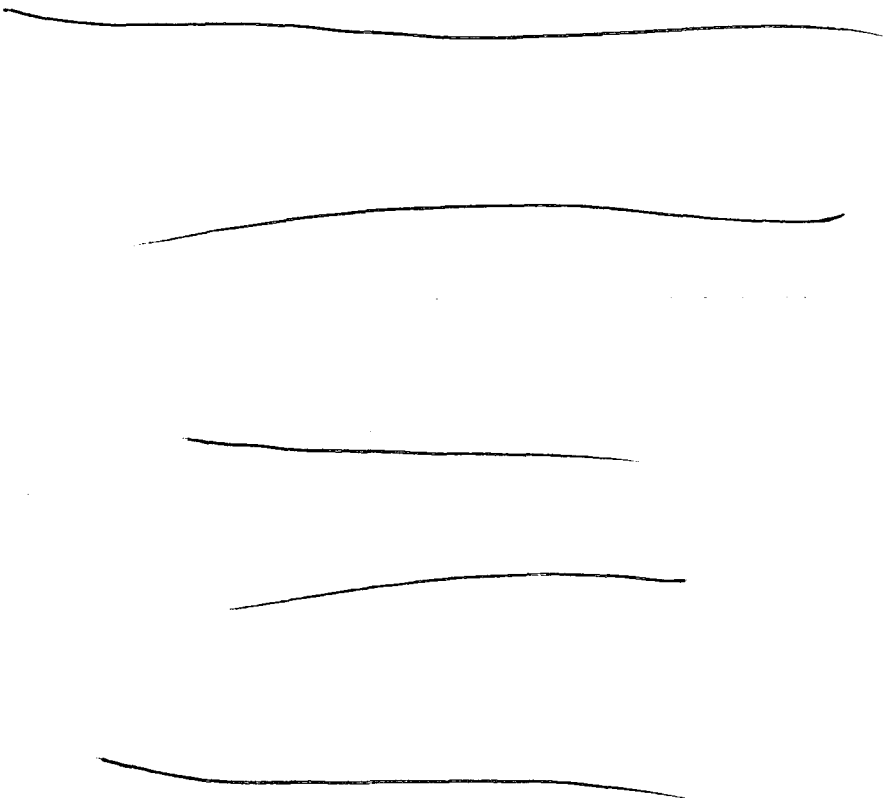
1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.



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

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

Re-Analysis Of Efficacy Data Excluding Site #8

Dr Sharon Yan has repeated the primary efficacy analysis for the 2 key efficacy studies, OMC-GHB-2 and OMC-SXB-21, excluding data from Site #8. The results may be summarized as follows

OMC-GHB-2

The overall p-value for the overall GHB (all groups) vs placebo comparison was 0.0023, with GHB being superior to placebo. For the comparison of individual dose groups vs placebo, a statistically significant difference was seen only between the 9 g dose and placebo.

OMC-SXB-21

The p-value for the GHB-placebo comparison was ≤ 0.0001 with GHB being superior

Note that at the time the Hagaman site was inspected, it was possible for those conducting the inspection to confirm the accuracy of the efficacy data for the OMC-GHB-2 and OMC-SXB-21 studies using patient diaries for that site as source documents

Comments

- A total of 38 unique patients with narcolepsy were enrolled in Orphan-sponsored clinical trials at the Hagaman study site (site #8). Note that the entire safety database for this NDA (excluding the Scharf open-label trial) consists of only 466 patients with narcolepsy.
- All except 2 of the patients at this site participated in longer-term safety studies.
- The initial results of the inspection of the Hagaman site, based on the FDA Form 483 and direct feedback from those who conducted the inspection raises a very serious concern about the reliability of the safety data obtained from this site. Key items contributing to this concern were as follows

    - An inability to match data noted in Case Report Forms with those noted in source documents in many instances
    - The impression that data in the Case Report Forms and source documents may not have adequately captured the full range of more troublesome adverse events seen in patients at this study site. Contributing to this impression were the general lack of clinic/progress notes, and phone logs and the indication that studies were inadequately supervised by Dr Hagaman (she was residing in —— for many months while the study site was located in Nashville)

- More importantly, the results of the inspection have raised equally serious concerns about Orphan's oversight of its clinical trials. Inspections of one or more additional centers, particularly large centers, also contributing to the safety database appear to be warranted.
- Dr Hagaman has submitted a detailed response to the Form 483 which is currently being reviewed; however, it will not be possible for our concerns

regarding this site to be adequately resolved during the course of the current review cycle.

- There is no concern at present that efficacy data obtained from the Hagaman site for studies OMC-GHB-2 and OMC-SXB-21 have been compromised in any way

Recommendations

- In my earlier review of this Amendment, completed on 3/4/02, I had recommended that Xyrem® "be approved for the treatment of cataplexy, provided, and only if, key elements of a risk management plan are imposed as a condition for approval; these key elements are prohibition of the off-label use of Xyrem®, and the imposition of Subpart H of the Accelerated Approval Regulations."
- Since that time
  - Fresh concerns have emerged about the respiratory depressant effects of Xyrem®, especially in patients with obstructive sleep apnea, a condition that is reported to co-exist frequently with narcolepsy
  - The reliability of the long-term safety data from a study site, and, more importantly, of the sponsor's overall oversight of its clinical trial program have been seriously called into question
- Under these changed circumstances I would recommend that an Approvable letter be issued again for this application, instead of an Approval letter as originally recommended.
- As the next steps in addressing the above concerns I would recommend the following
  - Inspection by the Agency of one or more additional study sites involved in the treatment IND study OMC-SXB-7; the site chosen should have recruited a fairly high proportion of patients participating in the trial. The purpose of such an inspection would be to determine if deficiencies of safety data are more widespread than hitherto supposed.
  - Completion by the sponsor of a controlled study of the effects of Xyrem® on respiration in patients with compromised pulmonary function, including those with obstructive sleep apnea.

Ranjit B. Mani, M.D.
Medical Reviewer

J. Feeney, M.D. _____

rbm 3/29/02
cc:
HFD-120
NDA 21196 (N-B2)

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

/s/

Ranjit Mani
4/3/02 02:07:05 PM
MEDICAL OFFICER

John Feeney
4/3/02 02:24:26 PM
MEDICAL OFFICER
see my cover memo for my thoughts on this application

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21196 (N-B2)**
Sponsor:	**Orphan Medical Inc.**
Drug:	**Xyrem®**
Proposed Indication:	**Narcolepsy**
Material Submitted:	**Amendment To NDA**
Correspondence Date:	**10/5/01**
Date Received / Agency:	**10/9/01**
Date Review Completed	**3/4/02**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This submission, an Amendment to the sponsor's NDA, is a response to an Approvable letter dated 7/2/01.

The Approvable action was based on the original NDA for Xyrem®, which was submitted on 9/30/00, and a Major Amendment submitted on 3/23/01; the original NDA was granted priority review status. The application was also discussed at a meeting of the Peripheral And Central Nervous System Drugs Advisory Committee which was held on 6/6/01. Please see the following Agency-created documents for full details

- The efficacy and safety reviews of the original NDA
- The clinical review of the Major Amendment
- The transcript of the Advisory Committee meeting
- The text of the Approvable letter

Subsequent to the issuance of the Approvable letter, 2 further meetings were held with the sponsor

- A meeting on 7/16/01 to discuss the sponsor's action plan in response to the Approvable letter; and the structure of the current Amendment
- A meeting on 10/1/01 to discuss the items in the Approvable letter (pertaining to the risk management plan and labeling) that the sponsor disagrees with.

Please see the minutes of these meetings and pertinent reviews for full details.

In addition to the above meetings a communication from the sponsor on 7/25/01 outlined the proposed contents of the Amendment including the Safety Update. The Division agreed with the sponsor's proposal.

The indication currently being pursued by the sponsor is as follows:

"Xyrem® (sodium oxybate) oral solution is indicated for the treatment of cataplexy in patients with narcolepsy"

Xyrem® has been developed by Orphan Medical, Inc. for the treatment of narcolepsy under IND # —— and Treatment IND # —— Data obtained from individual sponsor-investigator INDs #s —— (M. Scharf) and (L. Scrima) have also been used in support of this application.

In this review the words/phrases "γ-hydroxybutyrate (GHB)", "sodium oxybate", and "Xyrem®" have been used interchangeably.

Prior to reviewing the contents of the submission, it will be helpful to list in tables all clinical studies that have been included in this NDA, including those described for the first time in the current submission.

2. List of All Clinical Studies In This Application

I have listed these studies in 2 categories

- Efficacy and safety studies
- Pharmacokinetic studies

2.1 Efficacy And Safety Trials

All patients enrolled in these trials had narcolepsy.

Study #	Design	Number of Patients	Duration	Status
OMC-GHB-2	Randomized, double-blind, placebo-controlled, parallel-arm	136 patients	4 weeks	Complete
OMC-GHB-3	Open-label, uncontrolled, extension study	118 patients	Up to 24 months	Complete
OMC-SXB-6	Open-label uncontrolled study	185 patients	6 months	Complete
OMC-SXB-7	Open-label uncontrolled study	268 patients	24 months or until approval	Ongoing
Scrima	Randomized, double-blind, placebo-controlled, cross-over study	20 patients	4 weeks*	Complete
Lammers	Randomized, double-blind, placebo-controlled, cross-over study	25 patients	4 weeks*	Complete
Scharf	Open-label uncontrolled study	143 patients	17 years	Complete
OMC-SXB-21	Randomized, double-blind, placebo-controlled, parallel-arm, RANDOMIZED WITHDRAWAL study after long-term open label treatment	55 patients	2 weeks**	Complete
OMC-SXB-20	Open-label, uncontrolled, dose-escalation study	27 patients	10 weeks	Complete

*GHB and placebo were each used for 4 weeks
**Period of randomized withdrawal
The number of patients listed for ongoing studies are those enrolled as of 6/30/01.
OMC-GHB-2 and OMC-SXB-21, as well as the Scrima and Lammers studies, were primarily intended to assess the efficacy of Xyrem® in treating cataplexy.
is primarily intended to assess the efficacy of Xyrem® in treating the excessive daytime sleepiness of narcolepsy
OMC-SXB-20 was intended to assess the effects of 4 different doses of Xyrem® on sleep architecture

Further comments about some of the above studies are below

Study #	Comments
OMC-GHB-3	Extension to OMC-GHB-2.
OMC-SXB-6	Treatment-naïve patients (except for a single patient previously in OMC-GHB-2 and OMC-GHB-3)
OMC-SXB-7	Extension to OMC-GHB-3 (53 patients) OMC-SXB-6 (121 patients) Scharf Study (66 patients) OMC-SXB-20 (20 patients) The numbers in parentheses in this cell refer to the number of patients entering OMC-SXB-7 from each study

2.2 Pharmacokinetic Trials

125 healthy subjects and 19 narcoleptic patients participated in these trials

Study #	Number of subjects/patients
OMC-GHB-4	6*
OMC-SXB-8	36
OMC-SXB-9	13
OMC-SXB-10	13**
OMC-SXB-11	36
OMC-SXB-12	15
OMC-SXB-14	12
OMC-SXB-17	13

*The 6 narcoleptic patients participating in this study also enrolled in the Scharf study
**The 13 narcoleptic patients participating in this study also enrolled in OMC-SXB-6

3. Contents Of Submission

The submission is in electronic format and has been provided on a CD-ROM. The cover letter is also available in paper.

