

DC, a male patient enrolled in Studies ——— (a randomized, double-blind, placebo-controlled study intended to assess the effectiveness of Xyrem® for excessive daytime sleepiness accompanying narcolepsy) and ——— (an open-label, uncontrolled extension study at Dr Mamelak's study site. The patient had recently spoken with a representative of the Division of Scientific Investigations. In that conversation, the patient indicated that while participating in ——— he had recorded an increase in his own blood pressure; an elevation in blood pressure had also reportedly been recorded during a polysomnogram done at Dr Mamelak's study site while he participated in the ——— study. The patient also indicated that he had been discontinued from that study after being told that he did not have narcolepsy; this report was somewhat disconcerting to us, since a confirmed diagnosis of narcolepsy with cataplexy was a key requirement for enrollment in both studies.

Note that this patient participated in Studies ——— from October 2001 to March 2002. No safety data for this patient have been formally submitted to us by the sponsor: the cut-off date for all safety data

submitted under this NDA so far is 6/30/01; and this event does not appear to qualify as a special safety report that is to be submitted under the IND.

18.2 Extent To Which Site #41 Enrolled Patients In Orphan-Sponsored Studies

The table below is based on data submitted through the cut-off date of 6/30/01

Study #	Number Enrolled At Site #41	Number Enrolled In Entire Study
OMC-GHB-2	0	136
OMC-GHB-3	0	118
OMC-SXB-6	0	185
OMC-SXB-7 (Cohort 1*)	0	236
OMC-SXB-7 (Cohort 2**)	10	32
OMC-SXB-21	0	55
OMC-SXB-20	11	25

*Cohort #1 is composed of all patients enrolled in the OMC-SXB-7 study through 9/30/00, the cut-off date for the initial (120-Day) safety update included in this NDA.
** Cohort #2 is composed of all patients enrolled in the OMC-SXB-7 study from 9/30/00 through the cut-off date for the current safety update (6/30/01) included in this NDA
Trials OMC-SXB-7 and [redacted] are ongoing, open-label studies, that are being undertaken as part of Treatment IND's [redacted]
[redacted] is a randomized, double-blind, placebo-controlled, parallel-arm study being conducted to determine the efficacy of Xyrem® for excessive daytime sleepiness in narcolepsy

18.3 Teleconference With Dr Mamelak: May 30, 2002

Our Division spoke with Dr Mamelak to obtain his description of the events that occurred with this patient. The teleconference was arranged with the consent of the sponsor, and was chaired by Dr R. Katz.

Prior to the teleconference, Dr Mamelak had sent us documents that consisted of

- A letter that he wrote to the Orphan Medical study monitor describing what happened
- The patient's polysomnogram report.

The key points that Dr Mamelak conveyed to us were as follows

- This patient participated in both [redacted]
- When the patient was screened for enrollment in [redacted] Dr Mamelak had reviewed his previous sleep studies, including a polysomnogram and Multiple Sleep Latency Test; these were quite consistent with narcolepsy, as was the patient's clinical history
- The patient reported no improvement while participating in [redacted] but could have been receiving either Xyrem® or placebo during that trial
- While participating in [redacted] he reported that his blood pressure, recorded 15 minutes after taking GHB, had risen from normal, prior to taking the drug, to 150/90. Dr Mamelak had recorded blood pressures of 140/92 and 136/86, at entry into [redacted] respectively
- During [redacted] he had reported that he was not sleeping well and that his cataplexy was not coming under control, both of which were unusual in Dr Mamelak's experience with patients administered GHB; these symptoms were reported despite a staged increase in his dose of GHB to 4.5 g twice

each night. The patient attributed the lack of improvement in his cataplexy to not sleeping well.

- Dr Mamelak then decided to perform a polysomnogram after the patient was taken off GHB
- About month after the patient was believed to have discontinued taking GHB a polysomnogram was performed on this patient (the results of which had been made available to us earlier by Dr Mamelak). Several hours prior to the study, and prior to GHB being administered, elevations in blood pressure were noted by Dr Mamelak. During the polysomnogram, which was performed after he had received a dose of GHB similar to what he had taken earlier during the study, episodic elevations of blood pressure were again noted: however, the patient slept well, and did not have sleep apnea during the recording.
- Dr Mamelak informed the patient after the polysomnogram was performed (but before the study was scored) that, in view of his unusual symptoms (difficulty sleeping and lack of improvement in cataplexy, while taking GHB), his condition would need reassessment after the polysomnogram results were reviewed.
- Many subsequent attempts by Dr Mamelak to contact the patient were unsuccessful; he left multiple messages on the patient's voice mail, and when the patient did not return (Dr Mamelak's) phone calls, was concerned enough to contact the police in the patient's hometown of [redacted]. The police checked on the patient and confirmed that he was well. However, the patient has not contacted Dr Mamelak and his supply of Xyrem® has not been returned (although Dr Mamelak understands that the patient may be making arrangements with Orphan Medical to return the latter)
- Dr Mamelak believes that this patient has both narcolepsy-cataplexy and hypertension. He has already recommended that the patient contacts his general practitioner to obtain treatment for his hypertension. Dr Mamelak would have liked for the patient to remain in the study; however, his failure to reply to phone messages led to his being withdrawn. He does feel that the patient could benefit from having his narcolepsy-cataplexy reassessed and treated.

18.4 Conclusions

- Our Division believes that, in all likelihood, the patient misinterpreted what he was told about his condition by Dr Mamelak.
- No further action is called for on the part of this Division in this specific instance.
- We informed Orphan Medical, Inc. of our conversation with Dr Mamelak, and the conclusions that we reached after speaking to him.

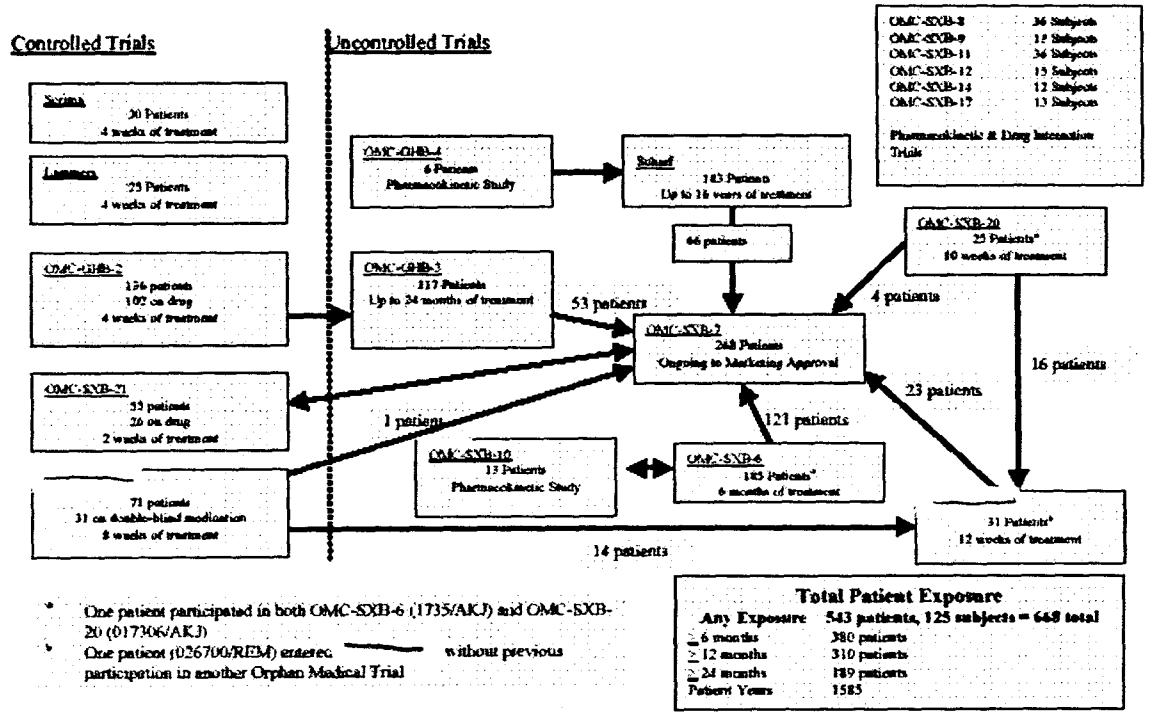
19. Exposure Data

At the request of this reviewer the sponsor submitted on 2/18/02 updated exposure tables for Xyrem®. These were reviewed along with the previous Response To Approvable Letter (see my review completed on 3/4/02)

