13.10.2 Patient # 0232

This patient has already been described in Section 10.5.2. The adverse event occurred shortly after she finished participating in Study OMC-SXB-21.

13.10.3 Patient # 0931

This 29 year old woman had taken Xyrem® from 7/5/99 until she developed the serious adverse event listed in the table above in April 2000. At screening, she did not disclose that she had a past history of depression.

Her dose of Xyrem® at the time of the adverse event was 4.5 g/day. She was also receiving modafinil 600 mg/day.

On 4/27/00 the study coordinator was informed that the patient had been hallucinating and had lost her job owing to a diminished ability to function at work. On 4/29/00 the patient was found to be unarousable in her car by emergency personnel: on being awakened she became violently agitated, but was also slow in responding to questions. She was hospitalized and treated with multiple medications for agitation. Her urine drug screen was positive for benzodiazepines. The patient later reported that on 4/29/00 she pulled off the road to sleep at which time she took both nightly doses of Xyrem® together without dilution. She was diagnosed to have a bipolar disorder.

She did not take any Xyrem® after 4/29/00 and at a follow-up visit on 6/14/00 appeared mentally well.

13.10.4 Patient # 1131

This 46 year old man was begun on Xyrem® on 4/30/99. At study entry he did not disclose that he had a past history of depression and a previous suicide attempt. Concomitant medications at study entry included modafinil 400 mg/day, ibuprofen, an aspirin-acetaminophen-caffeine combination pill, dextroamphetamine and bupropion (for smoking cessation).

His regular dose of Xyrem® at the time of the serious adverse event described below was 9 g/day.

He took an overdose of Xyrem® (subsequently estimated at 150 g) on 2/2/00. His wife found him unresponsive and incontinent of urine and feces that day. He was initially unresponsive with apneic spells, but with normal arterial blood gases. He later became combative and finally awoke, at which time he was observed to be depressed. He reported multiple major sources of stress. He required psychiatric hospitalization and did not resume Xyrem®.

13.10.5 Patient # 14043

This 26 year old woman had previously participated in the Scharf trial and had received GHB since 7/5/89. She entered the OMC-SXB-7 trial on 8/30/99. Her past medical history was remarkable for obsessive compulsive disorder. Concomitant medications during the OMC-SXB-7 trial include fluvoxamine, buspirone and methylphenidate.

On 4/2/00 she took her usual dose of Xyrem® (7.5 g/day) and then attempted suicide by taking 56 tablets of buspirone 5 mg. She immediately told her father what had happened, was taken to an emergency room where she was treated and released. She

reported being increasingly self-critical from January 2000 onward after beginning methylphenidate. After discontinuing Xyrem® (last dose on 4/4/00) she became more negative in outlook and noted an increase in cataplexy and in sleepiness.

13.10.6 Patient # 2030

This 18 year old man began taking Xyrem® on 5/28/99 and was maintained on a stable dose of 9 g/day thereafter. Concomitant medications included zolpidem, protriptyline, modafinil (200 mg/day), fluoxetine 20 mg/day, methylphenidate 40-45 mg/day. He reported no previous psychiatric history.

On 12/15/99 he began experiencing paranoia, confusion and hallucinations. He reported increasing his dose of methylphenidate earlier while preparing for examinations. He was hospitalized and treated with multiple medications. Xyrem® was stopped on 12/22/99. He improved and his psychosis was attributed to methylphenidate overuse and to sleep deprivation.

13.11 Adverse Event Discontinuations

10 patients, including the patient who died, discontinued treatment on account of an adverse event. They are summarized in the following table. With the exception of Patient 1305 all the others are listed under Deaths and Serious Adverse Events

Patient No. [a]	Xyrem Dosage at Onset (g/d)	COSTART Preferred Term	Relationship to Trial Drug	SAE (Y/N)
0214	9.0	Liver function tests abnormal[b]	Unknown	Y
0332	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
1131	9.0	Intentional overdose	Definitely related	Y
1305	9.0	Movement disorder[c]	Unknown	N
14043	7.5	Suicide attempt[d]	Possibly related	Y
1509	6.0	Back pain	Not related	Y
2030	9.0	Psychosis	Possibly related	Y
2536	9.0	Fractured Ankle[e]	Possibly related	Y

13.11.1 Patient 1305

This 75 year old woman entered the OMC-SXB-7 trial after participating in the OMC-GHB-2 and OMC-GHB-3 trials. She had received Xyrem® since 8/5/97 and was on a stable dose of 9 g/day from 7/8/99. Her neurological history was unremarkable except for narcolepsy with cataplexy. Her concomitant medications included ibuprofen, conjugated estrogen, medroxyprogesterone, and long and short-acting methylphenidate.

On 2/12/00 she began experiencing an intermittent "movement disorder". A nocturnal polysomnogram confirmed that she had periodic leg movements (it is unclear if the

- Every patient and prescribing physician will be registered with ——— in a secure database. The database will contain the physician's name, address, telephone and facsimile numbers, DEA and state license numbers and prescribing frequency. The database will be made available for review by the DEA as well as other federal and state agencies upon request. From this database it will be possible to obtain the following information
  Prescriptions by physician specialty
  Prescriptions by patient name
  Prescriptions by volume (frequency)
  Prescriptions by dose
- If required by the patient's insurance company the product may be shipped by ——— to another pharmacy for patient pick-up. The sponsor anticipates that this will be an unusual occurrence, and has a mechanism for verifying the second pharmacy's ability to protect against diversion of GHB before shipping the drug there.
- Prescription refills will be permitted in the number specified in the original prescription. In addition
  - If a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned by the pharmacist
  - A lost, stolen, destroyed, or spilled prescription/supply will be documented and the prescription replaced to the extent necessary to honor the original prescription (e.g., a destroyed or spilled bottle will reduce the prescription refill amount). The pharmacist has the discretion to grant or not grant refill requests under those circumstances and at a minimum will contact the prescribing physician to determine if the physician has any special concerns in regard to that refill request. New supplies of Xyrem® will be sent to the patient only if the pharmacist and physician are in agreement.
  - Repeat instances of lost, stolen, destroyed, or spilled prescriptions/supplies will be flagged for monitoring and future instances thoroughly questioned
- The quantity of medication to provided with each refill will be guided by the following
  - With the first prescription it is planned to provide the patient with only one month's supply of Xyrem®.
  - Following further contact between the pharmacy and patient, and verification that the patient understands the material in the Xyrem® Patient Success Program, supplies of Xyrem® that are intended to last longer than a month may be shipped
  - The quantity of drug shipped to the patient with each refill may also be regulated based on the requirements of the patient's health insurance plan and the terms of the prescription itself
  - It is anticipated that the majority of patients will receive only one month's shipment at a time and never more than 3 months' supply per shipment.

14.1.2 Drug Product Kit

The drug product kit will consist of

- The drug product, a clear solution, in a ——— amber bottle with a closure mechanism that is child-resistant
- The Press-In-Bottle-Adapter (PIBA Well) which will be inserted into the bottle by the pharmacist

- An Exacta-Med Dispenser which allows the patient to withdraw the appropriate dose of drug
- Two child-resistant dosing cups, one for each of 2 nightly doses. The first dose will be consumed just prior to lying down at bedtime and the second dose will be placed at the bedside, and sealed with a childproof lid until consumed by the patient 2.5 to 4 hours later.
- A package insert which includes a patient information sheet*

Every box of Xyrem® shipped to the patient will contain all the above items

*The patient information sheet includes the following information

- Dosing instructions
- Preparation of dose
  The steps involved in dose preparation and use are as follows
  - Remove bottle cap
  - Insert measuring device into bottle containing PIBA Well
  - Draw up prescribed dose
  - Remove measuring device from bottle
  - Empty dose into first dosing cup
  - Dilute with 60 mL of water
  - Repeat procedures with second dosing cup
  - Place second dosing cup at bedside after securing lid
  - Set alarm for no later than 4 hours after first dose
  - Drink first dose sitting up and immediately lay down
  - Awake for second dose.
  - Drink second dose sitting up
- Side-effects
- Special concerns: memory problems, dependence, withdrawal, changes in behavior and thinking, pregnancy
- Safe use of Xyrem®:
  - scheduling
  - self-observation for behavioral changes
  - cautions regarding concurrent use of medications and alcohol, driving, operating machinery, piloting an aircraft and pregnancy
  - caution against sharing Xyrem® with others
  - safe storage and disposal

14.1.3 Xyrem® Physician Success Program

This program consists of a videotape and printed material.