The contents of the submission include the following separate sections

- Cover letter
- Proposed labeling
- Risk management program
- Proposed advertisement
- Report of an in-vitro study evaluating the inhibitory potential of GHB towards human hepatic microsomal cytochrome P450 isozymes
- Information about the status of 11 patients who were enrolled in the Scharf study and had not entered the treatment IND study #OMC-SXB-7 as of 5/31/99
- Analysis of sleepwalking
- Report on the respiratory effects of Xyrem® in Study #OMC-SXB-20
- Data about stimulant use in clinical trials of Xyrem®
- Safety update
- References supporting labeling annotations
- Pertinent FDA correspondence

Each of the above items, except the last two, are reviewed below, although not in the same order

4. Cover Letter

The cover letter

- Outlines the contents of the submission
- Requests that the submission be assigned a 2-month user fee goal
- Addresses individual items in the Approvable letter

The following summarizes the sponsor's view of how individual items in the Approvable letter have been addressed in this submission. The items in the approvable letter are themselves highlighted in bold and/or italic headings, in the

same order as in the cover letter accompanying this submission, with the sponsor's response under each heading.

4.1 Risk Management And Other Clinical Issues

4.1.1 Prescribers must state, in writing, that a patient has narcolepsy with cataplexy before drug will be released to the patient

The company's view is that this requirement "impinges on the practice of medicine" and "goes against 30 years of FDA policy and numerous Congressional debates that FDA's jurisdiction does not extend to the practice of medicine."

The sponsor has proposed an alternative plan outlined below. This issue was discussed at the meeting between the sponsor and the Division that was held on 10/1/01, and the sponsor understands that this issue will undergo further review inside the Agency and additional discussion with Orphan Medical before any final determination is made. The alternative plan proposed by the sponsor is as follows:

- Prescribers must certify in writing with each prescription that they have read the product labeling and physician education materials for Xyrem®
- Prescribers must certify that they understand that Xyrem® is only approved for the treatment of cataplexy with narcolepsy
- Prescribers must certify that they have educated the patient with respect to dosage preparation and administration
- Prescribers must state the diagnosis of each patient
- A sample of the proposed prescription sheet has been enclosed in this submission together with the Physician Success Program, as have the types of information that will be collected as part of the Patient Registry.

4.1.2 Prescribers must state in writing that they have read the educational materials provided to them before educational materials will be sent to the patient

The prescribing and enrollment forms that are proposed as part of the Physician Success Program includes certification by the physician of having read the educational materials

4.1.3 Patients must state, in writing, that they have read the educational materials provided to them before their first prescription is filled.

The sponsor states the following

- Based on agreement reached at the sponsor-Division meeting on 10/1/01 the prescription could be filled based on the patient confirming to the pharmacist on the phone that he/she had read the education materials
- The sponsor will ensure that the patient receives the Patient Success Program education materials prior to receiving the first prescription; these materials will be provided either by the physician or the pharmacy in advance of the first shipment of Xyrem®.

4.1.4 A single prescription must be limited to a maximum of 3 months supply of drug, and the maximum dose prescribed must be no more than 9 gms/day, given in 2 equally divided doses. Prescriptions for a dose greater than 9 gms/day, or for more than 3 months supply, must not be filled by the pharmacist.

The sponsor's response is as follows:

- The sponsor agrees to limit the quantity of drug supplied to a patient at any single time to 3 months and anticipates that most insurance companies will limit such a supply to one month
- The sponsor proposes that after completion of the post-marketing surveillance program and after review of this program by the Agency, individuals could receive upto a 6-month supply (which is permitted under Schedule III)
- 11 patients in the current treatment IND are using Xyrem® doses in excess of 9 g/day (upto 12 g/day). These doses have been reached by titration and have been well-tolerated. The sponsor therefore believes that it is not appropriate for a prescription in excess of 9 g/day to be refused by a pharmacist solely on the basis that the 9 g/day dose is being exceeded. A clear statement has however been made in the labeling and educational materials that safety and efficacy has not been established beyond a dose of 9 g/day

4.1.5 Patients must be seen and evaluated by the prescriber with the issuance of each new prescription (every 3 months), at which time a detailed account of the patient's experience on treatment must be provided. Prescribers must submit reports of all serious adverse reactions to you every 3 months initially, with the longer term reporting requirements to be further negotiated with the Agency. The patient registry that is an intrinsic part of this program must also be used to actively monitor for evidence of abuse, misuse, and diversion. You will need to incorporate these elements into your Risk Management Program documents.

The sponsor has responded as follows

- The physician will complete the safety data collection form at each visit as part of a post-marketing commitment. A description of this requirement and a form to collect the required safety data are included in the Physician Success Program. The sponsor states: "It was agreed that this is a temporary requirement which when completed would no longer be required."
- In addition the sponsor proposes the following
  - The physician be required to evaluate the patient every 3 months until the post-marketing surveillance database is reviewed by the Agency
  - The safety data form be completed twice for each patient (at 3 and 6 months) at the time of prescription renewal for the first 1000 patients entered into the registry
- The registry will include information on dosage and refills will be available for review by regulatory agencies charged with policing abuse, misuse and diversion (i.e., the DEA and state boards of pharmacy). Orphan Medical guarantees the creation and maintenance of the registry (which is incorporated into the contract with the central pharmacy). However the sponsor has no legal right of access to patient pharmacy records to actively monitor for diversion, abuse and misuse

4.1.6 The educational materials you have prepared must note prominently that Xyrem® is gamma hydroxybutyrate, or GHB, and that this is the same compound that is used illicitly.

This is clearly stated in the educational materials that are part of the Physician and Patient Success Programs, and in the labeling and patient medication guide.

4.1.7 The individual dosing cups must be labeled with the dose and name of the drug.

On each occasion when the drug is dispensed the pharmacist will place stick-on labels on the dosing cups and medication bottle. These labels will contain patient specific instructions about dosing. The patient will receive the Xyrem® kit in a box; the kit will

include the bottle with labeling, place-in-bottle-adaptor (PIBA Well) inserted by the pharmacist, oral syringe and 2 dosing cups with labels that include the dose and name of drug

4.1.8 A safety update for the ongoing studies, OMC-SXB-7 and [redacted] should be provided (the latter study is intended to assess the efficacy of Xyrem® in treating excessive daytime sleepiness). Even though the data for Study [redacted] may still be blinded, safety data may still be submitted. We would be happy to discuss with you appropriate ways in which this might be accomplished.

The safety update is included in this submission and is consistent with what the sponsor proposed in the communication of 7/25/01. The safety update includes data from Studies OMC-SXB-7, [redacted]

4.1.9 The status of the 11 patients who were enrolled in the Scharf study and had not entered the treatment IND study #OMC-SXB-7 as of 5/31/99, needs to be described to the extent possible.

The response to this request is included in this submission.

4.1.10 An analysis should be provided of all patients in the entire safety database listed as having "sleepwalking" as an adverse event. Such an analysis should include detailed clinical descriptions of the episodes, whenever they can be obtained from source documents, and the following additional elements: demographics, relationship to dose, frequency, seriousness, reason for discontinuation, further evaluations (e.g., EEGs and polysomnograms) and outcome.

The requested analysis is included in the submission.

4.1.11 As a CNS depressant, sodium oxybate is capable of producing respiratory depression. However, your application contains no formal assessment of this potential. Such assessments are routinely required in the evaluation of sedative-hypnotic drug products. For this reason, you should perform such a study. 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.). In addition, plasma level data should be obtained at appropriate times. We would be happy to discuss the design of such a study with you. We believe there is sufficient suggestion of occasional respiratory depression in the clinical studies to ask that these data be collected prior to marketing.

The sponsor states the following (both of which were agreed to by the Division earlier)

- A report is included in this submission for Study OMC-SXB-20 that describes the effects of escalating doses of Xyrem® on oxygen saturation and the frequency and severity of events representing sleep-disordered breathing
- A study in pulmonary-compromised patients is planned post-approval; a draft protocol for such a study will be submitted shortly

4.1.12 While there do not appear to be any important effects of sodium oxybate on the major CYP 450 metabolizing enzymes, the levels of sodium oxybate used in your studies were far below those expected to be seen clinically. Please assess the effects of sodium oxybate on these enzymes at clinically relevant exposures.

A study to assess the effect of Xyrem® on CYP450 isoenzymes at higher concentrations has been completed and the report is included in the Amendment

4.2 Labeling Issues

The package insert has been modified by the sponsor with the changes highlighted and annotated and with supporting documentation provided as needed.

4.3 Chemistry and Manufacturing Issues

- The sponsor understands that the re-inspection of ———, the manufacturer, by the Agency has continued to show deficiencies in Good Manufacturing Practices; the sponsor also understands that a stepwise corrective plan has been agreed to between the manufacturer and the Atlanta District office of the FDA.
- The sponsor states that given that this NDA was originally granted priority review status and that there is an unmet need for drugs to treat patients with cataplexy, the product should be approved while ——— continues to take corrective action.

4.4 Postmarketing Issues

4.4.1 Because sodium oxybate is ionized in the GI tract, we would like you to perform drug interaction studies with drugs that alter gastric pH, such as antacids, proton-pump inhibitors, and H2 blockers, all of which may alter the absorption of sodium oxybate.

The sponsor indicates that

- This study will be performed as part of a post-approval commitment
- Based on an agreement which was reached at the above meeting one study with one of the above classes of drugs should be sufficient
- A protocol using a proton pump inhibitor will be sent to the Agency for review and approval prior to initiation of this trial

4.4.2 Please submit the results of the rat carcinogenicity study when available.

The rat carcinogenicity study is complete and the report will be forwarded following approval of Xyrem®. The sponsor states that the study was negative

4.4.3 Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

The safety update has been submitted in this amendment. The sponsor further states that

- There are no substantive new adverse events that affect the proposed labeling as a result of the safety update
- There are no non-clinical studies available or complete that have not already been submitted as part of the NDA

5. Safety Update

5.1 Studies Included In Safety Update

Data from 3 studies are included in the safety update: these studies are OMC-SXB-7, [redacted]. The studies are summarized in the following table

Study	OMC-SXB-7	[redacted]	
Main Objective	Long-term safety	Efficacy in treating excessive daytime sleepiness of narcolepsy	Safety
Design	Open-label uncontrolled study	Randomized, double-blind, placebo-controlled, parallel-arm study	Open-label uncontrolled study
Number Enrolled*	268	71 (total number screened)	31
Dose of GHB**	3.0, 4.5, 6.0, 7.5, 9.0 g/day	4.5, 6.0, 7.5, 9.0 g/day	3.0, 4.5, 6.0, 7.5, 9.0 g/day
Duration	24 months or until marketing approval	8 weeks	12 weeks
Current Status	Ongoing	Ongoing	Ongoing

*As of 6/30/01
**Divided into 2 nightly doses

5.2 Study OMC-SXB-7

5.2.1 Protocol Outline

The following protocol was originally submitted as part of Treatment IND #, [redacted]

5.2.1.1 Objectives

- To evaluate the safety of sodium oxybate when used in patients with narcolepsy for upto 24 months or until the time of marketing approval at 5 specified doses
- To evaluate changes in the primary narcolepsy symptoms during the study including cataplexy attacks, daytime sleepiness, inadvertent naps during the day, awakenings during the night, hypnagogic hallucinations, and sleep paralysis