19.1 Overall Schematics For Clinical Trials In Narcoleptic Patients Included In NDA

The submission contained 2 schematics

19.1.1 Schematic For Clinical Trials Sponsored By Orphan Medical Plus Scharf Trial



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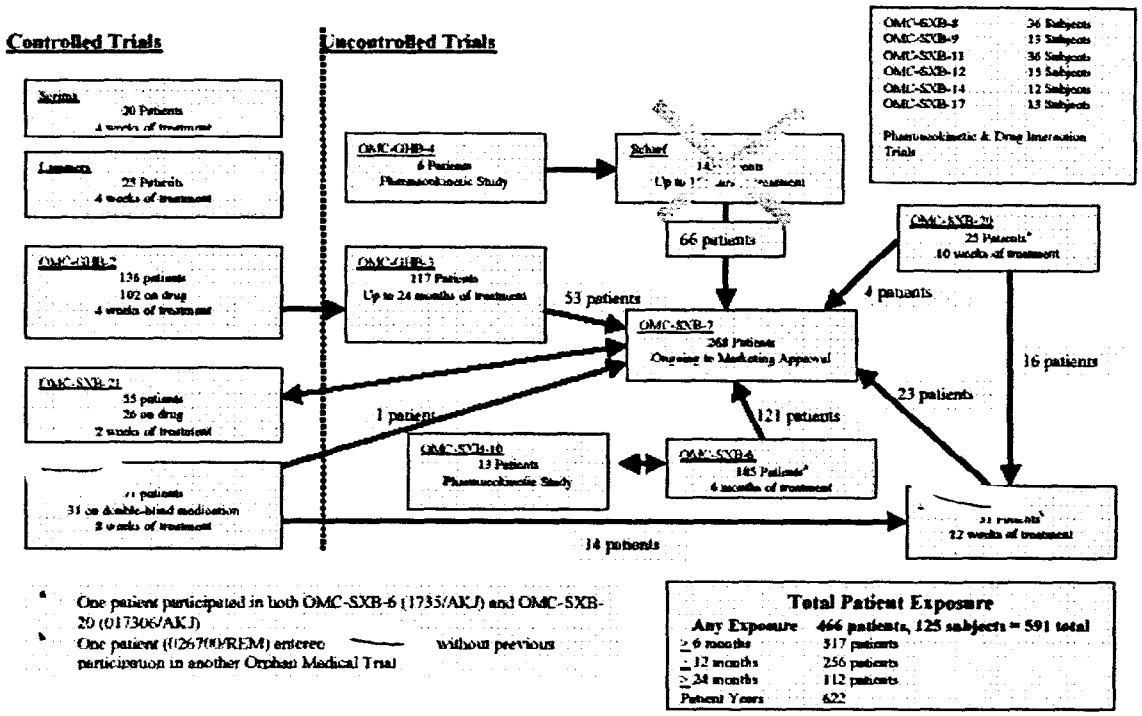
19.1.2 Schematic For Clinical Trials Sponsored By Orphan Medical Alone



19.2 Tables

19.2.1 Sponsor's Methods For Creating Tables

Tables were created for 2 different groups of patients

- The updated Integrated Clinical Trials database which included the following studies through the cut-off date of 6/30/01: OMC-GHB-2, OMC-GHB-3, OMC-SXB-6, OMC-SXB-7, Scrima, ———, and OMC-SXB-20
- All patients subsumed by the above bullet plus the Scharf study

The sponsor used the following methods for creating these tables

- Each patient dose was classified into one of 5 "standard" dose groups as in the following table

Patient Dose g/day	"Standard" Dose Group Category g/day
0 to 3.5	3.0
> 3.5 to 5.5	4.5
> 5.5 to 7.0	6.0
> 7.0 to 8.5	7.5
> 8.5	9.0

- Each patient's exposure to these 5 standard doses was calculated for both groups of patients and the number of patients at each dose level for each duration of exposure recorded in the tables. Assignment of patients to a dosing category was made based on continuous exposure time in that dosing category
- For the "overall duration of exposure" category each patient's time of exposure was calculated regardless of dose.

- Patients who received placebo only were not included in the tables
- Duration of exposure was calculated based on a 28-day month
- Since each patient could be represented in more than one dose category for the specified duration of exposure the overall exposure numbers do not represent arithmetical summations of the numbers in individual dose categories

19.2.2 Tables

The sponsor has presented tables for different durations of exposure

19.2.2.1 Duration of Exposure ≥ 6 Months

The sponsor's table is presented below

Patients	3.0 g/d	4.5 g/d	6.0 g/d	7.5 g/d	9.0 g/d	Overall
ISS Only	9	55	127	74	74	317
ISS + Scharf	25	92	182	98	82	380

19.2.2.2 Duration of Exposure ≥ 12 Months

The sponsor's table is presented below

Patients	3.0 g/d	4.5 g/d	6.0 g/d	7.5 g/d	9.0 g/d	Overall
ISS Only	5	38	83	53	52	256
ISS + Scharf	12	63	133	75	60	310

19.2.2.3 Duration of Exposure ≥ 24 Months

The sponsor's table is presented below

Patients	3.0 g/d	4.5 g/d	6.0 g/d	7.5 g/d	9.0 g/d	Overall
ISS Only	2	11	30	18	24	112
ISS + Scharf	6	34	61	38	29	189

19.2.2.4 Sponsor's Comments About Above Tables

The sponsor has drawn attention to the following:

- The most commonly used dose of GHB across the 3 durations of exposure was 6 g/day regardless of whether data from the long-term Scharf trial were included or excluded
- The vast majority of patients used doses ranging from 4.5 to 9 g/day, across durations of exposure. The sponsor has proposed a starting dose of 4.5 g/day with a range of 3 to 9 g/day after titration (reviewer's note: this does not match with the dose range proposed by the sponsor in the proposed labeling)

19.3 Sponsor's Overall View Of Adequacy Of Exposure

- The sponsor has provided comparisons of the adequacy of exposure to Xyrem® with and without the Scharf study database. The following table summarizes the data presented by the sponsor

Study Pool	Integrated Clinical Trials Plus Scharf		Integrated Clinical Trials Only	
	Patients	Healthy Subjects*	Patients	Healthy Subjects*
Any Exposure	543	125	466	125
Exposure ≥ 6 Months	380	0	317	0
Exposure ≥ 12 Months	310	0	256	0
Exposure ≥ 24 Months	189	0	112	0
Patient-Years Of Exposure	1585	Not calculated	622	Not calculated

*Healthy subjects were exposed to single doses only

- The entire database contains sufficient patient exposure sufficient to meet the ICH guidelines at 6 months (> 300 patients) and 1 year (> 100 patients) even if the Scharf study data are excluded.

19.4 Additional Request For Information From Sponsor

On 2/22/01, an additional request for information regarding exposure data was transmitted to the sponsor. The request and the sponsor's response are summarized below

19.4.1 Request For Information

What is the total number of narcoleptic patients exposed to a 6-9 g/day dose range, and to a 9 g/day dose, of Xyrem® for any duration in the following groupings? (These data should be updated through 6/30/01, consistent with your submission of 2/18/02).

- Integrated Clinical Trials
- Integrated Clinical Trials plus Scharf Study

19.4.2 Sponsor's Response

The sponsor has submitted a table that represents patient exposure ≥ 1 day, for doses of ≥ 6.0 g/day and for a dose of 9.0 g/day in the following 2 groups of patients

- The updated Integrated Clinical Trials database which included the following studies through the cut-off date of 6/30/01: OMC-GHB-2, OMC-GHB-3, OMC-SXB-6, OMC-SXB-7, Scrima, [redacted] and OMC-SXB-20
- All patients subsumed by the above bullet plus the Scharf study

The sponsor used the following methods for creating this table

- Each patient dose was classified into one of 5 "standard" dose groups as in the following table

Patient Dose g/day	"Standard" Dose Group Category g/day
0 to 3.5	3.0
> 3.5 to 5.5	4.5
> 5.5 to 7.0	6.0
> 7.0 to 8.5	7.5
> 8.5	9.0

- Inclusion in the ≥ 6.0 g/day dose group required patients to have had at least 1 day of exposure at the 6.0 g/day, 7.5 g/day or 9 g/day dose
- Inclusion in the 9.0 g/day dose group required patients to have had at least 1 day of exposure at the 9.0 g/day dose

The table submitted by the sponsor is below, as copied from the submission

Patients	≥ 6.0 g/day	9.0 g/d
ISS Only	362	141
ISS + Scharf	434	171

* Any patient with at least one day of exposure at the given dose was included. Exposure was not calculated for the 3 patients who received placebo only. Exposure was also not calculated for patients who had a first visit, but no follow-up visit, before data cutoff (June 30, 2001), since no data on drug exposure would have been collected.