14.1.3.1 Distribution

This program will be distributed as follows

- "Customer targets." This phrase refers to a database of physicians who have prescribed modafinil more than 4 times (about 4000 physicians have done so at present but the data will be refreshed when Xyrem® is launched). When Xyrem® is launched the program will be mailed to the target physicians as well as handed to them by sales representatives. The mailing as well as the receipt from sales representatives will be documented. No physician samples will be provided by the sales representatives
- When a physician prescribes the drug for the first time, he/she will receive also be mailed the program: the mailing will be documented as will a follow-up phone call to the physician confirming receipt

14.1.3.2 Videotape

The draft video "story-board" prepared by the sponsor contains the following elements

- The identity and medical uses of Xyrem®
- A short history of the development of this drug
- The need for patients to follow the physician's instructions in their entirety. Among other instructions the physician will need to tell patients that
  - The optimal dose of Xyrem® will need to be reached by titration over a number of weeks
  - Improvements in symptoms may not be fully apparent until 60-90 days after the drug is first begun
- Instructions regarding the frequency of dosing, emphasizing the need to take the medication twice every night.
- Very detailed instructions regarding the preparation of individual doses
- The need to place the second nightly dosage cup in an area not accessible to children, to store the medication bottle in a secure location and to consume the entire content of both dosing cups, sitting up.
- Directions as to when the bottle is to be disposed of (i.e., when the solution can no longer be drawn out of the bottle with the dispensing device), and emphasis on the need to empty the bottle completely and deface the label with a marker pen before throwing it away
- Federal scheduling of Xyrem® for legal and illegal use, the latter for punitive purposes
- The need to follow all standard procedures used for prescribing controlled substances
- A listing of types of patient behavior that may indicate misuse or abuse of Xyrem®
- The need to make clear to the patient that he or she may be legally responsible for the careless use and/or illicit distribution of Xyrem®
- Penalties for misusing or abusing Xyrem®
- The provision of an optional Patient Consent ("Patient/Physician Responsibility Contract") form in the information package. The form is intended to have patients acknowledge in writing that they understand the safety, abuse, diversion and other issues that relate to the use of Xyrem®, and their responsibility to use the medication as prescribed by that patient; this form is intended to be kept as part of the patient's medical record.

14.1.3.3 Printed Materials

These are provided in a binder and consist of the following items

- A medical record template that covers the history, physical examination, assessment, treatment plan, prescription record, and a checklist of questions for the patient at each visit that covers the following: what dosage the patient is taking, whether the patient is taking 2 nightly divided doses, whether the patient is experiencing any side effects and whether the patient's symptoms have improved.
- A tabular outline of how Schedules I and III apply to the dispensing, distribution, diversion potential, patient access, tracking ability and manufacturing of drugs, and how the same items apply to Xyrem®
- An outline of how to identify patients who may be abusing Xyrem®
- Adverse effects associated with the use of Xyrem®

- A "Patient Physician Responsibility Contract" to be signed by both the patient and physician
- A series of instruction cards (contain print and graphics) to be used for by a physician for educating patients about all aspects of Xyrem®

14.1.4 Xyrem® Patient Success Program

14.1.4.1 Videotape

The draft video "story-board" prepared by the sponsor contains the following elements (the patient is instructed to watch the videotape prior to reading the printed materials)

- The identity and medical uses of Xyrem®
- A short history of the development of this drug
- The need to follow the physician's instructions completely and precisely, and to contact the physician in the event of questions
- Instructions regarding the frequency of dosing, emphasizing the need to take the medication twice every night.
- Very detailed instructions regarding the preparation of individual doses
- The need to place the second nightly dosage cup in an area not accessible to children, to store the medication bottle in a secure location and to consume the entire content of both dosing cups
- Directions as to when the bottle is to be disposed of (i.e., when the solution can no longer be drawn out of the bottle with the dispensing device), and the need to empty the bottle completely and deface the label with a marker pen before throwing it away
- The patient's legal liability in relation to the use of Xyrem®
  - Federal scheduling for legal and illegal use
  - A statement that the patient may be legally responsible for the careless use and/or illicit distribution of Xyrem®
  - Penalties for misusing or abusing the drug

14.1.4.2 Printed Materials

These are provided in a binder and consist of the following items about Xyrem®

- The drug's identity, and the reason for its prescription
- Its most common side effects (dizziness, headache and nausea) and the less common ones (pain, sleep disorder, confusion, infection, vomiting and urinary incontinence)
- The mechanism for filling prescriptions
- The need to follow physician instructions and not to alter the dose of medication without consulting the doctor
- The contents of the drug product kit that will accompany every bottle of the drug
- Instructions regarding the frequency and variability of dosing, emphasizing the need to take the medication twice every night.
- The need to wait a period of weeks to months until titrated to the optimal dose and until the full therapeutic benefits of the drug are seen
- The lack of interactions with other medications
- Storage instructions
- Action to be taken in case of accidental ingestion
- Insurance coverage

- A brief statement about the scheduling of Xyrem®, the patient's legal liability for misuse, abuse and diversion of the prescribed drug and the penalties linked to that liability (it is clearly stated that the use of Xyrem® by an individual for whom it is not prescribed is illegal)
- A description of the Patient Success Program
- Resources for information (names, addresses, phone numbers and URLs) about Xyrem®, narcolepsy and sleep disorders in general
- A patient quiz about Xyrem®
- A patient registry application to be completed by the patient and is to contain the following information
  - Patient name, address, telephone number, fax number, e-mail address, date of birth gender, social security number, patient record number, and medical insurance details (company name, patient number and group number)
  - Physician name, specialty, clinic name and address
- At home storage and safety tips: these include the following
  - The method of shipping, and the need to sign the courier's receipt personally
  - To keep Xyrem® in its original container, in a secure location and away from children and pets
  - When mixing each nightly dose to always use the dosing cups with child-resistant caps,
  - to make certain the second nightly dose is kept in a secure place
  - To re-order the drug when a 7-day supply remains,
  - To report a missing or stolen supply of Xyrem® to the local police and the Xyrem® Patient Success Program
  - To call the prescribing physician or Xyrem® Patient Success Program in the event of questions
- Traveling tips: these include the following
  - To keep Xyrem® in its original container and to take only the number of bottles needed for the trip, making certain that what is not taken on the trip is in a secure place at home
  - To keep Xyrem® in a secure location at all times
  - To remember to take the dispensing device and dosing cups with child-resistant caps when traveling
  - Not to include Xyrem® in checked baggage
  - To return home with the Xyrem® taken on the trip
  - The need to be aware that, if traveling internationally, Xyrem® might be subject to different regulations in foreign countries
  - To contact the Patient Success Program in the event of traveling without Xyrem® or needing a fresh supply in the event of an extended stay.
- Reimbursement information

14.2 OPDRA Comments

The Office Of Post-Marketing Drug Risk Assessment reviewed the Risk Management Program proposed for Xyrem®. The opinion of that office was conveyed to this Division in a formal review and in a discussion held February 5, 2001.