5.2.1.2 Design

Open-label, uncontrolled study

5.2.1.3 Inclusion Criteria

- Informed consent
- Age ≥ 12 years
- Previous use of GHB for narcolepsy under an approved IND application: the trials that will feed into this study include OMC-GHB-3, OMC-SXB-6 and the Scharf trial under IND # [redacted] all of which are open-label studies: those in OMC-GHB-3 need to have completed at least 12 months of treatment; those in OMC-SXB-6 need to have completed at least 6 months of treatment; those in the Scharf trial could have received treatment for any length of time
- Willing and able to complete the entire trial
- If female must be
  - Surgically sterile OR

- 2 years post-menopausal OR
- If of child-bearing potential, not currently pregnant and using a medically accepted means of birth control

5.2.1.4 Exclusion Criteria

- Unstable diseases in any body system, other than narcolepsy, which would place the patient at risk or compromise the trial objectives
- Use of anticonvulsant medication
- History of substance abuse, as defined by DSM-IV, currently or within the past year
- Serum creatinine > 2 mg/dl; AST or ALT > 2 x upper limit of normal; serum bilirubin > 1.5 times normal; pre-trial electrocardiogram results demonstrating a clinically significant arrhythmia or 2nd or 3rd degree A-V block; history of myocardial infarction within the past 6 months
- Any untreated disorder other than narcolepsy that could be considered a primary cause of excessive daytime sleepiness
- Investigational therapy, other than GHB, within 30 days prior to screening visit
- History of porphyria

5.2.1.5 Sample Size

The study plans to enroll about 300 patients at 40 investigative centers

5.2.1.6 Duration

24 months or until marketing approval, whichever is sooner

5.2.1.7 Dosage

- The medication is to be taken twice each night, at bedtime and 2.5 - 4 hours later
- The dosage is to be titrated based on the diminution of symptoms (cataplexy, hypnagogic hallucinations, sleep paralysis and daytime sleepiness) during the day while awake, and adverse events
- The starting dose is that established in the previous trial
- If necessary, the dose may be increased upto 9.0 grams per day or decreased as far as 3.0 grams per day.
- If increments are made, it is suggested that they should consist of 0.75 grams per dose (1.5 grams per day)
- Allowing 2 to 4 weeks between dosage adjustments is recommended
- After an optimal dose of Xyrem^{TM} is reached that dose will be maintained throughout the trial but will be altered if clinically indicated

5.2.1.8 Concomitant Medication

- Stable doses of other agents may be used for the treatment of narcolepsy
- Alcoholic beverages should not be misused and should not be taken for 3 hours prior to bedtime
- Patients will be cautioned regarding the use of other drugs with central nervous system depressant actions.
- All concomitant medications will be documented in the Case Report Forms

5.2.1.9 Schedule

- Assessments will be at the following visits: baseline, and at months 3, 6, 9, 12, 15, 18, 21 and 24 ; these are also referred to as Visits 1 through 9, respectively.
- Written informed consent, medical history and a urinary pregnancy test will be obtained at baseline only; a baseline history may not be needed depending on which trial the patient is entering this protocol from
- Safety laboratory tests (hematology, clinical chemistry and urinalysis) will be checked at baseline and at Months 6, 12, 18 and 24
- Concomitant medication and adverse events will be checked at every visit.
- Vital signs will be checked at baseline and at Months 6, 12, 18 and 24
- Narcolepsy symptoms will be assessed at baseline and every subsequent visit by using a formal Narcolepsy Symptom Assessment Questionnaire (baseline and follow-up versions)

5.2.1.10 Statistical Considerations

- All patients who receive a single dose or more of medication will be included in the safety evaluation
- All patients who complete more than one assessment of the Narcolepsy Symptom Assessment Questionnaire will be included in the efficacy evaluation.

5.2.1.11 Safety Monitoring

This will be accomplished using vital signs, adverse events, concomitant medications, safety laboratory tests and electrocardiograms as outlined above under "Schedule". A scheme for categorizing and reporting adverse events has been outlined.

5.2.2 Safety Data In Update

5.2.2.1 Organization Of Safety Data And Patient Disposition

Safety data for this study have already been submitted to this Division in the 120-Day Safety Update (referred to in the current submission as Update #1) to the original NDA application; the 120-Day Safety Update was submitted 2/1/01 and consisted only of data from OMC-SXB-7 through a cut-off date of 9/30/00.

The summary of safety data from OMC-SXB-7 in the current submission is referred to as Update #2, and has a cut-off date of 6/30/01.

In the current submission the cohort of patients from OMC-SXB-7 originally described in Update #1 is referred to as Cohort #1. Between 9/30/00 and 6/30/01 an additional 32 patients entered the trial, and 20 patients discontinued. The 32 patients who entered the trial between 9/30/00 and 6/30/01 are referred to as Cohort #2.

The safety data for all patients (Cohorts #1 and #2) described in the current update (Update #2) are cumulative; they represent an additional (approximate) 9 months of exposure to Xyrem® as compared with Cohort 1.

In the current submission (which contains cumulative safety data from OMC-SXB-7), comparisons are made between Cohorts #1 and #2, and, for Cohort #1, between Updates #1 and #2.

A comparison of Updates #1 and #2 in regard to patient numbers and exposure is in the table below which I have copied from the submission.

	Number of Patients	Mean Duration of Xyrem Therapy
Update #1	236 (Cohort 1)	9.5 months
Update #2	236 (Cohort 1)	17 months
	32 (Cohort 2)	3.5 months

Patient disposition for both updates is compared below in a table that I have copied from the submission.

	Update #1	Update #2
Patients enrolled	236	268
Patients discontinued	25	46[a]
Patients ongoing	211	223

[a] These numbers include patient 0831 who discontinued due to an SAE which was reported after the data cutoff.

Of the 46 patients in Update #2 who had discontinued treatment, 43 were from Cohort #1 and 3 were from Cohort #2.

- The 43 patients in Cohort #1 who discontinued did so for the following reasons

Reason For Discontinuing	Number Of Patients
Adverse event	20
Patient request	12
Moving to another location	3
Protocol deviation	3
Patient non-compliance	2
Lost to follow-up	2
Lack of efficacy	1

- All 3 patients in Cohort #2 who discontinued did so on account of adverse events

5.2.2.2 Clinical Trials Leading Into OMC-SXB-7

The "sources" of patients entering OMC-SXB-7 are in the following table which I have copied from the submission.

TRIAL OF ORIGIN	Duration of Xyrem Treatment	COHORT 1 (236) Up to 9/30/00	COHORT 2 (32) 9/30/00-6/30/01
OMC-GHB-2/3	Up to 30 months	53	0
OMC-SXB-6	Up to 6 months	123	1
Scharf Open Label	Up to 16 years	63	0
[redacted]	12 weeks	0	1
OMC SXB 20	10 weeks	0	20
[redacted]	6 weeks	0	7
Other[1]	NA	0	3
TOTAL	--	236	32

[redacted] Double-blind trial with 4-weeks of Xyrem or placebo treatment
[1] Three (3) additional patients who transferred from the Scharf Open-label trial

5.2.2.3 *Patient Demographics*

Patient demographics in each cohort are summarized in the following table

Parameter	Cohort #1	Cohort #2
Mean Age (years)	48.3	52.5
Mean Weight (kg)	84.4	81.7
% Women	55	58

5.2.2.4 *Exposure*

Exposure data for each cohort through 6/30/01 while participating in OMC-SXB-7 is summarized in the following table

	Cohort #1	Cohort #2
Mean duration of exposure	520.4 days (range: [redacted]	105.3 days (range: [redacted]
Any exposure	236 patients	32 patients
Exposure for 6 months	219 patients	2 patients
Exposure for 9 months	208 patients	1 patient
Exposure for 12 months	201 patients	0 patients
Exposure for 18 months	122 patients	0 patients
Exposure for 24 months	61 patients	0 patients
Exposure for 27 months	5 patients	0 patients

Note that all patients enrolled in OMC-SXB-7 had in fact received Xyrem® for longer periods than indicated in the above table since they had participated in other Xyrem® trials prior to entering OMC-SXB-7.

5.2.2.5 *Xyrem® Dosage*

Patient distribution by last Xyrem® dose through 6/30/01 is in the following table, which I have copied from the submission.

Dosage	Total	Xyrem Oral Solution Dosage (g/d)				
		3.0	4.5	6.0	7.5	9.0
Cohort 1						
Last Dosage (6/30/01)	236(100%)	6(3%)	39(17%)	75(32%)	61(26%)	55(23%)
Patient Dosage*	236(100%)	8(3%)	50(21%)	112(47%)	79(33%)	62(26%)
Cohort 2						
Last Dosage (6/30/01)	32(100%)	0	3(9%)	12(38%)	10(31%)	7(22%)
Patient Dosage*	32(100%)	0	4(13%)	13(41%)	12(38%)	7(22%)

* Patient Dosage: the number of patients who took the specified dosage at any time during the trial. Patients may be counted multiple times, so the sum of patients exposed to specific dosages (Cohort 1, 311; Cohort 2, 30) exceeds the total number of patients treated in the trial (Cohort 1, 236; Cohort 2, 32).

5.2.2.6 Summary Of Adverse Events

The following table, copied from the submission, summarizes adverse events by cohort

	Cohort 1		Cohort 2
	Through 9/30/00	Through 6/30/01	Through 6/30/01
Number of Patients	236 (100%)	236(100%)	32 (100%)
AEs[a]			
Patients with at least 1 AE	146(62%)	195(83%)	21(66%)
Patients with SAEs[b]	16(7%)	32(14%)	4(13%)
Patients with related AEs	50(21%)	82(35%)	10(31%)
Patients with severe AEs	24(10%)	44(19%)	8(25%)
Patients discontinued due to an AE[c]	10(4%)	20(8%)	3(9%)
Patient deaths[d]	1(<1%)	2(<1%)	0

5.2.2.7 Display Of Adverse Events

5.2.2.7.1 Cohort 1

The following table, copied from the submission, summarizes the most frequently reported adverse events (reported by ≥ 5% of patients in any group) by body system, COSTART term, and dosage at onset.