19.5 Reviewer's Comments

- The size of the Xyrem® NDA does meet ICH guidelines for drug exposure for 6 months and a minimum of 1 year if one assumes that the effective dose ranges from 3 to 9 grams/day. The ICH guidelines are met even if the Scharf study is excluded
- However, if one concludes (from the efficacy studies) that the 9 g/day dose is the only effective dose, and is that to be recommended for general use, the number of those exposed to Xyrem® at that dose for ≥ 6 months and ≥ 12 months does not meet ICH guidelines. If it is concluded from the efficacy studies that the effective dose of Xyrem® ranges from 6-9 g/day, the number of those exposed at that dose range for ≥ 6 months falls somewhat short of that specified in the ICH guidelines, whereas the number exposed for 12 months does not.

Note that ICH guideline E1A (July 1997) states the following (key phrases have been underlined by me):
"The number of patients treated for 6 months at dosage levels intended for clinical use should be adequate to characterize the pattern of adverse events over time. To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5% to 5%). Usually 300 to 600 patients should be adequate....

.....100 patients exposed for a minimum of 1 year is considered to be acceptable to include as part of the safety database. The data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use."

- The extent of exposure to GHB in patient-years is reduced by about 61% once the Scharf study data are eliminated. Admittedly, the ICH guidelines do not specifically address the issue of desirable exposure in patient-years.
- The total number of narcoleptic patients exposed Xyrem® 9 g/day or 6-9 g/day for any duration is very small. Even the total number of patients exposed to any dose of Xyrem® for any duration (n=543, with the Scharf study data included) represents only about 36% of that required under ICH guidelines
- There are no ICH guidelines that address exposure requirements for orphan drugs. The total number of patients exposed to Xyrem® might be arbitrarily considered appropriate for an orphan drug used for an orphan indication (i.e.,

cataplexy in narcolepsy); that may be especially true if the sponsor's estimate that the number of diagnosed/treated cataplexy patients in the United States is in the range of 20,678-22,917 is correct (this estimate was conveyed to this Division at a meeting held on 2/28/01). The total number of patients exposed to Xyrem® is certainly not adequate to cover its potential use for a variety of much more common non-orphan off-label indications.

- Note that the exposure data have not been updated beyond 6/30/01.

20. Advisory Committee Meeting

A meeting of the Agency's Peripheral and Central Nervous System Drugs Advisory Committee was held in Bethesda, Maryland, on June 6, 2001, to discuss this application. Note that this meeting was held prior to the earlier Approvable action on this application, and well prior to the current submission being received. As the deliberations at this meeting are relevant to the current submission I have provided a summary below.

The overall agenda for the meeting was as follows:

"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"

A full transcript of the meeting has been posted at the following website:

www.fda.gov/ohrms/dockets/ac/acmenu.htm

The following is a summary of the main outcomes of the meeting as prepared by this reviewer

20.1 Key Items Voted On

20.1.1 Question #1

The original question addressed to the sponsor was as follows:

Has the sponsor demonstrated efficacy of Xyrem® for the proposed indication to treat cataplexy and excessive daytime sleepiness in patients with narcolepsy?

If no, is there any reasonable claim for which the sponsor has presented substantial evidence of effectiveness?

The final questions voted on are below

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

Yes = 5 *No = 4*

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

Yes = 0 *No = 9*

20.1.2 Question #2

The original question posed to the committee was as follows:

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

This question was voted on only in relation to cataplexy and to a dose range of 6-9 grams/day.

Yes = 4 *No = 4* *Abstain = 1*

20.1.3 Question #3

Is the adoption of a risk management plan necessary for the safe use of Xyrem®?

Yes = 8 *No = 1*

20.2 Additional Recommendations

The following additional recommendations were made by the committee after discussion, based on questions posed by the Agency. Other questions posed by the Agency were also discussed by the committee, but with either a lack of consensus, or with a recommendation that the particular measure not be instituted

- Labels on Xyrem® dosing cups should indicate the nature of the contents and dose
- Patients should sign an informed consent document (possibly to be combined with a completed registration document) prior to receiving the first shipment of Xyrem®
- Physicians should be required to document that they have read the educational materials supplied by the sponsor prior to the first prescription for Xyrem® being filled
- Prescription of Xyrem® should be restricted to patients with cataplexy
- The patient educational materials should clearly state that the active ingredient contained in Xyrem® is gammahydroxybutyrate (GHB), that the drug has potential for being abused and that there are legal penalties for misuse and diversion of the drug

Note that the committee did NOT feel there was a need in the Risk Management Program for

- Certification of physicians prescribing Xyrem®
- A formal requirement for physicians or their staff to demonstrate the safe use of Xyrem® to patients, and for formal documentation that they had done so prior to the first prescription being filled
- A formal requirement in the risk management program for additional safeguards in the patient's home, such as a locked filing cabinet for storage of the drug

20.3 Additional Comments

Among the additional views expressed by members of the Advisory Committee and consultants were the following:

- That patients enrolled in Study #OMC-GHB-2 consisted of a sample that was enriched based on their having cataplexy; such a population may not represent the narcolepsy population at large and may not be an appropriate population in which to assess the efficacy of GHB in treating excessive daytime sleepiness
- Whether the incidence of adverse events attributable to central nervous system depression in the Xyrem® database was suppressed by the concomitant use of stimulant medication (over 67% of patients concomitantly received stimulant drugs across studies and in some clinical trials > 80% of patients did)
- That the number of patients exposed to the 6 to 9 g/day dose of Xyrem® might not be adequate to evaluate the safety of the drug: this concern appear to be the reason why the committee was evenly divided in opinion about the safety of Xyrem® at the doses proposed for use.

21. Risk-Benefit Equation And Overall Conclusions

The comments below are based on review of all submissions under this application

- **Xyrem® is effective for treating cataplexy, a chronic and generally lifelong disorder, which is disabling, may lead to serious injury, and for which there is currently no approved treatment.** Hitherto, the treatment of this symptom has consisted of using tricyclic antidepressants and selective serotonin re-uptake inhibitors; although there are no published randomized, double-blind, controlled trials supporting their efficacy for cataplexy, they have been widely-used for that indication, and many experts in the field of sleep disorders have not hesitated to extol their efficacy in the published literature (based presumably on several small published case series and their own anecdotal experience). Nevertheless, the use of tricyclic antidepressants and selective serotonin re-uptake inhibitors to treat cataplexy is not evidence-based (by current standards), there is clearly no FDA-approved treatment for cataplexy, and on that basis, the approval of Xyrem® may fill a hitherto unmet need.

- The most clearly effective dose of Xyrem® in treating cataplexy is 9 g/day, with less robust evidence for efficacy at a range of 6 to < 9 g/day. The only evidence for efficacy at doses less than 6 g/day comes from 2 small studies that have many deficiencies, and have been considered "negative" by the Division.

- There is inadequate evidence at the present time for the efficacy of Xyrem® in treating excessive daytime sleepiness or other symptoms in narcolepsy

- The number of patients who have been exposed to a Xyrem® dose of 6-9 g/day in clinical trials subsumed under this NDA (and for which reliable data is available) is small, raising a valid concern that the full adverse event spectrum, (including relatively frequent and potentially significant events) of this drug may not yet be evident. Moreover, about 61% of the exposure (in patient-years) to Xyrem® contained in this application is derived from the Scharf study, irregularities in the conduct of which lead to the issuance of a Warning Letter by the Agency; the Division of Scientific Investigations recommended that data from this study not be used in support of the application. In addition serious concerns have been raised, after an Agency inspection, about the reliability of the safety data at an Orphan-sponsored study site (Site #8; Martha Hagaman, MD); this site enrolled a total of 38 unique patients, all but two of whom participated in long-term safety studies

  Xyrem® has, however, been demonstrated to have efficacy for a condition which has a low prevalence (an estimated 24,000 individuals in the United States have cataplexy, according to the sponsor) and "orphan" status.