The final recommendations of that Office were as follows:

- The verification process conducted by [redacted] on receiving a formal prescription should include confirmation of the patient's diagnosis
- Confirmation that physicians have read and grasped the educational material provided by the sponsor could be obtained by requiring each physician to complete a questionnaire prior to dispensing of the drug to the patient

- Total-free phone numbers that physicians and patients can contact in the event of questions should be clearly indicated on the product and on all printed materials
- The label on the bottle and all patient information enclosures should carry warnings of the risks of using Xyrem® especially if taken in combination with alcohol, benzodiazepines and other central nervous system depressant drugs
- Proper use, handling and disposal measures should also include the following
  - Child-resistant packaging
  - Storage in a secure container (e.g., a lock box)
  - Comprehensive patient, family and child safety educational programs
  - Instructions and training for patients and caregivers on dilution and measuring techniques and use of the PIBA Well and Exacta-Med dispenser

14.3.3 Appropriate Prescribing For The Labeled Orphan Indication

In order to ensure that Xyrem® will be appropriately prescribed for its labeled indication the following have been suggested

- The central pharmacy should be described in the product labeling and other educational and promotional materials
- The central pharmacy should track prescriptions and refills regardless of third-party payer participation in the monitoring of quantity and frequency of drug dispensing
- A sponsor-physician agreement should state that Xyrem® will be used only in the treatment of narcolepsy-cataplexy
- A physician-patient agreement should also be completed
- Documentation of patient and physician education regarding the use and risks of Xyrem® prior to dispensing the first prescription
- Certification of physicians for prescribing Xyrem®: the types of physicians who may prescribe Xyrem® should be described in the risk management program; the sponsor should also consider developing a course of instruction for physicians to train them in sleep disorders and in the safe and appropriate use of Xyrem® (this could be an additional requirement for certification)

14.3.4 Prevention Of Misuse And Overdose

The following have been suggested

- The penalties for abuse and diversion of Schedule I compounds under the Controlled Substances Act should be clearly indicated in material supplied to the patient
- An active post-marketing surveillance program that consists of the following
  - Spontaneous and solicited reports from physicians and other healthcare providers
  - Sponsor tracking of excessive or inappropriate prescribing
  - Plan to monitor signals of off-label use
  - Provision of periodic updates to the Agency regarding instances of misuse, abuse, diversion and overdose
- Voluntary restriction on quantity dispensed per month or per prescription

- A "Dear Healthcare Provider" letter advising of Agency action (i.e., approval of drug) and describing the risk management program
- A plan to measure the success of the risk management program

14.4 Joint Risk Management Recommendations

At a joint internal meeting chaired by Dr R. Temple, Office Director, that was held on 4/26/01 it was decided to ask the sponsor to consider including the following additional elements in the risk management program. Those present at the meeting included representatives of this Division, the Controlled Substances Staff and the Office Of Post-Marketing Drug Risk Assessment

- Obtaining physician agreement to use GHB only for cataplexy, at the time of the first prescription
- Obtaining a physician undertaking, at the time of the first prescription to report instances of misuse and overuse of GHB to the sponsor
- Requiring active post-marketing surveillance by the sponsor (e.g., through physician surveys) to look for specific adverse events
- Making certain that that the pharmacist carefully tracks all GHB prescriptions (even for cash-paying patients) to see if excessive quantities are being prescribed
- Obtaining the physician's signed confirmation that he/she fully understands how GHB is to be used prior to the first prescription being filled
- Obtaining the patient's signed confirmation that he/she fully understands how GHB is to be used prior to the first prescription being mailed

15. Labeling Review

This has been done in a separate document entitled "NDA 21196 Labeling Review"

16. Overall Comments

16.1 Clinical Safety

- When GHB is used to treat narcolepsy in doses of 3-9 g/day the most common, and seemingly drug and dose-related adverse events have included the following: headache, unspecified pain, nausea and dizziness. Urinary incontinence is slightly less common, but apparently dose and drug-related as well. More serious, but much less common, adverse events seen at the same dose range, and that could be attributed to Xyrem®, have included vomiting, confusion, restlessness, agitation, paranoia, hallucinations, somnolence and generalized weakness. No deaths that could be attributed to study drug have been reported at therapeutic doses of GHB
- One healthy 39 year old woman participating in a pharmacokinetic trial developed dizziness, nausea, vomiting, respiratory depression and fecal incontinence, after a single (and initial) oral dose of 4.5 g of GHB, administered after an overnight fast.
- A single older narcoleptic patient who had been taking GHB for approximately 1 ½ years was hospitalized after an overdose of GHB 18 g. At the time of hospitalization, he was comatose and unresponsive. He needed intubation and artificial ventilation, and awoke 6 hours later. This incident suggests that

the safety margin between therapeutic and toxic doses, even in narcoleptic patients maintained chronically on GHB, may not be very wide
- At therapeutic doses of GHB all adverse events appear to be reversible
- While currently there is no strong evidence that GHB in therapeutic doses is epileptogenic or that episodes of urinary and fecal incontinence due to GHB are due to seizures, there is insufficient data at present to rule out either possibility.
- "Recreational" use of GHB generally at doses presumed or known to be higher than the therapeutic has been associated with adverse events that included fatalities attributable to the depressant effects of this drug on the nervous system. However concurrent use of alcohol and of other drugs with effects on the central nervous system has been reported in many of these instances
- There is no evidence that GHB is toxic to any major organ other than the nervous system.

16.2 Clinical Efficacy

This may be summarized as follows (please see the NDA Efficacy Review for full details)
- Currently there are no drugs approved for the treatment of cataplexy. There are several drugs approved for the treatment of excessive daytime sleepiness accompanying narcolepsy, or for narcolepsy as a generic entity. These are modafinil, methylphenidate and dextroamphetamine.
- There appears to be adequate evidence in this application that GHB is superior to placebo in treating cataplexy. This evidence comes from at least two, and possibly three randomized, double-blind, placebo-controlled trials.
- The efficacy of GHB in treating narcolepsy is most consistently seen at a dose of 9 g/day. It does not appear that doses < 4.5 g/day are effective
- There is currently inadequate evidence that GHB is effective in treating daytime sleepiness accompanying narcolepsy

16.3 Withdrawal Phenomena And Abuse Potential

- There is no evidence from a small formal study with a randomized withdrawal paradigm (OMC-SXB-21) that the abrupt discontinuation of therapeutic doses of GHB used for 6 months to 3 ½ years leads to more than mild and infrequent withdrawal symptoms, except for a significantly increased frequency of cataplexy.
- There are however a number of anecdotal reports of an actual withdrawal syndrome and, possibly, addiction in illicit "recreational" users of GHB, GBL or 1-4 BD. In all these individuals high doses of GHB or related drugs were believed to have been used at frequent intervals around-the-clock.

16.4 Risk Management Program

The small clinical trial safety database, the narrow margin of safety and the risks of abuse and misuse all call for approval to be conditional on a risk management system that is more stringent than that proposed by the sponsor. Key additional elements of such a system should include

- Dispensing of the drug exclusively to patients with a diagnosis of cataplexy confirmed by their physicians
- Commitment by the sponsor to a detailed plan for active post-marketing surveillance for instances of diversion, abuse, misuse and adverse events of special concern
- Clear statements in the approved label, patient information sheet and patient and physician educational materials about the nature of the drug (i.e., that it contains the same active ingredient as illicitly-used GHB), the limited experience with the drug during development, the potentially serious toxicity of both therapeutic doses and overdoses
- Use of Subpart H of the Accelerated Approval regulations (21 CFR 314.500) so as to provide a means of restricting distribution of the drug and for enforcement of the risk management program. Justification for institution of these regulations is as follows
  - Xyrem® is intended to treat a serious disease (cataplexy)
  - Xyrem® provides meaningful benefit to patients over existing treatment
  - Xyrem® can be used safely only if its distribution or use is restricted

16.5 Additional Comments

See Section 20 for additional comments based on a review of an Amendment submitted on 3/23/01

17. Study Site Inspections

17.1 Sites Inspected

The following study sites pertinent to this application were inspected by the Division of Scientific Investigations (DSI) at the request of this Division

Site	Location	Study
Orphan Medical, Inc (Sponsor)	Minnetonka, MN	OMC-GHB-2
[redacted]		OMC-GHB-2
Jonathan Schwartz, MD (Investigator)	Oklahoma City, OK	OMC-GHB-2
Lawrence Scrima, PhD (Sponsor-Investigator)	Aurora, CO	Scrima Study
Martin Scharf, PhD (Sponsor-Investigator)	Cincinnati, OH	Scharf Study

The results of these inspections are described in detail in a Clinical Inspection Summary written by Constance Lewin, MD, of the Division of Scientific Investigations, dated June 11, 2001. Please refer to that document for full details.