Body System COSTART Preferred Term	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	236 (100%)[b]	8(100%)	50(100%)	112(100%)	79(100%)	62(100%)
Body as a Whole	112(47%)	3(38%)	18(36%)	41(37%)	31(39%)	27(44%)
abdominal pain	9(4%)	0	0	6(5%)	1(1%)	2(3%)
accidental injury	20(8%)	0	3(6%)	6(5%)	3(4%)	8(13%)
allergic reaction [c]	7(3%)	1(13%)	0	5(4%)	1(1%)	0
asthenia [c]	8(3%)	1(13%)	1(2%)	2(2%)	2(3%)	2(3%)
back pain	15(6%)	0	1(2%)	6(5%)	2(3%)	6(10%)
chest pain	7(3%)	0	1(2%)	2(2%)	5(6%)	0
flu syndrome	19(8%)	3(38%)	2(4%)	5(4%)	6(8%)	3(5%)
[illegible]	24(10%)	2(25%)	7(14%)	4(3%)	3(4%)	6(10%)
infection	24(10%)	0	2(4%)	9(8%)	6(8%)	7(11%)
pain	25(11%)	1(13%)	3(6%)	8(7%)	6(8%)	7(11%)
viral infection	8(3%)	0	2(4%)	1(<1%)	1(1%)	3(5%)
Cardiovascular System	24(10%)	1(13%)	5(10%)	9(8%)	6(8%)	5(8%)
hypertension	14(6%)	1(13%)	3(6%)	4(4%)	3(4%)	4(6%)
Digestive System	62(27%)	3(38%)	14(28%)	27(25%)	16(20%)	14(23%)
anorexia	3(1%)	0	3(6%)	1(<1%)	0	0
colitis [c]	2(<1%)	1(13%)	1(2%)	0	0	0
[illegible]	10(4%)	1(13%)	4(8%)	5(4%)	6(8%)	3(5%)
nausea	29(12%)	1(13%)	2(4%)	5(4%)	4(5%)	7(11%)

Body System COSTART Preferred Term	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	236 (100%)[b]	8(100%)	50(100%)	112(100%)	79(100%)	62(100%)
vomiting	15(6%)	0	2(4%)	4(3%)	1(1%)	4(6%)
Hemic and Lymphatic System	13(6%)	0	0	8(7%)	3(4%)	2(3%)
Metabolic and Nutritional System	37(16%)	2(25%)	4(8%)	8(7%)	15(19%)	8(13%)
creatinine increased [c]	2(<1%)	1(13%)	0	1(<1%)	0	0
hypokalemia [c]	4(2%)	1(13%)	1(2%)	2(2%)	0	0
peripheral edema	6(3%)	0	1(2%)	1(<1%)	4(5%)	0
SGPT increased	6(3%)	0	0	2(2%)	4(5%)	0
Musculoskeletal System	33(14%)	0	7(14%)	6(5%)	10(13%)	10(16%)
arthralgia	8(3%)	0	0	2(2%)	3(4%)	3(5%)
leg cramps	6(3%)	0	3(6%)	0	1(1%)	2(3%)
myalgia	5(2%)	0	3(6%)	0	2(3%)	0
Nervous System	82(35%)	1(13%)	15(30%)	29(26%)	20(25%)	22(35%)
convulsion	8(3%)	0	1(2%)	4(4%)	1(1%)	3(5%)
depression	8(3%)	1(13%)	0	1(<1%)	5(6%)	1(2%)
dizziness	9(4%)	0	2(4%)	3(3%)	1(1%)	4(6%)
insomnia	12(5%)	0	3(6%)	4(4%)	1(1%)	4(6%)
[illegible] disorder (sleepwalking)	12(5%)	0	3(6%)	2(2%)	4(5%)	4(6%)
somnolence	9(4%)	0	1(2%)	3(3%)	2(3%)	3(5%)

Body System COSTART Preferred Term	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	236 (100%)[b]	8(100%)	50(100%)	112(100%)	79(100%)	62(100%)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hemic and Lymphatic System	12(5%)	0	0	8(7%)	3(4%)	2(3%)
Metabolic and Nutritional System	37(16%)	2(25%)	4(8%)	8(7%)	18(23%)	5(8%)
Creatinine increased	2(<1%)	1(13%)	0	1(<1%)	0	0
Hypercholesteremia	4(2%)	1(13%)	1(2%)	2(2%)	0	0
peripheral edema	6(3%)	0	1(2%)	1(<1%)	4(5%)	0
SGPT increased	6(3%)	0	0	2(2%)	4(5%)	0
Musculoskeletal System	32(14%)	0	7(14%)	6(5%)	10(13%)	10(16%)
arthralgia	8(3%)	0	0	2(2%)	3(4%)	3(5%)
leg cramps	4(3%)	0	3(6%)	0	1(1%)	2(3%)
myalgia	5(2%)	0	3(6%)	0	2(3%)	0
Nervous System	82(35%)	1(13%)	15(30%)	29(26%)	20(25%)	22(35%)
[illegible]	8(3%)	0	1(2%)	4(4%)	1(1%)	3(5%)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
insomnia	12(5%)	0	3(6%)	4(4%)	1(1%)	4(6%)
sleep disorder (sleepwalking)	12(5%)	0	3(6%)	2(2%)	3(4%)	4(6%)
somnolence	9(4%)	0	1(2%)	3(3%)	2(3%)	3(5%)

Body System COSTART Preferred Term	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	236 (100%)[b]	8(100%)	50(100%)	112(100%)	79(100%)	62(100%)

[a] Patients are counted only once in each event category, and only once in each body system summary. However, patients could have had more than 1 instance of the same AE with different dosages at onset, so the sum of the patients in the groups of dosage groups may exceed the total number of patients in each event category or body system summary.

[b] Some patients were exposed to more than 1 dosage in the trial, so the sum of Cohort 1 patients exposed to specific dosages (N=311) exceeds the total number of Cohort 1 patients in the trial (N=236).

[illegible] group with maximum > 9.0 was 9.1 g/d, with a single patient (1/6 patients, 13%).

Of the adverse events listed above the most common (all dose groups combined) were as follows:

Adverse Event (COSTART)	Number Of Patients	Percentage Of Patients
Pharyngitis	39	17
Pain	25	11
Headache	24	10
Infection	24	10
Accidental injury	20	8
Flu syndrome	19	8
Diarrhea	19	8
Nausea	19	8
Rhinitis	18	8
Sinusitis	18	8
Back pain	15	6
Bronchitis	14	6
Hypertension	14	6
Insomnia	12	5
Sleep disorder (Sleepwalking)	12	5
Urinary incontinence	12	5

5.2.2.7.2 Cohort 2

The following table, copied from the submission, summarizes all adverse events in this cohort by body system, COSTART term, and dosage at onset.

Body System	Xyrem Oral Solution Dosage (g/d) at Onset					
COSTART Preferred Term	3.0	4.5	6.0	7.5	9.0	Total(a)
Number of Patients	0(100%)	4(100%)	13(100%)	12(100%)	7(100%)	32(100%)
Body as a Whole	0	1(25%)	2(15%)	2(17%)	1(14%)	6(19%)
allergic reaction	0	0	0	0	1(14%)	1(3%)
cyst	0	0	0	1(8%)	0	1(3%)
headache	0	0	2(15%)	0	0	2(6%)
infection	0	0	0	1(8%)	0	1(3%)
pain	0	1(25%)	0	0	0	1(3%)
Cardiovascular System	0	0	1(8%)	3(25%)	0	4(13%)
arteriosclerosis	0	0	0	1(8%)	0	1(3%)
hypertension	0	0	1(8%)	0	0	1(3%)
migraine	0	0	0	1(8%)	0	1(3%)
postural hypotension	0	0	0	1(8%)	0	1(3%)
Digestive System	0	0	3(23%)	1(8%)	1(14%)	5(16%)
cholecystitis	0	0	1(8%)	0	0	1(3%)
liver function tests	0	0	1(8%)	0	0	1(3%)
mouth ulceration	0	0	0	1(8%)	0	1(3%)
nausea	0	0	2(15%)	0	0	2(6%)
tooth disorder	0	0	0	0	1(14%)	1(3%)
vomiting	0	0	1(8%)	0	0	1(3%)
Hemiclymphatic System	0	1(25%)	0	1(8%)	0	2(6%)
anemia	0	1(25%)	0	1(8%)	0	2(6%)
Metabolic and Nutritional System	0	0	0	2(17%)	0	2(6%)
hypercalcemia	0	0	0	1(8%)	0	1(3%)
hyperglycemia	0	0	0	1(8%)	0	1(3%)
hyperphosphatemia	0	0	0	1(8%)	0	1(3%)
peripheral edema	0	0	0	1(8%)	0	1(3%)
Musculoskeletal System	0	0	1(8%)	0	1(14%)	2(6%)
arthralgia	0	0	1(8%)	0	1(14%)	2(6%)

(a) Patients are counted only once in each event category, and only once in each body system summary.

Body System	Xyrem Oral Solution Dosage (g/d) at Onset					
COSTART Preferred Term	3.0	4.5	6.0	7.5	9.0	Total(a)
Nervous System	0	0	3(23%)	3(25%)	2(29%)	7(22%)
agitation	0	0	0	0	1(14%)	1(3%)
confusion	0	0	1(8%)	0	0	1(3%)
delirium	0	0	1(8%)	0	0	1(3%)
depression	0	0	1(8%)	1(8%)	1(14%)	3(9%)
dizziness	0	0	1(8%)	0	0	1(3%)
euphoria	0	0	0	0	1(14%)	1(3%)
hypertonia	0	0	0	1(8%)	0	1(3%)
libido increased	0	0	0	0	1(14%)	1(3%)
paresthesia	0	0	1(8%)	0	0	1(3%)
sleep disorder	0	0	1(8%)	0	0	1(3%)
vasodilatation	0	0	0	1(8%)	0	1(3%)
Respiratory System	0	0	0	1(8%)	0	1(3%)
dyspnea	0	0	0	1(8%)	0	1(3%)
Skin	0	0	0	1(8%)	0	1(3%)
furunculosis	0	0	0	1(8%)	0	1(3%)
Special Senses	0	0	0	1(8%)	0	1(3%)
conjunctivitis	0	0	0	1(8%)	0	1(3%)
Urogenital System	0	0	1(8%)	1(8%)	0	2(6%)
sexual function amor	0	0	0	1(8%)	0	1(3%)
urinary incontinence	0	0	1(8%)	0	0	1(3%)

(a) Patients are counted only once in each event category, and only once in each body system summary.

The most common adverse events (all dose groups combined) were as follows

Adverse Event (COSTART)	Number Of Patients	Percentage Of Patients
Depression	3	9
Headache	2	6
Nausea	2	6
Anemia	2	6
Arthralgia	2	6

5.2.2.8 Deaths

A total of 3 deaths has occurred during OMC-SXB-7: 1 of these deaths (Patient #0531) was previously reported in Update #1 and summarized in my original safety review of NDA 21196. All 3 deaths, which occurred in Cohort #1 are summarized below.

5.2.2.8.1 Patient #0531

Patient # 0531 was a 47 year old woman who had earlier participated in the OMC-SXB-6 trial and had been taking Xyrem® 6 g/day since 6/3/99. Her past medical history that the investigator was aware of at screening was remarkable for a bipolar disorder, a

previous head injury with coma and a morphine allergy. Concomitant medications included thyroxine, zolpidem, an albuterol inhaler, loratadine, risperidone and temazepam. Subsequently the investigator realized that she had previously made a suicide attempt

In May 2000 she began experiencing worsening insomnia. On 6/12/00 she underwent an elective surgical procedure for metrorrhagia.

On 7/4/00 she asked friends to leave a gathering at her home as she felt unwell. After a friend was unable to contact her, emergency personnel entered her home and found her dead the following day. A post-mortem toxicology screen was positive for opiates, acetaminophen and benzodiazepines. Quantitative testing showed toxic levels of multiple drugs including hydrocodone, oxycodone, morphine, hydromorphone, nordiazepam and zolpidem. It was presumed that she had committed suicide by taking an overdose of multiple drugs. The death certificate listed multiple drug toxicity as the cause of her death with atherosclerotic cardiovascular disease also being listed as a significant factor.

Post-mortem toxicology screening for GHB was not done, but the sponsor believes that this patient did not take an overdose of that drug for the following reasons

- At her last trial visit on 5/23/00 the patient received 6 bottles of Xyrem®, each containing 200 mL of the drug (each bottle contained 500 mg/mL)
- On 7/11/00 the patient's family returned to the investigator 5 bottles (4 full and 1 empty)
- The 6th bottle containing some drug was retained by the medical examiner but the quantity of drug in that bottle is not known
- The sponsor states that the although the patient's compliance with the drug could not be precisely estimated it was calculated as being between 39 and 78%

5.2.2.8.2 Patient #08070

This patient was a 64 year old woman who had undergone coronary artery bypass surgery 16 years prior to her death. She had been enrolled in the Scharf open-label study from 5/12/87 to 10/2/99. She then entered the OMC-SXB-7 open-label trial taking Xyrem® in a dose of 7.5 g/day which she had been taking for over a year.