- In clinical trials, adverse events of concern that could be causally attributed to Xyrem®, and have occurred at therapeutic doses are almost entirely related to the effects of the drug on the central nervous system. These have included confusion, sleepwalking, somnolence, depressed respiration, and urinary as well as fecal incontinence. The incidence of these events has been low, and they have almost always been reversible. However, such events have had at even more serious consequences in some instances (as evidenced in some patients with sleepwalking). The margin of safety between doses that are clinically effective and those that have serious or potentially serious adverse events, may be very narrow, or even non-existent, in some patients. Given the use of stimulant medications in the vast majority of patients enrolled in clinical trials included in this NDA, there may be a possibility that the central nervous system-related adverse events of Xyrem® were made less evident by the co-administration of stimulants; this is despite the pharmacokinetic half-lives of stimulants and GHB being brief, and stimulants being taken during the day and GHB at night (the pharmacodynamic effects of Xyrem® presumably extend far beyond the very brief pharmacokinetic half-life of approximately 1 hour, if this drug is effective in the treatment of cataplexy).

  The potential for Xyrem® to cause respiratory depression, especially in those with pre-existing respiratory compromise (e.g., those with chronic obstructive pulmonary disease or sleep apnea; the latter disorder may frequently co-exist with narcolepsy) has not been satisfactorily assessed so far in a formal study, and the results of the completed study OMC-SXB-20 (which was not designed to assess the effects of Xyrem® on respiration) do not suffice to allay concerns about that potential; in fact, the results of OMC-SXB-20 do raise at least some questions about whether Xyrem® can be administered

safely to patients with moderate-to-severe obstructive sleep apnea, a condition that appears to be not uncommon in the general population and in those with narcolepsy.

It is unclear to what extent respiratory depression secondary to Xyrem® could have been responsible for a proportion of the adverse events in the safety database for this NDA that were categorized using COSTART terms such as "sleepwalking," and "confusion" (especially that occurring at night).

Despite the above concerns, clear-cut instances of respiratory depression appear to have been very uncommon in the (admittedly small) Xyrem® clinical trials database. Nevertheless, if Xyrem® is to be approved for the treatment of cataplexy, the current uncertainties regarding the respiratory depressant effects of Xyrem® need to be clearly conveyed in labeling, as in the edited version that accompanies this review. I do not feel that the degree of concern regarding the respiratory depressant effects of Xyrem® makes it obligatory for the sponsor to perform the proposed definitive study of such effects prior to approval, as long as use of the drug is strictly limited to patients with cataplexy; nor do I feel that there is a need to exclude co-existing obstructive sleep apnea of more than mild severity in cataplexy patients to whom Xyrem® is prescribed.

- Note also that no safety update has been included in the current submission. The last safety update (cut-off date: 6/30/01) was submitted with the earlier Response To Approvable Letter dated 10/5/01. The only subsequent safety data received by this Division have been IND safety reports submitted under treatment IND ——; these reports do not include any adverse events that have not been reported earlier in this application.

- The abuse of illicitly manufactured and distributed GHB appears to be widespread in this country and increasing; it has been extensively highlighted not merely in the media, but also in the peer-reviewed medical literature . Such abuse has been associated with many reports of central nervous system toxicity, including fatalities, at widely varying (estimated) doses; however, many such reports have been confounded by the co-ingestion of alcohol, and of other drugs with effects on the central nervous system. There have also been reports of the development of a dependence syndrome and of addictive behavior in individuals taking high and frequent (round-the-clock) doses of GHB from the same sources, although not with Xyrem® used in clinical trials included in this NDA; however the exposure to GHB in clinical trials has not been extensive.

  A presentation by Dr Jo-Ellen Dyer, of the California Poison Control System – San Francisco, at the Advisory Committee meeting on 6/6/01 described a prospective cohort of 15 patients with GHB overdoses (that occurred with "street" use); 5 of these patients had no evidence from laboratory testing of

ingestion of other drugs of abuse or alcohol, but were deeply obtunded (Glasgow Coma Scale score 3 – 6). Several of these patients had (apparently) random serum GHB levels that overlapped with those seen in pharmacokinetic trials of Xyrem®. However, it is unclear at what time, in relation to dose, the blood samples to determine GHB blood levels were drawn; peak blood levels could possibly have been much higher than those seen in clinical trials.

The abuse potential of GHB has yet to be specifically evaluated in a human clinical trial, although only minimal symptoms that might be attributable to withdrawal were seen in the small randomized withdrawal efficacy study #OMC-SXB-21.

- GHB has been proposed in the scientific literature, as well as in lay publications, as a treatment for a variety of conditions known or presumed to have a medical basis including insomnia, alcohol and opiate withdrawal, fibromyalgia, diseases causing weight loss such as AIDS, as well as many other entities (see full list below). Based on the medical literature review submitted with this application, and other publications seen by this reviewer, there is virtually no evidence-based endorsement for its use for these additional indications. However, if Xyrem® were to be approved without any limitations on off-label use, it is very likely that the drug will be prescribed for these entities at least some of which are known or perceived to be common. Under such circumstances it is also likely to be prescribed by physicians with much less familiarity with Xyrem® than those who specialize in sleep disorders.

  It is also to be expected that if Xyrem® is approved without any restrictions on off-label use, it is likely that it will be prescribed not just for the daytime sleepiness of narcolepsy (for which there is inadequate evidence for efficacy at present), but for daytime sleepiness due to other causes and even for daytime fatigue. The sponsor has already indicated to the Division of Drug Marketing, Advertising, and Communications, that it intends to promote the use of Xyrem® for the hitherto unapproved indication of excessive daytime sleepiness due to narcolepsy, and it is unlikely that the sponsor will completely desist from publicizing several additional off-label uses of the drug that are based on publications in the medical literature.

  The current safety database for Xyrem® may be marginally sufficient in size to support the marketing of this drug for the treatment of cataplexy alone, when the seemingly established efficacy of Xyrem® for that indication, and the current lack of any alternative approved treatment for cataplexy are also considered. The safety database is not however of a size that would support the much wider use of Xyrem® for treating the conditions listed above, off-label, especially since the safety of this drug for those indications has not been adequately studied (as already noted), let alone established.

The full list of "off-label" entities for which GHB use has been proposed is as follows (this list is based on Internet searches performed by me):

Insomnia*
Alcohol* and opiate* withdrawal. Alcoholism*
Cocaine withdrawal*
Fibromyalgia*
Excessive daytime sleepiness (including that in narcolepsy*)
Obstructive sleep apnea*
Periodic leg movements of sleep*
Night eating syndrome*
Diseases causing weight loss such as AIDS
"Aid to childbirth"/ obstetric anesthetic*
Depression
Schizophrenia*
Nocturnal leg cramps
Impaired memory
Hyperactivity and learning disability in children
Huntington's disease
Parkinson's disease
Dystonia musculorum deformans
Tardive dyskinesia
Anxiety
Elevated cholesterol
Brain tumors*
Myocardial infarction*
Resuscitation (i.e., tissue protection in hypoxic states)*
Head injury*

*Based on publications listed in MEDLINE. These publications are inadequate to assess safety or efficacy for those indications.

- There is no valid reason to presume that prescribed Xyrem® will not be subject to diversion and abuse, and to the risk of accidental or deliberate overdose, as well as other forms of misuse. The risk of such events occurring must be expected to increase the more widely it is prescribed, and the less experienced the physicians who prescribe it. In addition, the safety of Xyrem® in patients who have conditions other than cataplexy, and in healthy individuals has not been systematically studied to any significant extent

- In summary, therefore, while there is evidence that Xyrem® is effective for the treatment of cataplexy, and while there may be a medical need for the drug for treating that specific indication, the small clinical trial safety database, the narrow margin of safety, and the risks of abuse and misuse, all make it imperative that approval be conditional on a risk management system that is more stringent than both that proposed by the sponsor, and that agreed to so far by the Agency (based on the Approvable letter of 4/9/02). A vital additional element, in the opinion of this reviewer, which is not included in the risk management system as currently proposed, is a requirement that the drug be dispensed exclusively to patients with a diagnosis of cataplexy confirmed by their physicians. In this regard, it is noteworthy that the Peripheral and Central Nervous System Drugs Advisory Committee, at its meeting held on 6/6/01 was also of the opinion that the prescription of Xyrem® should be restricted to patients with cataplexy.

- As noted in the Approvable action letter of 4/9/02, this application has been reviewed under the restricted distribution regulations contained in 21 CFR 314.520 of Subpart H.