These inspections uncovered a number of deficiencies, the most prominent of which pertained to the Scharf open-label study and are summarized below

17.2 Scharf Study Inspection

At the request of this Division the Division of Scientific Investigations carried out an inspection of the Scharf long-term safety study. This inspection was requested after the Agency was informed that the Institutional Review Board for Dr Martin Scharf's sponsor-investigator IND # [redacted] had withdrawn approval for that IND; the approval was stated to have been withdrawn based on protocol violations in a study conducted under that IND in patients with fibromyalgia.

In the FDA Form 483 issued to Dr Martin Scharf on 2/23/01 which was based on an inspection conducted from 2/6/01 to 2/23/01, the following deficiencies that are relevant to this application (and to the Scharf study in narcolepsy/cataplexy) were noted. These deficiencies were based on a review of records for 13 patients which was apparently all that could be accomplished over the inspection period given the disorganized state in which the study records were maintained

- Records of subjects were not adequately maintained by the investigator to assure accurate reporting of the subjects' data with respect to adverse events, test article accountability, informed consent and patient diaries
- Serious adverse events for 6 patients were not reported to the appropriate Institutional Review Board
- 2 separate diaries were noted for the same subject for the same period of time (November 1999): the handwriting in the diaries was different as was the data which was conflicting
- In each of 5 patients, a number of adverse events in source documents were not reported to Orphan Medical, Inc.
- In 2 patients diaries covering periods of 1-2 years could not be found
- In a number of patients drug dispensing records were not available (the absent records were for periods from 1 to 7 years). When dispensing logs were actually available, they were incomplete

In an effort to ensure that major adverse events in this study were captured the Division made a number of recommendations to the sponsor during meetings and teleconferences held in February-March 2001.

- Obtaining as much information as possible about the status of the 80 patients in the Scharf study who did not enter the OMC-SXB-7 (treatment IND) study; if their current status was not known their health at the time of discontinuation from the Scharf study (which the majority of the 80 patients did leave) and for 1-2 months afterward needed to be ascertained.
- Obtaining as much information as possible about all patients listed as having convulsions during the study.
- Obtaining as much information as possible about all patients whose adverse events were listed as "unevaluable"
- Obtaining as much information as possible about patients with the following adverse events: confusion and other neuropsychiatric symptoms, and urinary and fecal incontinence
- Tracing drug dispensing records

A further inspection of the study site was conducted from 5/7/01 to 5/11/01. This second inspection was intended to validate the data presented in the Major Amendment of 3/23/01, using source documents. A sample of 31 patient records were inspected; all 31 were patients who did not enter the OMC-SXB-21 study through the cut-off date of 5/31/99. Based on discussions that I had with Dr Lewin who conducted the inspection, and on her report (Clinical Inspection Summary dated 6/11/01), it did appear that, in this sample, the data presented in the Amendment were supported by the source documents in all but 6 patients in whom significant discrepancies were noted.

Overall, however, Dr Lewin recommended that the data from the Scharf Study were unacceptable on account of many deficiencies including missing drug accountability records. She recommended that the study not be used in support of the NDA.

17.3 Division Of Scientific Investigations Conclusions

These conclusions are summarized in the following table

Site	Study	DSI Conclusions and Recommendations
Orphan Medical, Inc (Sponsor)	OMC-GHB-2	Data acceptable
[redacted]	OMC-GHB-2	
Jonathan Schwartz, MD (Investigator)	OMC-GHB-2	
Lawrence Scrima, PhD (Sponsor-Investigator)	Scrima Study	Data unacceptable*. Recommendation: Study not be used in support of NDA
Martin Scharf, PhD (Sponsor-Investigator)	Scharf Study	Data unacceptable** Recommendation: Study not be used in support of NDA

*Drug accountability records largely missing
**Multiple deficiencies including missing drug accountability records

18. Financial Disclosure Certification

Financial disclosure certification has been submitted with this application.

18.1 Components Of Certification

This certification has 2 components

18.1.1 Certification Pertinent To Dr Lawrence Scrima

The sponsor has supplied required financial disclosure information for Dr Scrima.

Orphan Medical, Inc, entered into a financial contract with Dr Scrima on 11/10/99. The contract allowed Orphan Medical to access documentation associated with the double-blind, placebo-controlled, cross-over trial in 20 narcoleptic patients. The trial was conducted from April 5, 1986 to December 14, 1987.

The sponsor states that payments to Dr Scrima were made over 10 years after completion of the trial. While the payment was financially disclosable it did not have any impact on data collection, interpretation or analysis

18.1.2 Certification Pertinent To Other Investigators

The sponsor has supplied a list of 32 Investigators who conducted clinical trials on behalf of Orphan Medical, Inc. In regard to this list the sponsor has

- Certified that it has not entered into any financial agreement with the clinical investigators listed in the application whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)
- Certified that each listed clinical investigator required to disclose to the sponsor that whether the investigator had a proprietary interest in this product

or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements
- Certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)

18.2 Reviewer's Comment

It appears unlikely that the financial arrangement disclosed above introduced significant bias into the results of studies carried out with Xyrem®, and submitted with this NDA.

19. Major Amendment

On March 23, 2001, the sponsor submitted a Major Amendment to this NDA

The purpose of the amendment was to address the following
- The deficiencies in the Scharf study outlined previously
- A number of questions pertaining to the safety data for clinical trials conducted by Orphan Medical
- Several related issues.

In submitting the Major Amendment the sponsor requested a 90-day extension to the original Prescription Drug User Fee Act deadline of April 2, 2001.

This Major Amendment is reviewed in a separate document. Please refer to that review for full details. My comments based on that review are below

20. Additional Comments Based On Review Of Major Amendment

My comments are summarized below. In order to understand the context of the comments further, the reader will need to refer to the review of the Amendment itself which is in a separate document.

- The manner in which data for the Scharf study have been collected, recorded, and presented in this submission cannot be said to be ideal.
- Of the 80 patients who participated in the Scharf study and did not enter the currently ongoing Orphan Medical Treatment IND study OMC-SXB-7, 64 patients might be stated to have be "accounted for" although the basis for doing so is less-than-optimal in a significant number. Further efforts need to be made by the sponsor to account fully for 11 of the remaining 16 (unsuccessful recent efforts have been made to contact 5 patients out of those 16). The 11 patients are listed below. Adverse events that were ongoing at the time of discontinuation are reasons for obtaining further follow-up in at least some of these 11 patients

01-004/ —
01-027/ —
01-054/ —
01-065/ —
01-228/ —

01-240/
01-262/
01-269/
01-283/
01-268/
01-256/

- None of the "adverse events" in the "unevaluable" category that occurred in the Scharf study appear to be attributable to GHB
- Urinary and fecal incontinence both appear to be unusually common adverse events in patients taking GHB and the key issues are whether such episodes are accompaniments of unrecognized convulsions, and whether GHB is capable of causing convulsions at therapeutic doses. Currently the evidence that the vast majority of episodes of incontinence in the entire NDA are related to unrecognized convulsions is weak. There does appear to be at least 1 patient in the Scharf study in whom incontinence clearly accompanied a true convulsion.
- While there are clearly a few patients (n = 2) in the entire NDA safety database who experienced, or may have experienced, convulsions while taking GHB, the presence of confounding factors (e.g., possible benzodiazepine withdrawal) makes it difficult to link the convulsions causally to GHB. Whether GHB is capable of causing other types of seizures, e.g., absence or partial complex, is even less clear
- In this NDA, and especially in the Scharf Study, the term "sleepwalking" has been used as a verbatim (investigator) term for a common adverse event. Detailed clinical descriptions of such episodes are not available for the majority of patients and their mechanism has not been delineated. A separate analysis of these episodes has not been performed by the sponsor and it is not clear how common they are in the Integrated Clinical Trials grouping, but such episodes have been associated with serious consequences (e.g., overdose, pyrogenesis, consuming toxic chemicals) in patients enrolled in the Scharf study
- The information available in this NDA does suggest that GHB is capable, at therapeutic doses, of causing a confusional state (which may be accompanied by psychotic symptoms). The incidence and seriousness of such adverse events may be slightly more pronounced at higher doses, and especially if higher doses are administered without titration. However a confusional state also appears to be capable of occurring at lower and even sub-therapeutic doses of GHB, and after maintenance treatment for several months. The presence of true confusion in patients taking GHB could lead to their taking GHB in a manner other than as prescribed. The symptoms that have been subsumed under the COSTART term "confusion" are not unusual for a sedative-hypnotic drug.
- In the majority of patients who developed "neuropsychiatric" adverse events (e.g., paranoia, hallucinations, anxiety, stupor, etc) while taking GHB in the Integrated Clinical Trials it is not possible to attribute causality for the adverse event to GHB. Pre-existing psychiatric illness, and concomitant medications such as stimulants, as well as other factors, could be contributory. Even in