On 12/7/00 the patient had chest pain and was hospitalized the next day at which time Xyrem® was discontinued. Investigation showed narrowing/occlusion of 2 coronary vessels and on 12/11/00 she underwent coronary artery bypass surgery. Following surgery she developed "complications" including renal failure and died on 12/27/00.

5.2.2.8.3 Patient #0936

This patient was a 51-year-old woman who had a medical history of narcolepsy, depression, gastric bypass surgery for obesity, arthritis of both knees and tubal ligation.

Prior to entering OMC-SXB-7 she had participated in OMC-SXB-6. At the time of her death she had been taking Xyrem® in a dose of 6 g/day for about 18 months.

While participating in the above trials, she was hospitalized on 2 occasions for (apparently symptomatic) kidney stones: the hospitalizations were on 11/20/99 and

2/10/01. Treatment during the second hospitalization included an antibiotic and an analgesic, and placement of a left urethral stent.

On 2/22/01 she was seen at the study site, where she reported her hospitalizations for kidney stones; she also reported seeing a psychiatrist on 2/21/01 who diagnosed a bipolar disorder and prescribed lithium and paroxetine which she had not yet begun taking. She stated that she was taking iron for anemia. At that visit she was prescribed approximately 1300 mL of Xyrem® (500 mg/mL).

She was found dead in her home on 2/24/01. An autopsy was not performed but the medical examiner ruled that the cause of her death was "atherosclerotic cardiovascular disease."

After her death the trial coordinator ascertained the following

- A total of 740 mL of Xyrem® was returned to the study site suggesting that 600 mL (i.e., 300 g) may have been consumed between 2/22/01 and 2/24/01
- The patient filled her prescriptions for lithium (60 tablets; strength not stated) and paroxetine (45 tablets; strength not stated) on 2/23/01. Both bottles were empty
- A bottle of Percocet® was also empty (it had originally contained 20 tablets and the patient claimed to have taken only 2 tablets at her visit to the study site on 2/21/01)

The investigator believed that she had died as a result of an overdose of multiple drugs.

5.2.2.9 Serious Adverse Events

Serious adverse events that occurred in Cohort #1 between 9/30/00 and 6/30/01, and in Cohort #2 upto 6/30/01 are summarized in the following table (which uses COSTART preferred terms), which I have copied from the submission

Patient No.	Age and Sex	COSTART Preferred Term	Xyrem Dosage at Onset (g/d)	Time on trial (days)	Relationship to trial drug	Outcome
Cohort 1 (from 9/30/00 to 6/30/01)						
05024	67 F	Myocardial infarction	4.5	638	Not related	Recovered
05257	41 M	Nausea & vomiting	14.0	546	Not related	Recovered
0532	59 F	Uterine fibroids enlarged	6.0	422	Not related	Recovered
05[illegible]	[illegible] F	Arthritis	9.0	500	Not related	Recovered
0544	30 F	Depression	6.0	348	Possibly related	Discontinued
08070	64 F	Chest pain	7.5	433	Not related	Death
0814	57 M	Paresthesia	4.5	474	Not related	Recovered
0841	[illegible] F	Elevated serum creatinine	2.0	167	Not related	Discontinued
0936	51 F	Kidney stones	6.0	355	Not related	Recovered
		Death (Possible overdose)	6.0	369	Not related	Death
1032	42 F	Dyspnea	4.5	439	Not related	Recovered
14045	79 F	Cerebrovascular accident	6.0	494	Possibly related	Discontinued
14[illegible]	[illegible] F	SGPT increased	6.0	176	Possibly related	Discontinued
1604	68 M	Overdose	7.5	565	Probably related	Recovered
1609	56 M	Chest pain	7.5	662	Not related	Recovered

Patient No.	Age and Sex	COSTART Preferred Term	Xyrem Dosage at Onset (g/d)	Time on trial (days)	Relationship to trial drug	Outcome
1630[3]	60 M	Chest Pain	7.5	39	Not related	Recovered
		Pain [illegible] pharyngitis	7.5	37	Not related	Recovered
1704	70 F	Colitis	3.0	540	Unknown	Recovered
1832[4]	49 F	Cholecystitis / Cholelithiasis	7.5	242	Not-related	Recovered
[illegible]	78 M	Card-spasm	4.5	526	Not related	Recovered
3552	52 F	Gastrintestinal carcinoma	4.5	1	Unknown	Discontinued
3834	38 M	Back pain	9.0	110	Not related	Recovered
Cohort 2 (Through 6/30/01)						
05700	70 M	Dyspnea	7.5	38	Not related	Ongoing
		Arteriosclerosis	7.5	161	Not related	Ongoing
05701	35 M	Liver function tests abnormal	6.0	203	Possibly related	Discontinued
17301	61 M	Cholecystitis	6.0	240	Unknown	Recovered
38027	72F	Anemia (caused by GI bleeding)	4.5	6	Not Related	Recovered

[3] Patient 1644 discontinued after data cutoff.

[4] Patient 1832 experienced one SAE of cholecystitis with cholelithiasis. The data listings currently record 2 SAE's for this single event. A correction to the database will be made prior to the final report for this trial.

[5] Patient 1630 experienced one SAE of pain with pharyngitis. The data listings currently record 2 SAE's for this single event. A correction to the database will be made prior to the final report for this trial.

I have read through the narratives for all the above patients; I have also referred to the corresponding Case Report Forms when necessary. More detailed descriptions are warranted for the following individuals.

5.2.2.9.1 Patient #05257

This 41-year old man experienced repeated nausea and vomiting on a single day. Xyrem® was interrupted for that, and the following day. He was hospitalized the day after his vomiting began and discharged the next day after his symptoms had resolved. He was then able to resume Xyrem®

5.2.2.9.2 Patient #0544

This 30 year old woman with narcolepsy had a history of depression for 3 years prior to entering the OMC-SXB-6 trial on 6/30/99. She received Xyrem® initially in a dose of 4.5 g/day until 10/11/99, and later in a dose of 6 g/day.

While participating in the OMC-SXB-7 trial she was hospitalized twice for the treatment of depression, from 1/23/01 to 2/2/01, and again from 2/9/01 to 2/15/01. During these hospitalizations she received electroconvulsive therapy, and a number of antidepressant and neuroleptic medications. She had no history of prior hospitalizations for depression. Diagnoses made at the time of her hospitalizations included major/severe depression with suicidal ideation, and alcohol abuse/dependence for which she had a past history.

She was discontinued from the OMC-SXB-7 trial on 2/22/01 on account of concomitant and previous alcohol use and depression.

5.2.2.9.3 Patient #0831

This 56 year old woman with a past history of possible "lupus" for which she was on long-term corticosteroid therapy, entered the OMC-SXB-6 trial at which time the following screening laboratory values were abnormal.

AST	53 IU/L	(Reference Range: 9-24)
ALT	47 IU/L	(Reference Range: 6-34)
Serum creatinine	1.2 mg/dL	(Reference Range: 0.4-1.1)

At the end of the OMC-SXB-6 trial her serum creatinine was 1.3 mg/dL. She also had an elevated alkaline phosphatase of 131 IU/L (reference range 31-110), an elevated LDH of 344 IU/L (reference range: 53-234). Her AST and ALT were however normal at that time (22 IU/L and 16 IU/L, respectively).

During the course of the OMC-SXB-7 trial the patient's creatinine rose to 2.3 mg/dL resulting in her being discontinued from the trial. Her Xyrem® dose varied during that study from 2.0 to 4.5 g/day. She continued to be on maintenance steroid therapy throughout her participation in OMC-SXB-6 and OMC-SXB-7. A follow-up serum creatinine was planned.

5.2.2.9.4 Patient #1433

This 57 year old woman had no relevant past medical history other than narcolepsy. She entered the OMC-SXB-6 trial on 9/28/99, transferred to the OMC-SXB-7 trial on 3/22/00 and discontinued Xyrem® on 12/6/00 on account of the serious adverse event described in this section. Her Xyrem® dose varied from 4.5 to 6 g/day, and ended at 6 g/day.

On 7/25/00 a mammogram was reported to be "positive." A biopsy on 8/7/00 was reported to have revealed "benign" tissue; however the patient was begun on treatment with tamoxifen and the Case Report Form suggests that a diagnosis of carcinoma in situ was made.

Elevations in ALT and AST were detected from 9/13/00 onward and are displayed in the following table

Date	AST (reference range: 9-34 IU/L)	ALT (reference range: 6-34 IU/L)
9/13/00	35 IU/L	63 IU/L
9/28/00	25 IU/L	38 IU/L
10/30/00	42 IU/L	65 IU/L
12/6/00	111 IU/L	268 IU/L

Both Xyrem® and tamoxifen were discontinued on 12/6/00. Follow-up transaminase data were as follows:

Date	AST (reference range: 9-34 IU/L)	ALT (reference range: 6-34 IU/L)
1/12/01	66 IU/L	135 IU/L
2/26/01	48 IU/L	75 IU/L

Note: Transaminase elevations and clinically overt hepatitis (including steatohepatitis) have been associated with tamoxifen use (as per the current approved labeling and a number of published reports in the medical literature), although the occurrence of such adverse events does not appear to be frequent.

5.2.2.9.5 Patient #1604

This 68 year old man began taking Xyrem® in February 1998 while participating in the OMC-GHB-2 trial. He entered OMC-SXB-7 on 4/8/99 following which he took Xyrem® in a dose of 7.5 g/day.

On 10/23/00 the patient believes he took 2 doses of Xyrem® rather than one at the time of his second dose. About 1 hour after he took his second dose his wife awoke and found him rigid, sweating profusely, sleeping deeply and breathing rapidly. Medical assistance was not sought and the patient slept soundly for the next 1.5 hours after which the event "resolved" and no sequelae were noted. He continues to be in the trial.

5.2.2.9.6 Patient #05701

This 35 year old man with narcolepsy had no prior history of liver disease, diabetes mellitus, or alcohol abuse. He initially began taking Xyrem® as part of the Scharf open-label trial on 2/14/00. On 11/17/00 he entered the OMC-SXB-7 trial throughout which he took a dose of 6 g/day. His concomitant medications included dextroamphetamine and testosterone.

On account of rising transaminases he was discontinued from the trial on 6/24/01, stopping Xyrem® on 6/30/01. After discontinuation of Xyrem® his transaminases continued to rise over the next month. His laboratory data are in the following table copied from the submission.

Normal Range	V-1 (11/17/00)	V-3 (5/18/01)	F/U (6/7/01)	F/U#2 (7/27/01)
ALT (6-43)	57	112	125	248
AST (11-36)	34	64	107	206
LDH (62-234)	160	211	303	318

Hepatitis B and C titers, drawn on 6/27/01 were reported to be negative. Hepatic ultrasound on 7/6/01 was reported to show fatty infiltration of the liver.

No liver function tests were checked prior to 11/17/00.

The patient was reported to have gained 70 lbs in weight since his symptoms of narcolepsy began in October 1999.

5.2.2.9.7 Patient #38027

This 72 year old woman had anemia which appears to have been secondary to bleeding cecal angiodysplasias for which she underwent extensive intestinal surgery. She discontinued Xyrem® which she had taken for a total of about 17 years at the time of her hospitalizations

5.2.2.10 Discontinuations Due To Adverse Events

Discontinuations due to adverse events in Cohort #1 and Cohort #2 are summarized in the following table which I have copied from the submission.