- Overall, this application can be considered to have provided sufficient evidence for the efficacy and safety of Xyrem® to justify approval for the treatment of cataplexy accompanying narcolepsy, but only on condition that the full risk management plan described by me above is adopted. A critical element of this plan is the dispensing of the drug exclusively to patients with cataplexy; currently neither the plan proposed by the sponsor in the current submission nor that proposed by the Agency in the Approvable letter of 4/9/02 provides for such a restriction. I therefore strongly recommend that Xyrem® not be approved based on the application, as it currently stands. On the other hand, should off-label use of Xyrem® be prohibited under the risk management plan, I would recommend that Xyrem® be approved under the conditions of use proposed in the labeling accompanying this application as subsequently edited by me.

  I must emphasize that, in making such a recommendation, I am in no way suggesting that the prescription of Xyrem® be denied to patients with cataplexy accompanying narcolepsy; in that population there is a clear need for the drug (currently Xyrem® is available to such patients through a treatment IND). In fact, it would be most unfortunate for patients with cataplexy, if the drug had to be withdrawn from marketing after approval as a result of adverse events that occurred specifically as a result of off-label use.

  While this Agency has traditionally avoided limiting the off-label use of marketed drugs, I believe concerns about the safety of Xyrem® that I have already outlined fully justify an exception to that policy.

22. Recommendations

I strongly recommend that this application not be approved and that a Not-Approvable letter be issued.

Ranjit B. Mani, M.D.
Medical Reviewer

J. Feeney, M.D. _____

rbm 6/13/02
cc:
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NDA
Homonnay 21196

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/s/

Ranjit Mani
7/9/02 11:37:20 AM
MEDICAL OFFICER

John Feeney
7/15/02 06:08:12 PM
MEDICAL OFFICER
See my memo

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21196 (N-B2)**
Sponsor:	**Orphan Medical Inc.**
Drug:	**Xyrem®**
Proposed Indication:	**Narcolepsy**
Material Submitted:	**Response To Approvable Letter**
Correspondence Date:	**10/5/01**
Date Received / Agency:	**10/9/01**
Date Review Completed	**3/29/02**
Reviewer:	**Ranjit B. Mani, M.D.**

Background

This document is an **addendum** to my main review of an Amendment to the sponsor's NDA. The Amendment, submitted 10/5/01, was itself a response to an Approvable letter dated 7/2/01.

Please see my main review of the submission, completed 3/4/02, for full details about the contents of this Amendment.

This addendum is intended to address 2 key items that were either not included in my main review, or developed since that review was completed

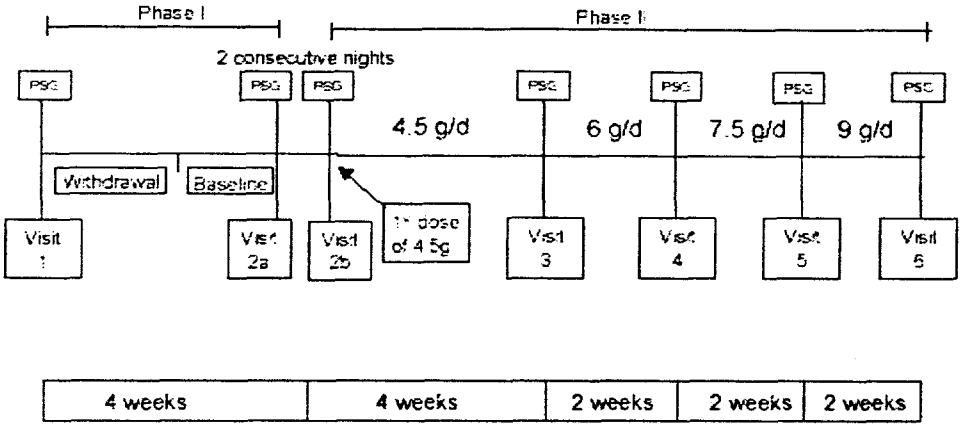
- Respiratory event and oxygen saturation data on patients with sleep apnea who were included in the OMC-SXB-20 study
- The inspection of a key study site (site #8; Principal Investigator: Martha Hagaman, MD) participating in the OMC-SXB-7 treatment IND and other studies.

Sleep Apnea Patients In OMC-SXB-20

Background

Outline Of Study Design

OMC-SXB-20 was an open-label, uncontrolled, sequential escalating-dose study that was originally, and primarily, intended to evaluate the effects of Xyrem® on EEG-based sleep architecture in patients with narcolepsy. The design of the study is summarized in the following figure



Dosing Regimen

Each total nightly dose of GHB shown in the above figure was administered in 2 equal divided doses, 2.5 to 4 hours apart.

Subjects Enrolled And Their Disposition

Patients with narcolepsy were enrolled in the study; a protocol-specified exclusion criterion was the presence of sleep apnea.

The number of patients screened and enrolled in this study, and the study groupings used for analysis purposes is summarized in the following tables

Category	Criteria
Enrolled	All patients enrolled
Treated	Enrolled patients who completed at least Visit 1
Completed	Treated patients who completed all visits (through Visit 6)
Intent-To-Treat	Treated patients who completed at least one post-treatment evaluation. "For this open-label dose-escalation study, patients were considered intent-to-treat when they completed a dose-escalation, at least through Visit 4, and where the data was readable."

Grouping	Number	Comments
Screened	27	One screened patient (Initials. — #17305) did not pass the drug screen
Enrolled	26	One enrolled patient (#41305) did not continue past Visit 1 and was never exposed to Xyrem®. The patient was dropped from the study on account of an elevated sleep apnea index, an exclusionary criterion
Treated	25	4 treated patients did not complete all visits • Patient #17304 discontinued at Visit 5 on account of an adverse event but was included in the intent-to-treat analysis as the patient did complete Visit 4 • Patient #17306 was lost to follow-up after Visit 2 • Patient #41310 withdrew consent after Visit 2 • Patient #42305 had an adverse event after Visit 2
Completed	21	One patient who completed the trial (#26300) was not included in the intent-to-treat cohort in the formal study report, or in the original analysis included in the current submission because the data were not readable
Intent-To-Treat	21	The intent-to-treat cohort consisted of 20 completers (i.e., all completers minus patient #26300) plus patient #17304

Relevance Of Study To Current Submission

The final study report for OMC-SXB-20 was submitted and reviewed by me prior to the Approvable Letter of 7/2/01 being issued

Arterial oxygen saturation data from all-night recordings, and data on the frequency and severity of specific respiratory-event-related measures were collected as part of the polysomnogram recordings in this study but were not included in the final clinical trial report.

In the Approvable letter that was issued on 7/2/01 it was noted that although GHB was a central nervous system depressant and therefore capable of producing respiratory depression, no formal assessment of its effects on respiration had been performed. It was recommended that a study be performed to assess the effects of GHB on respiration. The following was stated in the Approvable letter:

"The study should examine the effects of the recommended dosing regimen (2 doses nightly, including the highest recommended dose-9 gms divided), with both doses given in the fasted state. The study should include patients who are and who are not receiving concomitant stimulant treatment, a positive control, and patients with concomitant illnesses that might increase their risk of respiratory depression (e.g., patients with COPD, sleep apnea, etc.)."

At a meeting with the sponsor held on 7/16/01 it was agreed that an analysis of respiratory data from OMC-SXB-20 could be submitted as part of the Amendment currently under review. The Division also agreed that if the respiratory data from the OMC-SXB-20 study provided some degree of reassurance that Xyrem® did not have a respiratory depressant effect, the study recommended in the previous paragraph could be done as part of a post-marketing commitment.

The respiratory event and oxygen saturation data for this study have been largely addressed in my main review of the submission

Respiratory Event And Oxygen Saturation Outcome Measures For Study

Respiratory Effect Measures

These include respiratory event data and oxygen saturation data

Respiratory Event Measures

These are defined as follows (the definitions are standard ones)

Apnea-Hypopnea Index (AHI)

The apnea-hypopnea index is the incidence (events per hour) of apnea and hypopnea events associated with sleep calculated separately for NREM and REM sleep

This is calculated as follows

Number of central apneas + Number of obstructive and mixed apneas + Number of hypopneas

(during REM or NREM sleep) / Number of hours of (NREM or REM) sleep

The severity of sleep apnea is defined as follows based on this index

Mild	5 to 15 events per hour
Moderate	15 to 30 events per hour
Severe	> 30 events per hour

Respiratory Disturbance Index (RDI)

The respiratory disturbance index is the incidence (events per hour) of apnea and hypopnea events associated with sleep, independent of sleep stage, represented by all sleep apnea events during the sleep period (obstructive + central + mixed) + all hypopnea events / number of hours of sleep during the study period.