patients in whom there was no recorded premorbid history of psychiatric illness the extent to which they were screened for such illness is not clear. However the occurrence of neuropsychiatric adverse events in patients taking GHB, even if not directly caused by the drug, could place them at risk of intentional or accidental overdose, as is suggested by the narratives in this review

- There is no firm evidence that any patients participating in the Integrated Clinical Trials had drug-induced lupus. However antinuclear antibody and antihistone antibody testing was not performed for patients participating in this study
- There is no evidence suggesting a causal link to GHB for the small number of hypoglycemic and hyperglycemic blood test readings in the NDA; several of the apparently hypoglycemic readings could in fact have represented laboratory errors. Neither is there firm evidence in AERS or in the medical literature that GHB is capable of causing hypoglycemia.
- GHB is unlikely to have been the cause of transaminase elevations seen in a few patients in the Integrated Clinical Trials.
- As noted above the manner in which the Scharf study was conducted was deficient in many ways. Of particular concern was the lack of systematic active surveillance for adverse events and missing drug accountability records. As also noted earlier in this review (see Section 17) the Center's Division of Scientific Investigations is of the opinion that the Scharf Study data are unacceptable and has recommended that this study not be used in support of the application. From this reviewer's perspective the best that can be said about this study is that the vast majority of those enrolled have been "accounted" for in the sense that it is unlikely that they have suffered any catastrophic events that this Agency is unaware of. I would, therefore, recommend that this study not be used in estimates of the adequacy of exposure to Xyrem® in the safety database (see next bullet)
- The total number of patients exposed to GHB in the NDA Safety Database minus the Scharf study appears sufficient to meet ICH guidelines at the 6-month and 1-year levels but not in regard to the total number of patients exposed; however allowance can be given for GHB being designated as an orphan drug and the total number exposed may therefore be acceptable.

Note that the extent of exposure to GHB in patient-years is reduced by about 79% once the Scharf study data are eliminated. Admittedly, the ICH guidelines do not specifically address the issue of desirable exposure in patient-years.

Further if one concludes (from the efficacy studies) that the 9 g/day dose is the only effective dose and is that to be recommended for general use, the number of those exposed to Xyrem® at that dose for ≥ 6 months and ≥ 12 months does not meet ICH guidelines. If it is concluded from the efficacy studies that the effective dose of Xyrem® ranges from 6-9 g/day, the number of those exposed at that dose range for ≥ 6 months falls somewhat short of

that specified in the ICH guidelines, whereas the number exposed for 12 months does not. Note that the sponsor has not supplied data for the **total** number of patients exposed for any duration (including or excluding the Scharf study) for the 6-9 g/day dose range or at the 9 g/day dose itself

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

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

21. Pharmacodynamic Interactions Between Xyrem® And Commonly Used Concomitant Medications

21.1 Background

At the request of the Biopharmaceutics staff at the Agency, the following request was passed on to the sponsor on April 4, 2001

"The clinical study database should be investigated further to ascertain potential pharmacodynamic interactions in narcoleptic patients with other commonly used drugs in this patient populations."

The structure of the sponsor-proposed analysis of these interactions was discussed between the Division and sponsor at a teleconference on 4/18/01. The sponsor suggested the following, which was acceptable to the Division:

- The analysis would focus on the differences in observed effects, as they related to both safety and efficacy in narcoleptic patients

  and would compare the following groups

- Patients who received sodium oxybate alone

  Patients who received a selected concomitant medication alone

  Patients who received a combination of sodium oxybate and a selected concomitant medication

The above analysis is the basis for an additional submission dated May 4, 2001 which is reviewed here.

21.2 Methods

21.2.1 General Observations

- Narcoleptic patients commonly use the following classes of medications to treat that disorder

  - Stimulants (e.g., methylphenidate, dextroamphetamine, methamphetamine, pemoline, modafinil) to treat excessive daytime sleepiness
  - Tricyclic antidepressants and selective serotonin re-uptake inhibitors to treat REM dissociation phenomena: cataplexy, hypnagogic hallucinations and sleep paralysis
- The entire NDA database did not include a trial specifically designed to investigate the potential pharmacodynamic interactions between Xyrem® and medications commonly used in patients with narcolepsy. Nevertheless, for analysis purposes all clinical trials in the database were examined
- However, in only the OMC-GHB-2, Lammers and Scrima trials was it possible to compare the following groups in a controlled setting
  - Patients who received sodium oxybate alone
  - Patients who received a selected concomitant medication alone
  - Patients who received a combination of sodium oxybate and a selected concomitant medication

  Even in the setting of these 3 controlled trials
  - Stimulants were the only medication class on which such an analysis could be performed
  - Both the Scrima and Lammers trials were not suitable for the analysis on account of a small sample size and variable use of stimulants

21.2.2 Stimulant Use In OMC-GHB-2

Of the 136 patients enrolled in this randomized, double-blind, placebo-controlled, parallel-arm trial of 4 weeks' duration (in which the treatment groups were GHB 3 g/day, 6 g/day and 9 g/day, and placebo)

- 115/136 (84.6%) maintained stable doses of stimulants during the trial
- 21/136 (15.4%) did not take stimulants
- The distribution of these patients by treatment group is below

Treatment Group	Placebo	3 g/day	6 g/day	9 g/day	Total
Number treated with stimulants	28	31	26	30	115
Number not treated with stimulants	6	3	7	5	21
Total	34	34	33	35	136

Of those taking stimulant drugs

- 41 were taking amphetamines
- 55 were taking methylphenidate
- 25 were taking pemoline
- Some patients took more than 1 stimulant drug
- The distribution of these patients by treatment group is in the following table

	Treatment Group	Placebo	3 g/day	6 g/day	9 g/day	Total
Amphetamines	Number not treated with amphetamine	26	23	20	26	95
	Number treated with amphetamine	8	11	13	9	41
Methylphenidate	Number not treated with methylphenidate	17	19	24	21	81
	Number treated with methylphenidate	17	15	9	14	55
Pemoline	Number not treated with pemoline	29	28	26	28	111
	Number treated with pemoline	5	6	7	7	25

21.2.3 Analysis Of Effects Of Stimulant Drugs On Efficacy

- The 2 outcome variables chosen for the analysis were
  - The frequency of all cataplexy attacks
  - Daytime sleepiness as measured by the Epworth Sleepiness Scale
- Descriptive statistics were calculated for each of the outcome variables, for each stimulant and for patients not taking stimulants, by treatment group
- Analysis of the total number of cataplexy attacks (after log transformation) and the change in Epworth scores was accomplished using ANCOVA: the model included baseline value of the variable being analyzed (the covariate) and site and treatment as terms.
- Separate analyses were performed for each treatment group of patients, based on type of stimulant used, and any stimulant use
- Adjustments were made for multiple comparisons using the Dunnett-Hsu procedure
- An additional analysis was performed to assess the possible interaction between stimulant use and GHB treatment. This used the same ANCOVA model as above with 2 additional terms: stimulant use (yes or no) and the stimulant-by-treatment interaction. This analysis was performed for each of the stimulants above and for the stimulant group as a whole