Patient No.[a]	Xyrem Dosage at Onset (g/d)	COSTART Preferred Term	Relationship to Trial Drug	SAE (Y/N)
Cohort 1 (From trial initiation through 9/30/00)				
0214[b]	9.0	Liver function tests abnormal	Unknown	Y
0232	9.0	Paranoid reaction	Probably related	Y
0531	6.0	Death (Suicide)	Not related	Y
0931	4.5	Manic depressive reaction (bipolar affective disorder)	Not related	Y
1151	9.0	Intentional overdose	Definitely related	Y
1205	9.0	Movement disorder (Hyperkinesia)[d]	Unknown	N
14043	7.5	Suicide attempt	Possibly related	Y
1509	6.0	Back pain	Not related	Y
2030	9.0	Psychosis	Possibly related	Y
2536	9.0	Fractured ankle	Possibly related	Y
Cohort 1 (From 10/1/00 through 6/30/01)				
0544	6.0	Depression	Possibly related	Y
06570	7.5	Chest pain (death)	Not related	Y
0831[c]	2.0	Elevated serum creatinine	Not related	Y
0936	6.0	Death (possible overdose)	Not related	Y
14045	6.0	Cerebrovascular accident	Possibly related	Y
1433	6.0	SGPT increased	Possibly related	Y
1535	7.5	Tremor	Unknown	N
1731	9.0	Abdominal pain	Possibly related	N
		Chest pain	Possibly related	N
		Weight loss	Possibly related	N
3532	4.5	Gastrointestinal carcinoma	Unknown	Y
4945	N/A	Tremor	Unknown	N
Cohort 2 (Through 6/30/01)				
05701	6.0	Liver function tests abnormal	Possibly related	Y
17302	6.0	Delirium	Unknown	N
		Confusion	Possibly related	N
		Nausea	Possibly related	N
		Vomiting	Possibly related	N
		Dizziness	Probably related	N
42300	6.0	Depression	Probably related	N

Patients who discontinued on account of adverse events on or prior to 9/30/00, have already been reviewed as part of Update #1 (the 120-Day Safety Update; see NDA Safety Review).

Of those patients in Cohorts #1 and #2 who discontinued on account of adverse events between 10/1/00 and 6/30/01, the following have already been described in some detail in Section 5.2.2.9: #s 0544, 0831, 0936, 1433 and 05701.

I have read through the narratives for all patients in the above table who were not described in Update #1; I have also read the corresponding Case Report Forms when necessary. More detailed descriptions are warranted for the following individuals.

Those patients who were documented in Update #1 (120-Day Safety Update) as having discontinued from this study on account of adverse events have been reviewed as part of my original NDA Safety Review.

5.2.2.10.1 Patient #1535

This 59-year-old woman began Xyrem® as part of the OMC-SXB-6 trial on 6/14/99 at a dose of 4.5 g/day. On 7/16/99 her dose was increased to 6.0 g/day which she continued after entering the OMC-SXB-7 trial. On 6/8/00 her dose was further increased to 7.5 g/day which she maintained until she discontinued taking Xyrem® on 10/23/00. She received Xyrem® for a total duration of 497 days.

Her medical history was remarkable for narcolepsy, hypertension, reactive airway disease, renal stones, depression, right optic atrophy, and mild headaches. Concomitant medications included conjugated estrogens, nifedipine, hydrochlorthiazide, glucosamine-chondroitin, ibuprofen, an acetaminophen-aspirin-caffeine combination, a multivitamin, and minerals

When screened for OMC-SXB-6 on 6/9/99, her weight was 158 lbs. During the first 6 months of treatment with Xyrem® her weight decreased to 142 lbs and the change was attributed by the investigator to a change in diet and to exercise. By 6/8/00 her weight had fallen to 117 lbs [on the same day her urine was positive (1+) for ketones].

On 9/5/00 she noted a tremor in her hands, but evaluation for hyperthyroidism was negative.

Study medication was discontinued on 10/23/00 on account of hand tremor, unexplained weight loss and extreme fatigue; the investigator was also in doubt about the extent of her compliance with study medication and about the adequacy of her support system. On 11/17/00 her weight 114 lbs. On 5/3/01 the patient's primary care physician indicated that the patient was regaining weight, but that her mild hand tremors continued.

5.2.2.10.2 Patient #1732

This 64 year old woman began taking Xyrem® in the OMC-SXB-6 trial at a dose of 4.5 g/day on 8/2/99. On 10/20/99 the dose was increased to 7.5 g/day, and further to 9 g/day on 11/3/99. On 11/13/99 the dose was decreased to 8.0 g/day (on account of an episode of nocturnal enuresis) and maintained at that level through the rest of that trial. She entered the OMC-SXB-7 study at the same dose of 8.0 g/day on 2/14/00 and continued the same dose until discontinuing study drug on 2/28/01. Over that period of time study drug had been taken for a total duration of 576 days.

Her past medical history was remarkable only for narcolepsy. Concomitant medications included conjugated estrogens-medroxyprogesterone, oxazepam, and a phenobarbital-hyoscyamine-atropine-scopolamine combination.

During the course of the trial the patient experienced the following adverse events

- Episodes of sleepwalking and unsteady gait beginning 2-3 hours after taking Xyrem® first noted 8/20/99 and continuing until she discontinued the drug
- A "bruised hip" on 3/8/00 as a result of a fall during an episode of sleepwalking
- Orofacial dyskinesias from 8/4/99 to 8/12/99.

- Nocturnal enuresis on 11/13/99
- Weight loss first reported on 10/5/00 and extending from 143 lbs on 7/28/99 to 121 lbs on 3/1/01.
- Epigastric pressure/pain and anxiety first reported on 10/5/00
- A diagnosis of gallstones and costochondritis first reported on 2/15/01.

As noted earlier Xyrem® was discontinued on 2/28/01. On 3/1/01 she was begun on treatment with venlafaxine 37.5 mg daily for her cataplexy. Later in March 2001 the patient reported that her epigastric discomfort had ceased, her appetite had improved, her sleepwalking had ended and her gallbladder surgery was cancelled.

5.2.2.10.3 Patient #3935

This 57 year old man began Xyrem® as part of the OMC-SXB-6 trial on 8/27/99 at a dose of 4.5 g/day and his dose of Xyrem® was increased to 7.5 g/day on 9/24/99. He entered the OMC-SXB-7 trial on 2/11/00 at the same Xyrem® dose of 7.5 g/day which he continued to take until he discontinued that drug on 10/7/00. While in OMC-SXB-7 he simultaneously participated in the randomized withdrawal efficacy trial, OMC-SXB-21 from 6/28/00 to 8/3/00.

His medical history was remarkable for narcolepsy, headaches, and impaired memory. Concomitant medications included quinapril, atenolol, methylphenidate, and dextroamphetamine.

He began noticing a tremor of both hands soon after beginning to take Xyrem®. The tremor continued and is described by the investigator as being mild and intermittent. While enrolled in OMC-SXB-21 he reported that he noted a reduction in his hand tremors during the 2-week period of double-blind treatment; it was subsequently confirmed that he received placebo during that period. On resuming Xyrem® as part of continuing in OMC-SXB-7 his tremor returned and he decided to discontinue taking Xyrem® on 10/7/00 to determine if that was the cause of his tremor. The tremor decreased "significantly" and the patient permanently discontinued from the trial.

5.2.2.10.4 Patient #17302

This 51 year old woman had a previous history of narcolepsy, and hypertension. She first received Xyrem® as part of the [redacted] trial, on 8/5/00, in a dose of 4.5 g/day; the dose was then increased consecutively to 6.0 g/day, 7.5 g/day and 9.0 g/day at 2-week intervals. After only 1 week at the 9 g/day dose she entered OMC-SXB-7 at a dose of 6 g/day which she continued until discontinuing from the trial on 11/11/00. She took Xyrem® for a total duration of 98 days.

Her medical history was remarkable for narcolepsy and hypertension. Concomitant medications included dextroamphetamine, hydrochlorthiazide-triamterene, and propranolol.

On 9/5/00 while taking a Xyrem® dose of 6 g/day she reported feeling "drugged and woozy." This adverse event continued until 10/16/00 at which time she was taking a dose of 9 g/day.

On 11/11/00 she was reported to have delirium, disorientation, nausea, vomiting and dizziness. She was taking Xyrem® in a dose of 6.0 g/day at that time. Xyrem® was

stopped and her symptoms had resolved by the next day. They had not recurred at the time of a follow-up visit on 11/29/00

5.2.2.10.5 Patient #42300

This 56 year old man had a past history of narcolepsy, asthma, arthritis and restless legs syndrome. He began taking Xyrem® when he entered the OMC-SXB-20 trial on 7/24/00: during the course of that trial his dose of Xyrem® was increased over 10 weeks to 9.0 g/day which he then took for a further 2 weeks before entering the [redacted] trial on 10/3/00 at a Xyrem® dose of 6 g/day. He then continued in [redacted] at the same dose until 1/11/01. He then entered OMC-SXB-7 where he continued Xyrem® in a dose of 6 g/day until 6/22/01 when the drug was discontinued. He received Xyrem® for a total of 332 days.

Concomitant medications included modafinil, pramipexole, aspirin, budesonide, venlafaxine, and methylphenidate

Throughout his participation in all 3 trials he was reported to have urinary incontinence and sleepwalking. He also reported a worsening of his arthritis during [redacted]

On 5/25/01 he was reported to have severe depression which resulted in the discontinuation of Xyrem® on 6/22/01. On 6/25/01 he began taking venlafaxine 37.5 mg daily for depression. At the same time he also received methylphenidate and modafinil. By 7/18/01 his depression had resolved. Enuresis and sleepwalking ceased after Xyrem® was stopped.

5.2.2.11 Adverse Events Of Special Interest

Adverse events of special interest looked at as part of this safety update included confusion, convulsions, incontinence, sleepwalking and vomiting. Only adverse events in this category that began during the OMC-SXB-7 trial are included in this section of the submission.

The following table, copied from the submission, summarizes the overall incidence of each adverse event of special interest in each cohort

AEs of Special Interest	Cohort 1		Cohort 2
	Through 9/30/00	Through 6/30/01	Through 6/30/01
Number of Patients	236 (100%)	236(100%)	32 (100%)
Confusion	3(1%)	4(2%)	1(3%)
Convulsion	4(2%)	8(3%)	0
Incontinence	6(3%)	12(5%)	1(3%)
Sleepwalking	9(4%)	12(5%)	1(3%)
Vomiting	10(4%)	11(5%)	1(3%)

Each of these adverse events is addressed separately below

5.2.2.11.1 Confusion

5 patients in each cohort were reported to have confusion (COSTART) as an adverse event. None of these adverse events was considered serious. One patient discontinued Xyrem® on account of confusion (see Section 5.2.2.10.4)

A summary of the adverse events of confusion by dose at onset is in the following table which I have copied from the submission.

AE of Confusion	Total*	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
Cohort 1 - Number of Patients	236(100%)	8(100%)	50(100%)	112(100%)	79(100%)	62(100%)
Patients with at least 1 AE*	4(2%)	0	0	2(2%)	0	2(3%)
Patients with SAEs	0	0	0	0	0	0
Patients with related AEs	4(2%)	0	0	2(2%)	0	2(3%)
Patients with severe AEs	0	0	0	0	0	0
Patients discontinued due to an AE	0	0	0	0	0	0
Patient deaths	0	0	0	0	0	0
Cohort 2 - Number of Patients	32(100%)	0	4(100%)	13(100%)	12(100%)	7(100%)
Patients with at least 1 AE*	1(3%)	0	0	1(8%)	0	0
Patients with SAEs	0	0	0	0	0	0
Patients with related AEs	1(3%)	0	0	1(8%)	0	0
Patients with severe AEs	0	0	0	0	0	0
Patients discontinued due to an AE	1(3%)	0	0	1(8%)	0	0
Patient deaths	0	0	0	0	0	0

[illegible] patients exposed to specific dosages (Nall) exceeds the total number of Cohort 1 patients in the [illegible] exceeds the total number of Cohort 2 [illegible]

* Treatment-emergent AEs.