It is calculated as a weighted average of AHI (NREM) and AHI (REM) with respect to the time spent in NREM and REM sleep, respectively.

The severity of sleep apnea is defined as follows based on this index

Mild	5 to 15 events per hour
Moderate	15 to 30 events per hour
Severe	> 30 events per hour

Number Of Obstructive And Mixed Apneas (OMAs)

Obstructive apnea is partial or complete upper airway obstruction during sleep. An obstructive apneic event is characterized by a transient cessation of breathing lasting > 10 seconds, in the presence of sustained respiratory effort, accompanied by oxygen desaturation of > 3% or arousal

Mixed apnea is a lack of respiratory effort during the initial apneic period followed by gradually increasing effort against an occluded upper airway. This is a variant of an obstructive apneic event during which respiratory effort is absent for several seconds after the onset of upper airway occlusion.

Number Of Central Apneas

Central apnea is defined as sleep apnea in the absence of upper airway obstruction and in the absence of inspiratory effort indicating reduced output to the muscles of inspiration from the central nervous system. A central apneic event is characterized by a cessation in airflow lasting ≥ 10 seconds, accompanied by oxygen desaturation of > 3%, or arousal, and a clear reduction in esophageal pressure swings from baseline, or absence of paradoxical respiratory effort which would indicate airway obstruction

Number of Hypopneas

Hypopnea is defined as a reduction in airflow despite ongoing inspiratory efforts. An obstructive hypopnea event is characterized by a transient reduction in breathing lasting > 10 seconds, with a clear decrease (> 50%) from baseline in the amplitude of breathing, or a decrease < 50% in the amplitude of breathing, accompanied by oxygen desaturation of > 3% or arousal.

Oxygen Saturation (SaO_2) Measures

These are as follows

Lowest SaO_2

Continuous SaO_2

These are data collected as mean values of 5 minutes of data during the recording period

Intermittent SaO_2

These are data collected as mean values of 1 minute of data at 8 dispersed timepoints during the recording period, including lights-out (immediately after dosing), after 30, 60, 90, 120, 150, and 180 minutes, and lights-on (about 240 minutes)

Duration Of Time That Artifact-Free Sao_2 Recordings Were < 80% And < 90% Of Saturation,

This is expressed as a percentage of the 240 minutes for the study duration and as a percentage of the total time that the SaO_2 channel was artifact-free.

Conclusions Derived From Earlier Review Of Respiratory Event And Oxygen Saturation Data In This Study

In my main review of the respiratory event and oxygen saturation data in this study, I had come to the following conclusions. Please see the review for full details

- It is difficult to draw any firm conclusions from this study regarding the effect of sodium oxybate on respiratory parameters; the reasons for such a view are as follows
  - The study was open-label and uncontrolled
  - The number of patients enrolled was small
  - There was considerable inter-patient variability in changes from baseline in all parameters with standard deviations consistently exceeding means
  - The study was intended to measure the effects of 4 different doses of GHB on sleep architecture and not to assess the effects of that drug on respiration.
  - The only true measures of respiratory function per se in this study were those related to arterial oxygen saturation. The "respiratory event parameters" used in this study were indices of sleep apnea and not of respiratory function, per se
- Among the numerous comparisons made in the sponsor's analysis, some were nominally statistically significant ($p < 0.05$). The clinical significance of the differences seen in most of these comparisons is however highly questionable.
- As the sponsor has also noted the most prominent mean inter-visit changes for the whole cohort were seen between baseline and Visit 3 (after 4 weeks at 4.5 g/day) with increases in obstructive and mixed apneas, and hypopneas, and a decrease in continuous SaO_2 (5-minute data). Again, although these changes were statistically significant they were clinically minimal and may have been driven largely by a single patient (#17301)
- There was no overall tendency in this cohort to a dose-response in regard to respiratory event parameters and SaO_2 (i.e., an increasing effect on respiratory event parameters and SaO_2 with increasing dose of GHB)
- The rather prominent increase in several parameters - obstructive and mixed apneas, hypopneas, apnea-hypopnea index and respiratory disturbance index – relative to baseline in a single patient (#17301) after 4 weeks of treatment with GHB at 4.5 g/day is at least somewhat noteworthy in itself. The same patient also showed a steady increase in the duration of time spent during the first half of the night at an SaO_2 less than 90%. However this patient did have pre-existing obstructive sleep apnea and there is no evidence that the changes in respiratory event parameters and SaO_2 were related to GHB; the respiratory event parameters in fact improved as the dose of GHB was increased through 6, 7.5 and 9 g/day, when it might have been expected that exposure to GHB was increasing.

- It is noteworthy that 18/21 patients who completed the study received stable doses of stimulant drugs throughout the trial. It is not inconceivable that such drugs may have led to any respiratory depressant effects of GHB becoming less apparent.
- While this study clearly had limitations it cannot be said to provide any evidence that Xyrem® has, or does not have, a respiratory depressant effect.

Focus Of Current Review

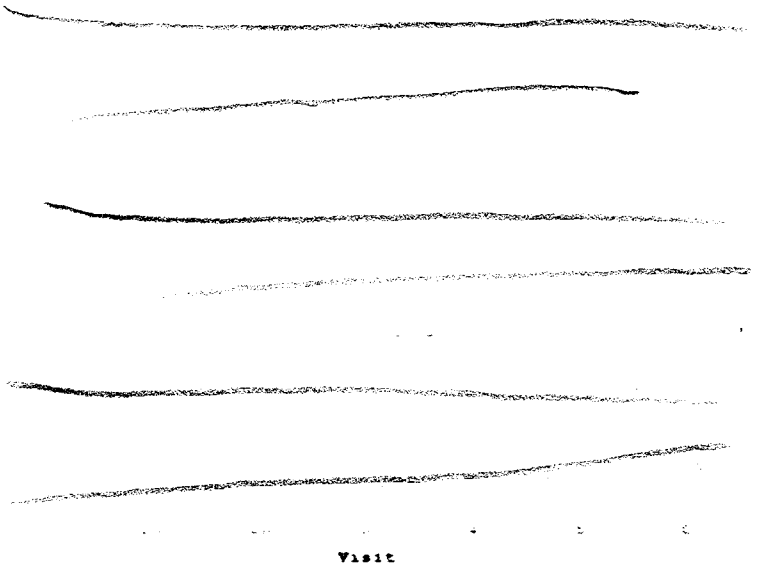
Through the efforts of Dr John Feeney, attention has been drawn to changes in respiratory event parameters in patients with pre-existing sleep apnea enrolled in the study (despite the presence of sleep apnea being an exclusion criterion) have been highlighted ,and have been considered a matter of concern. These patients will be described further in this review. The description of these patients is based upon the original submission of 10/5/02 and several recent responses to questions and requests for information from this Division.

The following table lists patients who may be considered to have had at least mild sleep apnea based on an RDI > 5 at Visit 1, Visit 2a or both, during any half of the night. Patients whose numbers are highlighted in bold type could be considered to have moderate-severe sleep apnea based on an RDI > 15 during any half of the night at Visit 1 or 2a. These patients are described further below

Patient Number	Visit	Respiratory Disturbance Index	
		First half of night	Second half of night
17301	1	7.08	3.74
	2a	14.12	32.42
17302	1	4.88	3.18
	2a	27.52	13.95
17304	1	54.36	87.09
	2a	27.39	36.02
02630*	1	10.1	2.4
	2a	3.7	2.1
42302	1	8.93	12.68
	2a	10.33	4.96
41304	1	8.13	3.25
	2a	0	1.46
41306	1	21.73	19.43
	2a	1.25	5.78
41308	1	3.08	9.59
	2a	0	0.59
41310	1	6.53	1.68
	2a	0.67	0.39
42300	1	3.13	10.14
	2a	3.01	8.65
42301	1	0.74	1.05
	2a	5.36	2.71
42303	1	32.07	20.88
	2a	24.07	45.24

*The overall all-night RDI at Visits 1 and 2a were 6.5 and 3.0, respectively

The patients with moderate-to-severe sleep apnea, and a single patient with mild sleep apnea are further described below.



Changes in RDI over the course of the study are summarized in the following table

Visit	Respiratory Disturbance Index	
	First half of night	Second half of night
1	7.08	3.74
2a	14.12	32.42
2b	7.96	21.36
3	100.9	76.36
4	39.58	39.63
5	24.67	56.88
6	31.2	42.04

The increase in obstructive and mixed apneas, hypopneas, AHI and RDI, seen at Visit 3 was not maintained despite further increases in dose of GHB during the remainder of the study .