21.2.4 Analysis Of Effects Of Stimulant Drugs On Safety

- The adverse event database for OMC-GHB-2 was examined and certain adverse event terms selected based on their frequency relative to placebo in the original OMC-GHB-2 study report or because they were of special interest. The adverse events studies were: infection, nausea, vomiting, dizziness, confusion, and incontinence of urine
- The 136 patients participating in the OMC-GHB-2 trial were sorted by Body System/Preferred Term, by GHB (all treatment groups combined) or placebo, and by stimulant (amphetamines, methylphenidate, pemoline, any) or no stimulant
- In each cohort the percentage of patients with each adverse event was calculated
- For each cohort sorted by Body System/Preferred Term, and by GHB/placebo, the stimulant group was compared with the non-stimulant group using Fisher's exact test

21.3 Results

21.3.1 Effect Of Stimulants On GHB Efficacy

The differences among treatment groups were consistent between those patients taking stimulants and those not taking stimulants; this was determined using the additional ANCOVA model which included the stimulant-by-treatment-group interaction. For each stimulant and each efficacy variable this interaction was not statistically significant.

Full tables describing the analysis are in the submission. I have not reproduced them here but they appear to confirm the sponsor's conclusions

21.3.2 Effect Of Stimulants On GHB Safety

The sponsor has provided tables comparing the incidence of adverse events in stimulant-treated versus non-stimulant-treated patients for each cohort sorted by Body System/Preferred Term, and by GHB/placebo.

None of the comparisons were statistically significant ($p < 0.05$) except for the following:

For those receiving GHB the incidence of adverse events coded to the Digestive System was higher for those receiving methylphenidate (44.7%) versus those not receiving methylphenidate (25.0%). The p-value for this comparison was 0.04987.

21.4 Sponsor's Conclusions

- In the analysis of cataplexy and daytime sleepiness there was no evidence of pharmacodynamic interaction between sodium oxybate treatment and concomitant stimulants
- In the analysis of adverse events there was only one body system (Digestive) in which a very weak signal of difference between those treated with GHB and methylphenidate and GHB alone was detected
- Within the realm of sensitivity offered by the OMC-GHB-2 trial there did not appear to be any signals of pharmacodynamic interaction between sodium oxybate and stimulant use

21.5 Reviewer's Comments

- The number of patients in most of the above cohorts was very small and the OMC-GHB-2 study was not specifically powered to detect statistically significant differences in the analyses described above
- The sponsor's analyses, intended to look at a possible pharmacodynamic interaction between stimulant medications used for narcolepsy and GHB, must be considered inconclusive for detecting a possible interaction of this nature; this was acknowledged by the Division at the time the analysis plan was discussed.
- Earlier, in the study report for OMC-GHB-2, the sponsor concluded that there was evidence that the 6 g/day and 9 g/day doses of GHB were superior to placebo in reducing the frequency of cataplexy attacks, and the severity of daytime sleepiness as measured by the Epworth Scale, as well as on other (secondary) measures of efficacy. The extent to which the analyses on which this conclusion was based were confounded by the concurrent administration of stimulant drugs is unclear from the sponsor's current analyses of pharmacodynamic interactions; the extent of confounding is especially important in relation to measures of daytime sleepiness (and, therefore, in regard to the sponsor's claim for efficacy in the treatment of the daytime sleepiness of narcolepsy). Although the overall incidence of stimulant drug use was very broadly similar across the 4 treatment groups, there were

considerable differences between these groups in the incidence of use of specific classes of stimulant drugs; in addition, there is no information available as to the doses of stimulant drugs used

22. Advisory Committee Meeting

A meeting of the Agency's Peripheral and Central Nervous System Drugs Advisory Committee was held in Bethesda, Maryland on June 6, 2001, to discuss this application. The overall agenda for the meeting was as follows:

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

A full transcript of the meeting is to be posted at the following site about 30 days after completion of the meeting:

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

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

22.1 Key Items Voted On

22.1.1 Question #1

The original question addressed to the sponsor was as follows:

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

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

The final questions voted on are below

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

Yes = 5 No = 4

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

Yes = 0 *No = 9*

22.1.2 Question #2

The original question posed to the sponsor was as follows:

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

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

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

22.1.3 Question #3

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

Yes = 8 *No = 1*

22.2 Additional Recommendations

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

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

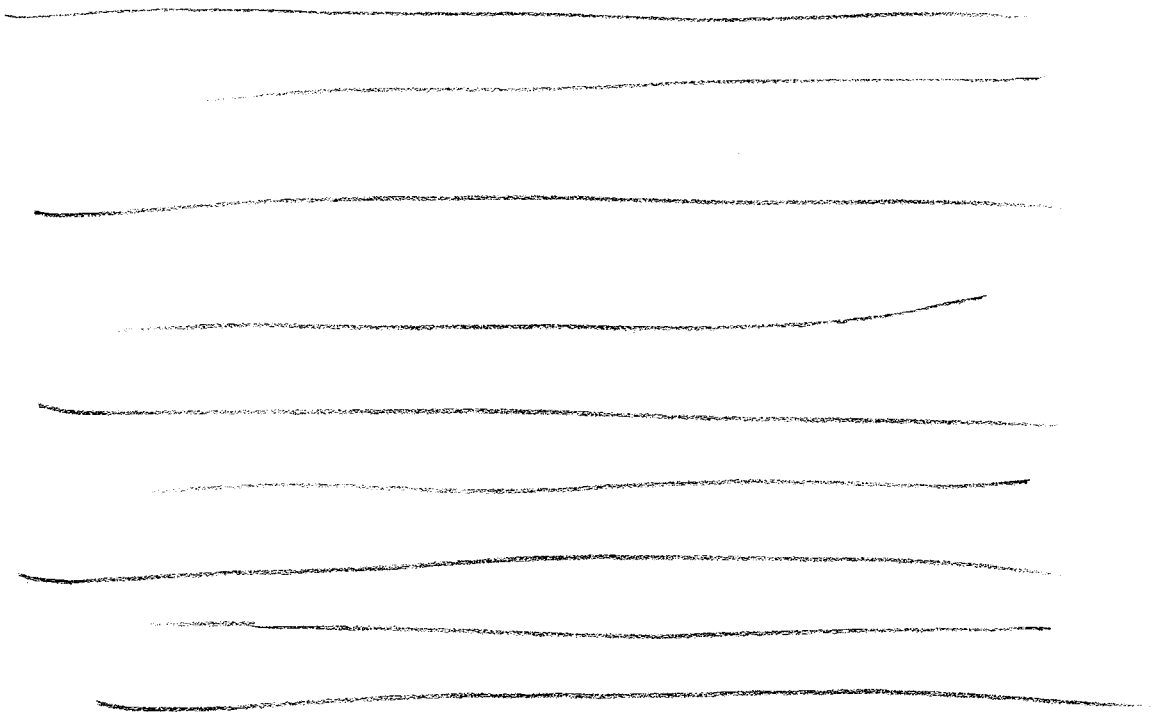
Note that the committee did NOT feel there was a need in the Risk Management Program for

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

22.3 Additional Comments

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

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



24. Risk-Benefit Equation And Overall Conclusions

- **Xyrem® is effective for treating cataplexy, a chronic and lifelong disorder, which is disabling, may lead to serious injury, and for which there is currently no approved treatment; there is thus a hitherto unmet medical need for this drug**. The most clearly effective dose of Xyrem® in treating cataplexy is 9 g/day, with less robust evidence for efficacy at a range of 6 to < 9 g/day. The only evidence for efficacy at doses less than 6 g/day comes from 2 small studies that have many deficiencies.