5.2.2.11.2 Convulsions

A total of 8 patients in Cohort 1 were reported to have "convulsions", based on the COSTART preferred term. Several of these patients were described in a Major Amendment to the NDA submitted on 3/23/01.

- 7 of these 8 patients (#s 21061, 0243, 05286, 0545, 0549, 0608, and 0835) actually had investigator terms that indicated that the event in question was cataplexy
- The remaining patient (#0814) had the investigator term "seizures" applied, but the sponsor considers that event may also have been cataplexy-related. A more detailed narrative for this patient is below, taken from my review of the Major Amendment

This 58 year old man had an additional medical history of esophagitis, diverticulitis, breast cancer and a penicillin allergy. Concomitant medications at study entry included tamoxifen, omeprazole, amitriptyline and promethazine.

He had narcolepsy and cataplexy for 3 years at the time of his entry into OMC-GHB-2. He later participated consecutively in OMC-GHB-3 and OMC-SXB-7. In all these studies he received a dose of 4.5 g/day of Xyrem®.

After taking GHB for 935 days he saw his neurologist (not the principal investigator) on a routine visit and described an episodic disturbance. Such events had occurred reportedly on Days 220 and 558 and the terms "fugue state", "patient reports being in limbo", and "trance-like state" were used to describe these episodes (the COSTART term was depersonalization). The neurologist suggested that he had seizures and treated him with phenytoin 100 mg daily; this drug was taken for slightly less than 2 months. Similar events have continued since and currently occur about once or twice a week. The investigator reportedly felt that the episodes are "consistent with mild cataplexy or memory loss." The investigator also reportedly felt that it was probable that the event termed "seizures" was cataplexy-related.

While on treatment with Xyrem® he developed congestive heart failure. He was treated with enalapril, digoxin, carvedilol and warfarin.

My comments about this patient at the time of my review of the Major Amendment were as follows:

Patient #0814 was considered to have a fugue state, the etiology of which is unclear. While partial complex seizures can be the cause of such states, a primary psychiatric disorder may also be responsible. Further details of this patient's episodes are unavailable and it is therefore not possible to make a determination whether he did have partial seizures. In addition it is somewhat difficult to understand the following

- The reason why the principal investigator felt these were episodes of cataplexy (attacks of narcolepsy can, however, be associated with automatic behavior)
- The reason why his neurologist chose to treat him with what was almost certainly an inadequate dose of phenytoin

No patient in Cohort #2 had convulsions

5.2.2.11.3 Incontinence

12 patients out of 236 in Cohort #1 and 1 patient out of 32 in Cohort #2 had urinary incontinence. In no instance was urinary incontinence considered a serious adverse event or a reason for treatment discontinuation.

A summary of the adverse events of incontinence by dose at onset is in the following table which I have copied from the submission.

		Xyrem Oral Solution Dosage (g/d) at Onset				
AEs of Incontinence	Total[a]	3.0	4.5	6.0	7.5	9.0
Cohort 1 - Number of Patients	236(100%)	8(100%)	50(100%)	112(100%)	79(100%)	62(100%)
Patients with at least 1 AE[b]	12(5%)	1(13%)	2(4%)	3(3%)	3(4%)	3(5%)
Patients with SAEs	0	0	0	0	0	0
Patients with related AEs	10(4%)	1(13%)	1(2%)	2(2%)	3(4%)	3(5%)
Patients with severe AEs	0	0	0	0	0	0
Patients discontinued due to an AE	0	0	0	0	0	0
Patient Deaths	0	0	0	0	0	0
Cohort 2 - Number of Patients	32(100%)	0	4(100%)	13(100%)	12(100%)	7(100%)
Patients with at least 1 AE[b]	1(3%)	0	0	1(8%)	0	0
Patients with SAEs	0	0	0	0	0	0
Patients with related AEs	1(3%)	0	0	1(8%)	0	0
Patients with severe AEs	0	0	0	0	0	0
Patients discontinued due to an AE	0	0	0	0	0	0
Patient Deaths	0	0	0	0	0	0

[a] Patients are counted only once in each category. Some patients were exposed to more than 1 dosage in the trial, so the sum of Cohort 1 patients exposed to specific dosages (N=711) exceeds the total number of Cohort 1 patients in the trial (N=236); the sum of Cohort 2 patients exposed to specific dosages (N=36) exceeds the total number of Cohort 2 patients in the trial (N=32).

[b] Treatment-emergent AEs.

5.2.2.11.4 Sleepwalking

12/236 Cohort #1 patients, and 1/32 Cohort #2 patients had sleepwalking (COSTART and investigator terms). In none of these instances was sleepwalking a reason for treatment discontinuation or a serious adverse event. In at least one of these patients (see Section 5.2.2.10.2) sleepwalking resulted in injury.

A summary of sleepwalking adverse events by dose at onset is in the following table which I have copied from the submission.

AEs of Sleepwalking	Total*	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
Cohort 1 - Number of Patients	236(100%)	8(100%)	50(100%)	112(100%)	79(100%)	62(100%)
Patients with at least 1 AE*	12(5%)	0	3(6%)	2(2%)	3(4%)	4(6%)
Patients with SAEs	0	0	0	0	0	0
Patients with related AEs	12(5%)	0	3(6%)	2(2%)	3(4%)	4(6%)
Patients with severe AEs	0	0	0	0	0	0
Patients discontinued due to an AE	0	0	0	0	0	0
Patient deaths	0	0	0	0	0	0
Cohort 2 - Number of Patients	32(100%)	0	4(100%)	13(100%)	12(100%)	7(100%)
Patients with at least 1 AE*	1(3%)	0	0	1(8%)	0	0
Patients with SAEs	0	0	0	0	0	0
Patients with related AEs	1(3%)	0	0	1(8%)	0	0
Patients with severe AEs	0	0	0	0	0	0
Patients discontinued due to an AE	0	0	0	0	0	0
Patient deaths	0	0	0	0	0	0

Patients are counted only once in each category. Some patients were exposed to more than 1 dosage in the trial, so the sum of Cohort 1 patients exposed to specific dosages (N=311) exceeds the total number of Cohort 1 patients in the trial (N=236); the sum of Cohort 2 patients exposed to specific dosages (N=47) exceeds the total number of Cohort 2 patients in the trial (N=32).

* Treatment-emergent AEs.

Detailed descriptions of the sleepwalking episodes are not available.

Sleepwalking has been more fully analyzed in Section 7.

5.2.2.11.5 Vomiting

11 out of 236 Cohort 1 patients had vomiting. In 1 out of the 11 (#05257; see Section 5.2.2.9.1) the vomiting was considered to be a serious adverse event.

2 out of 32 Cohort #2 patients had vomiting. In one of these patients (#17302; see Section 5.2.2.10.4) the vomiting was an adverse event leading to treatment discontinuation.

A summary of the adverse events of vomiting by dose at onset is in the following table which I have copied from the submission.

AEs of Vomiting	Total*	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
Cohort 1 - Number of Patients	236(100%)	8(100%)	50(100%)	112(100%)	79(100%)	62(100%)
Patients with at least 1 AE*	11(5%)	0	2(4%)	3(3%)	1(1%)	5(8%)
Patients with SAEs	1(<1%)	0	0	0	0	1(2%)
Patients with related AEs	1(<1%)	0	0	1(<1%)	0	0
Patients with severe AEs	1(<1%)	0	0	0	0	1(2%)
Patients discontinued due to an AE	0	0	0	0	0	0
Patient deaths	0	0	0	0	0	0
Cohort 2 - Number of Patients	32(100%)	0	4(100%)	13(100%)	12(100%)	7(100%)
Patients with at least 1 AE*	1(3%)	0	0	1(8%)	0	0
Patients with SAEs	0	0	0	0	0	0
Patients with related AEs	1(3%)	0	0	1(8%)	0	0
Patients with severe AEs	0	0	0	0	0	0
Patients discontinued due to an AE	1(3%)	0	0	1(8%)	0	0
Patient deaths	0	0	0	0	0	0

Patients are counted only once in each category. Some patients were exposed to more than 1 dosage in the trial, so the sum of Cohort 1 patients exposed to specific dosages (N=311) exceeds the total number of Cohort 1 patients in the trial (N=236); the sum of Cohort 2 patients exposed to specific dosages (N=47) exceeds the total number of Cohort 2 patients in the trial (N=32).

* Treatment-emergent AEs.

19 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

5.5 Reviewer's Comments About Safety Update

- The spectrum of adverse events seen in this safety update is broadly similar to that seen in earlier submissions under this NDA.
- 2 patients discontinued Xyrem® on account of elevated transaminases (ALT > AST; maximum ALT elevation < 8 x upper limit of normal). In both instances conditions other than Xyrem® (tamoxifen; marked weight gain) could have contributed to the enzyme increase

6. Status Of Patients Enrolled In Scharf Study Who Had Not Entered Treatment IND Study OMC-SXB-7 As Of 5/31/99

6.1 Background

The Scharf study was an open-label protocol conducted by Dr Martin Scharf under his own IND, and lasted > 16 years. 143 patients enrolled in the Scharf study. Of the 143 patients, 63 were subsequently transferred to the treatment IND study OMC-SXB-7 conducted by Orphan Medical, Inc., as of the cut-off date (for the original NDA submission) of 5/31/99.

Study OMC-SXB-7 began early in 1999.

At the time of review of the original NDA submission concerns were raised by this Division as to the validity of the data from the Scharf study that were submitted with the original NDA. These concerns were raised by an Agency inspection of the study site, conducted in February 2001. The same study site was again inspected in May 2001 following which a Warning Letter was issued. In a Clinical Inspection Summary, dated 6/11/01, the Division of Scientific Investigations recommended that data from this study not be used in support of the pending application: study records were inadequate and drug accountability could not be satisfactorily reconciled.

The Major Amendment to the original NDA that was submitted on 3/23/01 was intended in part to address the deficiencies in the Scharf study. In addressing these deficiencies the sponsor was requested by the Division to characterize the 80 patients who entered the Scharf study, and did not subsequently enroll in Study OMC-SXB-7. In the characterization of these 80 patients the Division was especially, but not solely, interested in

- Their reasons for discontinuing from the Scharf study
- Their status in the months after they discontinued from the Scharf
- For the patients who were deceased, their cause of death
- To what extent they actually received study medication, and proof thereof

The purpose of obtaining follow-up information on these 80 patients was to ascertain that they had been satisfactorily "accounted for," i.e., had not had any worrisome adverse event either while taking GHB or shortly afterward.
After review of the data for these 80 patients submitted as part of the Major Amendment of 3/23/01, the Division felt that the disposition of 11 out of these 80

patients still needed to be accounted for. These patients are listed below, and are grouped according to whether they actually continued to participate in the Scharf study or were discontinued from that study on account of non-compliance, prior to 5/31/99.

Continued In Scharf Study	Discontinuations For Non-Compliance
01-004	01-240
01-027	01-268
01-054	01-256
01-065	
01-228	
01-262	
01-269	
01-283	

In the Approvable letter issued on 7/2/01 the Division had requested the sponsor to provide further information about the disposition of these 11 patients. In the current submission the sponsor has attempted to provide that information.