This patient also had the following changes in a SaO_2 parameter, the duration of time spent with an SaO_2 less than 90% (see plots below). These changes did not correlate temporally with changes in respiratory event parameters

- For measurements done during the first half of the night a steady increase was seen over the course of the trial beginning at a dose of 6 g/day.
- For measurements done during the second half of the night this parameter showed prominent fluctuations during the course of the study.

The following plots taken from the study report for OMC-SXB-20 depict the duration of oxygen desaturation (percentage of each 4-hour period with SaO_2 less than 90%) by visit, for the first and second halves of each night, respectively

Patient #17302

Clinical information is not available for this patient. Based on the RDI at Visit 2a, the baseline visit, the patient does appear to have had moderate pre-existing sleep apnea.

RDI data for this patients are in the following table taken from the original data listings

Visit	Respiratory Disturbance Index	
	First half of night	Second half of night
1	4.88	3.18
2a	27.52	13.95
2b	Not available	Not available
3	29.63	37.66
4	9.2	14.02
5	2.08	11.88
6	1.72	5.82

In a subsequent submission the sponsor has provided a comprehensive table of the patient's respiratory event and oxygen saturation data, which I have copied below. Data for Visit 2b which were not included in the original data listings are highlighted in yellow.

Output Variables for Pabent D26300	Visit 1 (anti-cataplectic medication)	Visit 2a (BASELINE)	Visit 2b (First Night at 4.5g)	Visit 3 (4 wks@4.5g)	Visit 4 (2 wks@6g)	Visit 5 (2 wks@7.5g)	Visit 6 (2 wks@9g)
1st_Number_of_Central_Apneas_(REM)							
2nd_Number_of_Central_Apneas_(REM)							
1st_Number_of_Central_Apneas_(NREM)							
2nd_Number_of_Central_Apneas_(NREM)							
1st_Number_of_Hypopneas_(REM)							
2nd_Number_of_Hypopneas_(REM)							
1st_Number_of_Hypopneas_(NREM)							
2nd_Number_of_Hypopneas_(NREM)							
1st_No_of_Obstructive_and_Mixed_Apneas_(REM)							
2nd_No_of_Obstructive_and_Mixed_Apneas_(REM)							
1st_No_of_Obstructive_and_Mixed_Apneas_(NREM)							
2nd_No_of_Obstructive_and_Mixed_Apneas_(NREM)							
1st_Respiratory_Disturbance_Index							
2st_Respiratory_Disturbance_Index							
1st_Apnea/Hypopnea_Index_(REM)							
2nd_Apnea/Hypopnea_Index_(REM)							
1st_Apnea/Hypopnea_Index_(NREM)							
2nd_Apnea/Hypopnea_Index_(NREM)							
1st_Lowest_O2_Saturation_(%)_(NREM)							
2nd_Lowest_O2_Saturation_(%)_(NREM)							
1st_Lowest_O2_Saturation_(%)_(REM)							
2nd_Lowest_O2_Saturation_(%)_(REM)							

* In this table, the "n/a" for lowest O2 saturation% (REM) for the first half of the night refers to the fact that the saturated oxygen signal during REM sleep during the first half of the night for these visits was so noisy that the minimum level could not be established

Note that the Respiratory Disturbance Index (for both halves of the night) was highest for this patient at Visit 3 (after 4 weeks of treatment at 4.5 g/day)

Patient #17304

This patient who discontinued Xyrem® during this trial on account of an adverse event was a 67 year old woman with a known history of narcolepsy (for 25 years), tonsillectomy, breast cancer in remission (treated with lumpectomy and radiation) and obstructive sleep apnea-hypopnea syndrome (confirmed by polysomnogram done over 1 ½ years prior to her enrollment) . Concomitant medications included venlafaxine and modafinil.

At screening this patient had a reportedly false-positive urine test for benzodiazepines. After entering the OMC-SXB-20 trial she failed to attend Visit 3 (on trial date 29) and indicated a desire to discontinue medication. However she then changed her mind and attended Visit 3 on Day 36. On Day 51, a day after beginning Xyrem® in a dose of 7.5 g/day she reported being "really sensitive" and her husband noted worsening snoring, and frequent and more severe episodes of apnea. By that time she had been treated with the following doses of Xyrem®: 4.5 g/day for 35 days and 6.0 g/day for 14 days. Xyrem® was discontinued on Day 51 on account of a perceived worsening in her obstructive sleep apnea-hypopnea syndrome. The adverse event was reported to have resolved by Day 52.

Her last study visit was Visit 4.

Several objective parameters – AHI (NREM), OMAs and RDI – all measured during the second half of the night showed no worsening at Visits 3 and 4 as compared with Visits 1 and 2a. However the following were seen only at Visits 3 and 4

- Increased AHI (REM and NREM), central apneas, hypopneas, and RDI during the first half of the night
- Increased AHI (REM) and central apnea during the second half of the night

Changes in RDI over the course of the study are summarized in the following table which I have created from the data listings

Visit	Respiratory Disturbance Index	
	First half of night	Second half of night
1	54.36	87.09
2a	27.39	36.02
2b	Not available	Not available
3	99.42	100.87
4	57.92	47.77

Oxygen saturation data are further summarized below. Lowest SaO_2 data are summarized in the following table

Visit	Lowest oxygen saturation (%)	
	First half of night	Second half of night
1	89	87
2a	91	87
2b	Not available	Not available
3	89	87
4	84	86

Plots by visit for another oxygen saturation parameter, the percentage of the 4-hour period with an $SaO_2 < 90\%$ are below, copied from a submission provided by the sponsor

Visit	Respiratory Disturbance Index	
	First half of night	Second half of night
5	8.36	9.79
6	2.14	2.7

The lowest SaO_2 recorded in this patient at each visit is summarized in the following table which I have created from the data listings

Visit	Lowest oxygen saturation (%)	
	First half of night	Second half of night
1	83	85
2a	87	90
2b	87	89
3	90	90
4	87	86
5	89	89
6	88	88

APPEARS THIS WAY
ON ORIGINAL

Patient #42303

A clinical description is not available for this patient

Changes in this patient's RDI over the course of the study are summarized in the following table

Visit	Respiratory Disturbance Index	
	First half of night	Second half of night
1	32.07	20.88
2a	24.07	45.24
2b	35.39	33.06
3	31.21	30.76
4	11.81	21.59
5	36.61	26.45
6	23.69	12.8

APPEARS THIS WAY
ON ORIGINAL

The lowest SaO_2 recorded in this patient at each visit is summarized in the following table which I have created from the data listings

Visit	Lowest oxygen saturation (%)	
	First half of night	Second half of night
1	85	92
2a	92	92
2b	91	91
3	89	92
4	90	92
5	89	84
6	91	92

APPEARS THIS WAY
ON ORIGINAL

Description Of A Single Patient With Mild Sleep Apnea At Baseline

Patient #02630

Patient #02630 completed the study but the data were not included in the 10/5/01 submission as they were unreadable for the following reason: the nocturnal polysomnogram data for this patient were not convertible by the ——— ——— , (the central reading facility for this study) as Site #26 used an optical disk recording system instead of a CD-R based system. The data for this patient were instead submitted on 3/12/02, in response to a specific query from the Division seeking to fully account for all patients participating in the study.

The investigator for Site #26 was contacted and asked to score both the respiratory event and oxygen saturation data for this patient. The scoring of the overnight polysomnogram data was then carried out by the a single technician consistent with that site's clinical practice.

Narrative

This 58 year old man had a medical history significant for narcolepsy, obesity, "mild apnea," plastic surgery for ptosis and on the ears, a submucous resection for a deviated septum and smoking. Concomitant medication included sertraline (withdrawn during the study as per protocol), a nicotine patch, nabumetone, methylprednisolone and cyclobenzaprine. While on treatment with GHB he experienced brief, intermittent anxiety, dizziness, nausea, and vomiting.

Table

The following table provides respiratory event and oxygen saturation data for patient #026300. Note that he had a total AHI/RDI of 6.5 at Visit 1 which is consistent with mild sleep apnea.