- There is inadequate evidence at the present time for the efficacy of Xyrem® in treating excessive daytime sleepiness or other symptoms in narcolepsy
- The number of patients who have been exposed to a Xyrem® dose of 6-9 g/day in clinical trials subsumed under this NDA (and for which reliable data is available) is small, leading to a concern that the full adverse event spectrum, (including relatively frequent and potentially significant events) of this drug may not yet be evident. The drug has however been demonstrated to have efficacy for a condition which has a low prevalence (an estimated 24,000 individuals in the United States have cataplexy) and "orphan" status.
- In clinical trials, adverse events of concern that could be causally attributed to Xyrem®, and have occurred at therapeutic doses are almost entirely related to the effects of the drug on the central nervous system. These have included confusion, sleepwalking, somnolence, depressed respiration, and urinary as well as fecal incontinence. The incidence of these events has been low, and they have almost always been reversible. However, such events have had at least a potential for even more serious consequences (as evidenced in some patients with sleepwalking) . The margin of safety between doses that are clinically effective and those that have serious toxicity may be very narrow, or even non-existent, in some patients. Given the use of stimulant medications in the vast majority of patients enrolled in clinical trials included in this NDA, there may be a possibility that the central nervous system-related adverse events of Xyrem® were made less evident by the co-administration of stimulants; this is despite the pharmacokinetic half-lives of stimulants and GHB being brief and stimulants being taken during the day and GHB at night (the pharmacodynamic effects of Xyrem® presumably extend far beyond the very brief pharmacokinetic half-life of approximately 1 hour)
- The abuse of illicitly manufactured and distributed GHB appears to be widespread in this country and increasing. Such abuse has been associated with many reports of central nervous system toxicity, including fatalities, at widely varying (estimated) doses; however, many such reports have been confounded by the co-ingestion of alcohol and of other drugs with effects on the central nervous system. There have also been reports of the development of a dependence syndrome and of addictive behavior in individuals taking high and frequent (round-the-clock) doses of GHB from the same sources, although not with Xyrem® used in clinical trials included in this NDA; however the exposure to GHB in clinical trials has not been extensive. The abuse potential of GHB has yet to be specifically evaluated in a human clinical trial, although only minimal symptoms that might be attributable to withdrawal were seen in the small randomized withdrawal efficacy study #OMC-SXB-21
- GHB has been proposed in the scientific literature as well as in lay publications as a treatment for a variety of conditions known or presumed to have a medical basis including insomnia, alcohol and opiate withdrawal, chronic fatigue syndrome, fibromyalgia, diseases causing weight loss such as AIDS as well as other entities. Based on the medical literature review submitted with this application there is virtually no evidence-based endorsement for its use for these indications. However if Xyrem® were to be

approved without any limitations on off-label use it is very likely that the drug will be prescribed for these entities at least of which are known or perceived to be common. Under such circumstances it is also likely to be prescribed by physicians with much less familiarity with the drug than experts in sleep disorders

It is also to be expected that if Xyrem® is approved without any restrictions on off-label use it is likely that it will be prescribed not just for the daytime sleepiness of narcolepsy (for which there is inadequate evidence for efficacy at present), but for daytime sleepiness of other causes and even for daytime fatigue.

- There is no valid reason to presume that prescribed Xyrem® will not be subject to diversion and abuse and to the risk of accidental or deliberate overdose, as well as other adverse events. The risk of such events occurring must be expected to increase the more widely it is prescribed, and the less experienced the physicians who prescribe it. In addition, the safety of Xyrem® in patients who have conditions other than cataplexy, and in healthy individuals has not been systematically studied to any significant extent
- In summary therefore while there is evidence that Xyrem® is effective for the treatment of cataplexy and while there is a clear medical need for the drug, the small clinical trial safety database, the narrow margin of safety and the risks of abuse and misuse all call for approval to be conditional on a risk management system that is somewhat more stringent than that proposed by the sponsor. Key additional elements of such a system should include

    - Dispensing of the drug exclusively to patients with a diagnosis of cataplexy confirmed by their physicians
    - Commitment by the sponsor to a detailed plan for active post-marketing surveillance for instances of diversion, abuse, misuse and adverse events of special concern
    - Clear statements in the approved label, patient information sheet and patient and physician educational materials about the nature of the drug (i.e., that it contains the same active ingredient as illicitly-used GHB), the limited experience with the drug during development, the potentially serious toxicity of both therapeutic doses and overdoses
    - Use of Subpart H of the Accelerated Approval regulations (21 CFR 314.500) so as to provide a means of restricting distribution of the drug and for enforcement of the risk management program. Justification for institution of these regulations is as follows
        - Xyrem® is intended to treat a serious disease (cataplexy)
        - Xyrem® provides meaningful benefit to patients over existing treatment
        - Xyrem® can be used safely only if its distribution or use is restricted
- Overall, this application can be considered to have provided sufficient evidence for the efficacy and safety of Xyrem® to justify an approvable action. For the Agency to proceed later to actual approval would, in my opinion, require the submission of additional data (see Recommendations) and agreement on an adequate risk management program as outlined above. It should be added that, in this reviewer's opinion, the benefit-versus-risk equation for Xyrem® as a treatment for cataplexy is at the present time only

slightly tilted in favor of benefit and in favor of an approvable (versus a not-approvable) status.

25. Recommendations

I would recommend that this application be granted approvable status at the present time.

This recommendation is conditional upon the sponsor agreeing to the expanded risk management plan outlined by this reviewer above. Critical to this plan is that dispensing of the drug be restricted to those patients confirmed by their physicians as having cataplexy, and be carried out by a single central pharmacy.

Prior to considering final approval the following additional information should be requested from the sponsor and reviewed by this Division.

- A safety update for the ongoing Orphan studies of Xyrem®, OMC-SXB-7 and [redacted] should be provided (the latter study is intended to assess the efficacy of Xyrem® in treating excessive daytime sleepiness). The last safety update was submitted on 2/1/01 and had a cut-off date of 9/30/00. 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, needs to be accounted for to the maximum extent possible. These patients are listed below by ID# and initials

  01-004/[redacted]
  01-027/[redacted]
  01-054/[redacted]
  01-065/[redacted]
  01-228/[redacted]
  01-240/[redacted]
  01-262/[redacted]
  01-269/[redacted]
  01-283/[redacted]
  01-268/[redacted]
  01-256

- An analysis 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, whether leading to medication discontinuation, further evaluations (e.g., EEGs and polysomnograms) and outcome.
- The total number of patients exposed for any period of time to the following doses: 9 g/day; 6 to < 9 g/day.

Ranjit B. Mani, M.D.
Medical Reviewer

J. Feeney, M.D. _____

rbm 6/15/01
cc:
HFD-120
NDA 21196
Homonnay

Review and Evaluation of Clinical Data

NDA (Serial Number)	21196 (000)
Sponsor:	Orphan Medical, Inc.
Drug:	Xyrem
Proposed Indication:	Narcolepsy
Material Submitted:	Labeling Review
Correspondence Date:	9/30/00
Date Received / Agency:	10/3/00
Date Review Completed	6/14/01
Reviewer:	Ranjit B. Mani, M.D.

Background

This submission contains an original New Drug Application for Xyrem® (sodium oxybate; γ-hydroxybutyrate) oral solution.

This document reviews the sponsor's proposed labeling as proposed in the original application and as modified in a further submission dated 12/16/00.

The safety and efficacy data in this application have each been reviewed by me in separate applications.

The sponsor's draft labeling, as edited by me, is presented below. My editing and review of the label have been confined to sections subsumed under my clinical reviews

Edited Draft Labeling

Draft Professional Insert (December 15, 2000 Version) Modified to include information from Trial OMC-SXB-21 and OMC-SXB-20

R_x only

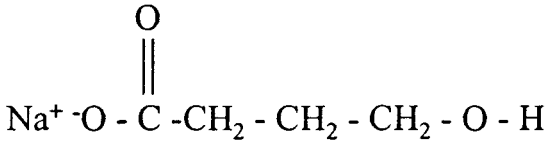
CIII

Xyrem® (sodium oxybate) oral solution

DESCRIPTION

Xyrem (sodium oxybate) is a neuroactive agent with effects on sleep architecture that include increased slow wave sleep, increased delta power, and decreased

nocturnal awakenings. Xyrem is intended for oral administration. The chemical name for sodium oxybate is gamma-hydroxybutyric acid (GHB), sodium. The molecular formula is $NaC_4H_7O_3$ and the molecular weight is 126.1 grams/mole. The chemical structure is:



Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions. Xyrem contains 500 mg of sodium oxybate per milliliter of USP purified water, neutralized to pH 7.5 with malic acid.

CLINICAL PHARMACOLOGY

Mechanism of Action

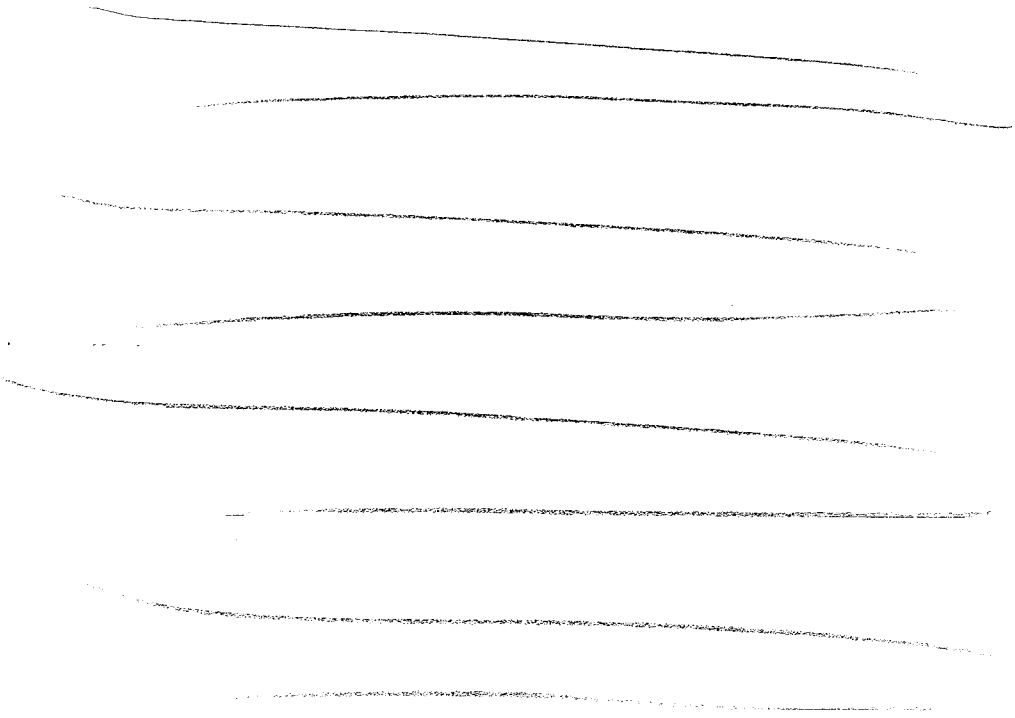
Pharmacokinetics and Metabolism

Absorption

is absorbed following oral administration. The average peak plasma concentration

Administration of after a high fat meal resulted in average T_{max} increasing from 0.75 hr to 2.0 hr and reductions in peak plasma levels (C_{max}) of 58% and systemic exposure (AUC) by 37%.

Distribution



Elimination

The clearance of oxybate is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible.

Special Populations

Geriatric

The pharmacokinetics of sodium oxybate in patients greater than the age of 65 years has not been studied.

Pediatric

The pharmacokinetics of sodium oxybate in pediatric patients under the age of 18 years has not been studied.

Gender

In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of sodium oxybate following a single oral dose of 4.5 grams.

Renal Disease

Because the kidney does not have a significant role in the excretion of oxybate, no pharmacokinetic study in patients with renal dysfunction has been conducted.

Hepatic Disease

Oxybate undergoes significant presystemic (hepatic first-pass) metabolism.

AUC values were double in the cirrhotic patients, with apparent oral clearance from 9.1 in healthy adults to 4.5 and 4.1 mL/min/kg patients, respectively. Elimination half-life was significantly longer in

Drug-Drug Interaction

CLINICAL TRIALS

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INDICATIONS AND USAGE

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

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Daily sodium intake in patients taking sodium oxybate ranges from 0.5 g (for 3 g Xyrem dose) to 1.6 g (for 9 g Xyrem dose), ~~therefore consideration to~~and the implications of ~~such~~ that sodium load must be ~~given~~ considered in hypertensive patients or patients with compromised renal function.

Hepatic

Patients with compromised liver function will have increased elimination half-life and systemic exposure [redacted] (see **Pharmacokinetics** [redacted]

Renal Insufficiency

No studies have been conducted in renal failure [redacted] less than 5% of sodium oxybate is excreted via the kidney [redacted] no dose adjustment should be necessary in patients with renal impairment. The sodium load [redacted] associated with administration of [redacted] should be considered in patients with renal insufficiency.

[redacted]

Gender, [redacted]

Drug Interactions

In animal models, oxybate and depressant drug combinations generally greater depressant effects t either drug alone. Concomitant administration of oxybate and benzodiazepines, barbiturates, or ethanol increases sleep duration. In primates, oxybate blood levels were elevated with phenytoin pretreatment and reduced with L-Dopa and ethosuximide, and trimethadione.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Approximately — of patients , _____ in 3 controlled clinical trials (n= —)

Incidence in Controlled Clinical Trials

Most Commonly Reported Adverse Events in Controlled Clinical Trials

The most commonly reported adverse events associated with the use of sodium oxybate and occurring with at least 5% greater frequency than seen in placebo-treated patients were dizziness (23%), headache (20%), nausea (16%), pain (12%), sleep disorder (9%), confusion (7%), infection (7%), vomiting (6%), and urinary incontinence (5%). These incidences are based on combined data from Trial 1 and two smaller randomized, double-blind, placebo-controlled, cross-over trials (n=181)

Trial 1, the parallel-group, placebo-controlled trial, — used 3 _____ fixed doses of sodium oxybate (3g, 6g, and 9g)i — In that trial

dizziness, nausea, urinary incontinence, and vomiting were more common at

Digestive System

Diarrhea	0 (0%)	0 (0%)	2 (6%)	2 (6%)
Dyspepsia	2 (6%)	0 (0%)	3 (9%)	2 (6%)
Nausea	2 (6%)	2 (6%)	5 (15%)	12 (34%)
Nausea and Vomiting	0 (0%)	0 (0%)	2 (6%)	2 (6%)
Vomiting	0 (0%)	0 (0%)	2 (6%)	4 (11%)

Musculoskeletal System

Myasthenia	0 (0%)	2 (6%)	1 (3%)	0 (0%)

Nervous System

Amnesia	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Anxiety	1 (3%)	1 (3%)	0 (0%)	2 (6%)
Confusion	1 (3%)	3 (9%)	1 (3%)	5 (14%)
Dizziness	2 (6%)	8 (24%)	10 (30%)	12 (34%)
Dream Abnormal	0 (0%)	0 (0%)	3 (9%)	1 (3%)

Hypertension	1 (3%)	0 (0%)	2 (6%)	0 (0%)
Hypesthesia	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Sleep Disorder	1 (3%)	2 (6%)	4 (12%)	5 (14%)
Somnolence	4 (12%)	5 (15%)	4 (12%)	5 (14%)
Thinking Abnormal	0 (0%)	1 (3%)	0 (0%)	2 (6%)

R

Skin

Sweat	0 (0%)	1 (3%)	1 (3%)	4 (11%)

Special Senses

Amblyopia	1 (3%)	2 (6%)	0 (0%)	0 (0%)
Tinnitus	0 (0%)	2 (6%)	0 (0%)	0 (0%)

Urogenital System

Dysmenorrhea	1 (3%)	1 (3%)	0 (0%)	2 (6%)
Incontinence Urine	0 (0%)	0 (0%)	2 (6%)	5 (14%)

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