6.2 Sponsor's Methods

According to the sponsor

- Source records, data listings and Case Report Forms were reviewed
- When necessary site personnel contacted patients to ascertain their reasons for study drug discontinuation (if they discontinued the drug) and their current status
- The most current status of these patients is reported in this submission

A summary table and text has been provided, along with a narrative for each patient

6.3 Overview

According to the sponsor

- As of 5/31/99, 8/11 patients had continued to receive GHB as part of Dr Scharf's then-ongoing IND. 3/11 patients had discontinued from the Scharf trial on account of non-compliance as of 5/31/99.
- "Present-day" follow-up was attempted for all 11 patients and was successful for 10. Follow-up was not possible for Patient 01-240
- 3 out the 8 patients who were still in the Scharf trial as of 5/31/99 subsequently entered the treatment IND study OMC-SXB-7 after the Scharf trial was closed. One of these patients later discontinued from the OMC-SXB-7 trial on account of a serious adverse event.
- 2 out of the 8 patients who were still in the Scharf study as of 5/31/99 discontinued from that study in June 1999 and August 2000, respectively and did not take GHB any further
- 3 out of the 8 patients who were still in the Scharf study as of 5/31/99 remained in that study until it closed

The results of the follow-up, according to the sponsor, are summarized in the table below which I have copied from the submission. Although the sponsor

states that "present-day" follow-up was successful on 10/11 patients there is no indication in the table when the last contact with each was made. In the next section I will indicate how recent the sponsor's contact with each of these patients has been.

Patient No.	Pt Initials	Sex	Age at Trial Entry (yrs)	Date Started GHB Treatment	Date of Last Dose	Reason for Discontinuation / Current Status
1-[illegible]	[illegible]	M	41	[illegible]	NA	[illegible] following the closure of the Scharf trial
01-027	[illegible]	F	38	3/26/1964	2/17/2001	Transferred to OMC-SXB-7, but was subsequently discontinued following hospitalization for anemia (a pre-existing condition)
1-[illegible]	[illegible]	M	63	2/10/1987	10/00/2000	Discontinued Scharf trial due to study closure
[illegible]	[illegible]	F	34	[illegible]	[illegible]	Discontinued due to non-compliance (failure to return logs and diaries)
1-[illegible]	[illegible]	M	16	2/17/1994	NA	Transferred to OMC-SXB-7 on 10/25/2000 following the closure of the Scharf trial
[illegible]	[illegible]	M	42	[illegible]	[illegible]	Discontinued for non-compliance. Present but follow-up not successful
[illegible]	[illegible]	M	[illegible]	[illegible]	[illegible]	Discontinued for non-compliance. Patient in poor health and currently taking [illegible] therapy.
01-262	[illegible]	F	63	3/27/1991	10/00/2000	Discontinued Scharf trial due to study closure. Patient is a nursing home resident and not able to participate in OMC-SXB-7.
1-268	[illegible]	M	22	7/11/1993	5/31/1997	Discontinued for non-compliance. Patient is currently taking Vivactil and Ritalin
[illegible]	[illegible]	M	[illegible]	7/8/1985	6/00/1990	Discontinued by patient request. Patient indicated that was not interested in participating in OMC-SXB-7 and felt his [illegible] was "not that bad".
[illegible]	[illegible]	M	[illegible]	[illegible]	[illegible]	Discontinued Scharf trial due to study closure

6.4 Summary Of Individual Patient Disposition And Time Of Most Recent Contact

Using the narratives supplied by the sponsor I have created the table below

Patient Number And Initials	Disposition	Most Recent Contact	Status At Most Recent Contact
01-004/	Continuing in OMC-SXB-7	Date not available	Participating in OMC-SXB-7
01-027/	Entered OMC-SXB-7 but discontinued from that trial on account of a serious adverse event	4/12/01, based on entry in hospital record Last dose of GHB on or about 3/24/01	Reported to be improving based on hospital record
01-054/	Discontinued Scharf trial when that study closed	October 2000	Sleep apnea worse
01-065/	Discontinued Scharf trial on account of non-compliance	August 2000	Not stated
01-228/	Continuing in OMC-SXB-7	Date not available	Participating in OMC-SXB-7
01-240/	Discontinued Scharf trial on account of non-compliance	Discontinued from Scharf study 7/5/88 "Present-day" attempted contact unsuccessful	Not available from Case Report Form supplied earlier
01-256/	Discontinued Scharf study on account of non-compliance	7/5/01 GHB discontinued 6/30/88	Good health. Taking fluoxetine for cataplexy. No recollection of adverse events related to GHB or withdrawal symptoms when GHB was discontinued
01-262/	Discontinued Scharf trial when that study closed	October 2000	Not stated
01-268/	Discontinued Scharf study on account of non-compliance	6/1/01 GHB discontinued 3/31/97	Taking methylphenidate and protriptyline for cataplexy

Patient Number And Initials	Disposition	Most Recent Contact	Status At Most Recent Contact
01-269	Discontinued Scharf study at his own request	June 1999	Not stated
01-283	Discontinued Scharf trial when that study closed	October 2000	Not stated

The following conclusions can be drawn from the above table

- True "present-day" contacts were made with only 2/11 patients rather than 10/11 patients, based on the records supplied by the sponsor. The 2 patients with whom such contacts could be made were #s 01-256 and 01-268
- Patient # 01-240 could not be satisfactorily accounted for, despite a recent attempt at follow-up. He began using GHB on 1/5/88 but did not subsequently submit daily diaries or sleep logs; no information regarding adverse events or compliance with medication is available. On 7/5/88 he was informed that he was being discontinued from the study, when he phoned for a refill, on account of his non-compliance.

Despite the lack of any recent contacts the remaining 8 patients could be "accounted for," i.e., it is unlikely that they were seriously ill while on GHB (except from an unrelated intercurrent illness) or shortly thereafter. However this conclusion is based on indirect inferences, and is therefore less than optimal.

The basis under which they were considered "accounted for" is indicated below

Patient Numbers	Basis Under Which Patients Were "Accounted For"
01-004, 01-228	Continuing participation in OMC-SXB-7
01-027	Hospital record several weeks after discontinuing GHB
01-054, 01-262, 01-283	Remained in Scharf trial until that study closed
01-065	Laboratory tests done 3 weeks after discontinuing GHB showed "no clinically significant abnormalities." Phone contact with patient about 3 months after discontinuing GHB indicated that the only event of note at that time was a worsening of sleep apnea
01-269	Discontinued Scharf study at his own request as he felt that his cataplexy was "not bad"

6.5 Narratives For Selected Patients

More detailed narratives have been provided by me for 2 of the patients discussed in this section.

6.5.1 Patient # 01-256 (Initials)

This 16 year old boy had a previous history of narcolepsy and of blurred vision following an injury to the left eye, but no preceding psychiatric illness was recorded. He took GHB while participating in the Scharf trial at a dose ranging from 2.3 g to 4.5 g. Concomitant medications included pemoline and clomipramine, as well as possibly imipramine.

At an unspecified point in the study he was recorded as "acting very paranoid." He carried a bat with him while at home, and felt someone was watching him. The time of onset of this adverse event, the dose of GHB that he was taking at that time, and whether this adverse event resolved or not is unclear .

He also reported nausea and a tendency to eat excessively at night and gained weight.

He was withdrawn from the study 2 years after entry, on account of non-compliance (failure to return his sleep logs). His last dose of GHB was reported to have been taken on 6/30/88.

Follow-up contact was made with this patient on 7/5/01. At this contact he indicated that he was well, except for being overweight. He was using fluoxetine to treat his cataplexy. At that time he did not recall having any "problems" related to GHB or to its withdrawal.

6.5.2 Patient # 01-027 (Initials —)

This 72 year old woman had a previous history of narcolepsy, hypertension, diabetes mellitus, angina, chronic obstructive pulmonary disease, gastritis, colonic polyps and chronic anemia.

She entered the Scharf study on 3/28/84 and remained in that study until October 2001, receiving GHB in doses that ranged from 2.3 g/day to 6.8 g/day. While in the Scharf study and prior to 5/31/01 she had many adverse events which included sleepwalking, urinary incontinence, confusion, nausea, vomiting, and pain in the chest, upper extremities, shoulders and throat (the latter events were believed to be manifestations of myocardial ischemia).

She transferred to the OMC-SXB-7 study on 12/5/00 and received GHB at that visit. In the next 4 months she was found to have continuing anemia with evidence of gastrointestinal blood loss, underwent multiple endoscopic that showed evidence of cecal angiodysplasias/arteriovenous malformations as well as cecal and rectal polyps, needed multiple blood transfusions, and on 3/24/01 was hospitalized underwent surgery that included a right hemicolectomy and sigmoid colectomy with anastomosis. GHB was discontinued at the time of her hospitalization. Hospital records dated 4/12/01 indicated that the patient had improved and that she was transferred to a nursing facility on that date.

The above was considered a serious adverse event.

6.6 Reviewer's Comments

- Out of 11 patients for whom further information was requested in the Approvable letter of 7/2/01, the status of 10 patients has been accounted for in this submission to the extent that it is unlikely that they had a serious illness, especially one causally related to GHB, that we are unaware of, either while on GHB or shortly thereafter.
- Judgments regarding the status of these patients have been made by indirect inferences in the majority.

7. Analysis Of Sleepwalking

7.1 Background

In the original NDA submission and in the amendment of 3/23/01 the term "sleepwalking" was used as a verbatim (investigator) term for a common adverse event. The COSTART preferred term under which this entity had been coded is "sleep disorder."

The few clinical descriptions of this adverse event that were available in the original NDA and in the Amendment of 3/23/01 suggested that during

"sleepwalking" episodes patients might be confused and might act or actually behaved in a manner that could be dangerous to themselves and to others.

Given the frequency of this event (especially in the Scharf study) and its potential consequences, and given that a detailed characterization of these episodes had not been previously attempted by the sponsor the following request was made in the Approvable letter dated 7/2/01

"An analysis should be provided of all patients in the entire safety database listed as having "sleepwalking" as an adverse event. Such an analysis should include detailed clinical descriptions of the episodes, whenever they can be obtained from source documents, and the following additional elements: demographics, relationship to dose, frequency, seriousness, reason for discontinuation, further evaluations (e.g., EEGs and polysomnograms) and outcome".

In addition to an actual analysis of "sleepwalking" in the NDA, the sponsor has provided a literature review of sleepwalking and related disorders

7.2 Literature Review Of "Sleepwalking" And Related Disorders

The sponsor has listed and described in detail the disorders that need to be considered in the differential diagnosis of "sleepwalking"

These disorders include

- Non-REM parasomnias
  - Sleepwalking (somnambulism)
  - Confusional arousals
  - Sleep terrors
- Automatic behavior in narcolepsy
- REM Behavior Disorder
- Nocturnal seizures
- Psychogenic dissociative states

The descriptions provided by the sponsor include the following

- Sleepwalking (i.e., true somnambulism) is a distinct disorder that is relatively infrequent in adults involving an estimated 4 -10% of the adult population. In only 1% of adult cases is sleepwalking chronic
- REM Behavior Disorder is also a distinct phenomenon known to occur more frequently in the elderly and in men. Narcoleptics and chronic users of tricyclic antidepressants and selective serotonin re-uptake inhibitors are more susceptible to developing REM Behavior Disorder during episodes of which behavior is often violent. Episodes are recalled, often fully, as dreams.