Output Variables for Patient 026300	Visit 1 (anti-cataplectic meds)	Visit 2a (BASELINE)	Visit 2b (1st nt@ 4.5g)	Visit 3 (4 wks@4.5g)	Visit 4 (2 wks@6g)	Visit 5 (2 wks@7.5g)	Visit 6 (2 wks@9g)
1st Half Number of Hypopneas and Apneas							
2nd Half Number of Hypopneas and Apneas							
1st Half Apnea/Hypopnea Index (NREM)							
2nd Half Apnea/Hypopnea Index (NREM)							
1st Half Apnea/Hypopnea Index (REM)							
2nd Half Apnea/Hypopnea Index (REM)							
1st Half Apnea/Hypopnea Index (Total) *							
2nd Half Apnea/Hypopnea Index (Total)							
Obstructive Apneas (NREM)							
Mixed Apneas (NREM)							
Central Apneas (NREM)							
Hypopneas (NREM)							
Obstructive Apneas (REM)							
Mixed Apneas (REM)							
Central Apneas (REM)							
Hypopneas (REM)							
Apnea/Hypopnea Index (REM)							
Apnea/Hypopnea Index (NREM)							
Apnea/Hypopnea Index (Total)							
Lowest O_2 Saturation (%) (NREM) **							
Lowest O_2 Saturation (%) (REM)							

The representation of "1st" and "2nd" in the labels for the output variables are as follows. "1st" refers to the first half of the night, which represents the 1st dosing. "2nd" refers to the second half of the night, which represents the 2nd dosing, taken four hours after the 1st dose.

* Terminology of "Apnea/Hypopnea Index" and "Respiratory Disturbance Index" are used interchangeably when combining REM and NREM indices.

** Lowest O_2 Saturation (%) represents the lowest measurement of O_2 Saturation (%) while the patient was having a respiratory event. This is unique for this site, in contrast to the centralized scoring from Stanford which recorded the lowest O_2 Saturation (%) value for the entire time period, whether the patient had a respiratory event or not.

Sponsor's interpretation of results

"In general, these data convey intra-patient variation across doses without a first night effect. This is consistent with the results demonstrated for the main OMC-SXB-20 respiratory events data obtained through centralized scoring."

Reviewer's Comments

- As noted earlier it is difficult to draw any firm conclusions from this study as a whole regarding the effect of sodium oxybate on respiratory parameters; the reasons for such a view are as follows
  - The study was open-label and uncontrolled
  - The number of patients enrolled was small
  - There was considerable inter-patient variability in changes from baseline in all parameters with standard deviations consistently exceeding means

- However when individual data listings for patients are reviewed concerns have been raised about the effects of Xyrem® on respiratory parameters in patients with pre-existing sleep apnea. Particularly noteworthy are 2 patients
  - Patient 17301 who had the following abnormalities:
    - An elevated RDI at baseline, falling in the 'moderate to severe sleep apnea' range increasing up to ~ 100 an extremely abnormal value, at Visit 3, after 4 weeks of treatment at 4.5 g/day
    - A steady increase over the course of the study (i.e., with increasing dose) in the period of time spent at an SaO_2 < 90%; by the end of the study almost 70% of a 4 hour period had been spent at an oxygen saturation in that range.
  - Patient 17304 who had the following abnormalities
    - An elevated RDI at baseline falling in the severe sleep apnea range increasing further to ~ 100 at Visit 3 , after 4 weeks of treatment at 4.5 g/day
    - A perception by her husband that the severity of her snoring as well as apneic episodes had increased over the course of the trial leading her to discontinue at Visit 4

  Admittedly,
  - No evidence of a dose response in the severity of sleep apnea were seen in either of these patients
  - Changes in oxygen saturation parameters in these patients did not correlate with changes in RDI
  - It cannot be proven that the changes in respiratory parameters in these 2 patients were due to Xyrem® as opposed to spontaneous variability in the severity of sleep apnea
- The study cannot therefore be considered to provide reassurance that Xyrem®, clearly a central nervous system depressant drug, does not have a respiratory depressant effect, especially in patients with pre-existing obstructive sleep apnea. In this regard, it is noteworthy that narcolepsy and obstructive sleep apnea are reported to co-exist frequently.
- In order to provide reassurance that Xyrem® does not have a respiratory depressant effect, a formal controlled trial evaluating the effects of Xyrem® on respiratory parameters and oxygen saturation in patients with already compromised pulmonary function, and especially in those with obstructive sleep apnea, appears warranted. An alternative approach, contraindicating use of the drug in patients with obstructive sleep apnea, appears less desirable without the availability of "hard" data to support restricting the use of the drug in what must be a significant proportion of those with narcolepsy.
- This concern is especially justified given that at least 2 subjects reviewed earlier in the NDA, one a healthy subject and the other a patient with narcolepsy, appear to have developed depressed respiration when given doses of Xyrem® within the recommended range. In addition, at least one further subject participating in earlier clinical trials of Xyrem® was reported to have developed breathing difficulty on 2 separate occasions, once at a dose of 9 g/day and later at a dose of 3 g/day, and needed to discontinue Xyrem® on each occasion; although a narrative supplied by the sponsor suggests that the cause of the patient's difficulty breathing may have been sleep paralysis that has not been substantiated.

Problems with Study Site #8 (Martha Hagaman, MD)

Background

- Dr Martha Hagaman is/has been a principal investigator for the following Orphan-sponsored clinical trials of Xyrem®: OMC-GHB-2, OMC-SXB-21, OMC-GHB-3, OMC-SXB-6 and OMC-SXB-7. Only the OMC-SXB-7 study is currently ongoing as part of Treatment IND # [redacted]

- This Division was first informed of a problem at this study site in a communication from Orphan Medical, Inc., dated 1/24/02 (the submission was made under IND [redacted], serial #056). In that submission we were informed that the St Thomas Hospital Institutional Review Board in Nashville, TN, had, in a letter dated 1/21/02 terminated the OMC-SXB-7 study at that hospital; Dr Hagaman was conducting the study at that site under the jurisdiction of that Institutional Review Board. A copy of the Institutional Review Board letter was provided by Orphan Medical, Inc., along with the submission.

  In the communication to this Division, the sponsor suggested at least one of the alleged irregularities in drug dispensing records, cited by the Institutional Review Board, may not have a valid basis. The sponsor planned to retain an external auditor to conduct an independent review of the study records

- The reasons cited in the Institutional Review Board letter of 1/23/02 for the termination of the study may be summarized as follows

  - Irregularities in the drug dispensing records (the primary reason)
  - Failure to store study drug in a secure location
  - Maintaining study records at another medical center with failure to move records to the registered site within the period stipulated by the Institutional Review Board
  - Use of an expired consent form
  - Failure to provide the Institutional Review Board with a Form 1572 after an earlier suspension (March to May 2001) for conducting the study while living in [redacted]
  - Failure to deliver protocol amendments on time to the Institutional Review Board
  - Attempts by Dr Hagaman to serve as the principal investigator for the study while living in [redacted]

- The Institutional Review Board's actions were discussed by the Division with the sponsor in a teleconference on 2/7/02. Among items discussed were the following:

The sponsor indicated that an independent auditor had visited the study site and not been able to substantiate the concerns of the Institutional Review Board

- In a subsequent submission dated 2/14/02 (under IND —— serial #058) the sponsor indicated that Dr Hagaman was in fact previously terminated by the Institutional Review Board as Principal Investigator for Study —— The sponsor further stated that she was replaced as Principal Investigator on 2/15/01 by Dr —— and was re-instated as Principal Investigator on 1/3/02*. FDA 1572 forms covering both these actions were not previously submitted to the Division [as required under 21 CFR 312.30 (c)]. In the same submission the sponsor indicated that for the period when Dr Hagaman was living while continuing to function as Principal Investigator, she was traveling to Nashville regularly to see patients.

*Note that, although the sponsor states that Dr Hagaman was re-instated as Principal Investigator on 1/3/02, the St Thomas Hospital Institutional Review Board in its letter of 1/23/02 terminating the OMC-SXB-7 study at the hospital, indicated that Dr Hagaman was in fact reinstated in May 2001.

- An independent audit of the study site was requested by Orphan Medical, Inc. The audit was performed by —— on January 28-30, 2002. He concluded that the site was "in substantial compliance with FDA's good clinical practices."

FDA Inspection

An inspection of the Hagaman study site was performed by Patricia Smith, Investigator, of the New Orleans District Office, and Ni Khin, MD, of the Division of Scientific Investigations, accompanied by John Feeney, MD, of this Division. The inspection was performed from March 11-14, 2002.

4 studies were reviewed at the time of the inspection: OMC-GHB-2, OMC-GHB-3, OMC-SXB-7, and OMC-SXB-21.

An FDA Form 483 was issued to Dr Hagaman at the end of the visit. The deficiencies listed in the form may be summarized as follows: