information regarding the proper handling of the drug with an outline of precautions to be taken against diversion
- If a patient has prescription drug coverage, [redacted] will then contact the patient's insurance company to obtain coverage. [redacted] will notify the patient of his/her approval status

10.1.1.3 Patient Services

- All patient assignment forms and registry information will need to be signed and sent back to the pharmacy before the initial prescription can be filled
- Comprehensive printed and video materials (see Xyrem® Patient Success Program below) that also contain information regarding the proper handling of the drug with an outline of precautions to be taken against diversion will be provided to the patient in advance of shipment.
- Once approval has been established, [redacted] will verify the patient's home address and availability for shipping and arrange shipment through Federal Express RapidTrac or a similar carrier
- Receipt of the initial drug shipment will be ensured through the following
  - A phone call by the pharmacy to the patient, no more than 24 hours after the shipment is delivered, to verify that the medication and educational materials have been received
  - The courier service's own tracking system for shipments which requires a signature by the patient
- If the patient or their designee is unavailable to accept a shipment of Xyrem® and execute the required receipt after two delivery attempts, the package will be returned to the pharmacy.
- If a shipment is lost, an investigation will be launched to find it.
- If required by the patient's insurance company the product may be shipped by [redacted] 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 sodium oxybate before shipping the drug there through NTIS and State Boards of Pharmacy

10.1.1.4 Registry

- Every patient and prescribing physician will be registered with [redacted] 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
- 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
- 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.

10.1.2 Drug Product Kit

The drug product kit will consist of

- The drug product, a clear solution, in a 180 mL 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 Medication Guide

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

10.1.3 Xyrem® Physician Success Program

This program consists of a videotape and printed material(s) to educate physicians about the features of Xyrem®. When a physician prescribes the drug for the first time, he/she will be mailed the program; the mailing will be documented as will a follow-up phone call to the physician confirming receipt and

the physician must verify that they have read the materials before the medication will be sent to the patient

10.1.4 Xyrem® Patient Success Program

This program consists of a videotape and printed educational material. The patient will receive this material prior to the first shipment of drug.

10.2 Proposed Physician Success Program

The components of this section are as follows

10.2.1 Dear Doctor Letter

In this letter the following are outlined

- Indication for which Xyrem® is approved
- Active ingredient in Xyrem®
- Reason for Xyrem® being marketed under a restricted distribution program
- Patient responsibilities and requirements
- Physician responsibilities and requirements
- That monitoring patients for efficacy and safety is a condition for approval. For that purpose evaluation forms have been provided which the physician has been asked to fill in every 3 months for the first 6 months.
- A toll-free number for the Xyrem® Physician Success Program

10.2.2 Booklet

The booklet has the following headings

- Prescribing Xyrem® - A Brief Guide
- Prescription and Enrollment Form
- Suggested Guidelines for Titrating Xyrem®
- Information You Need To Know About Xyrem®
- Contact Information
- Package Insert (copied below)

Prescription and Enrollment Form

Prescriber Information

Prescriber's Name: _____ Office Contact: _____
Street Address: _____
City: _____ State: _____ Zip: _____
Phone: _____ Fax: _____
License Number: _____ DEA Number: _____
MD Specialty: ☐ N ☐ PUD ☐ IM ☐ FP ☐ GP ☐ Other _____

Prescription Form

Patient Name: _____ SS#: _____ DOB: ____ Sex: M / F
Address: _____
City: _____ State: _____ Zip: _____
Rx: Xyrem Oral Solution (500 mg/mL) Quantity: ____ One Month's Supply
Sig: Take ____ gms p.o. diluted in 60mL water at h.s. and then again 2 1/2 to 4 hours later.
Refills (circle one): 1 2 3 (maximum of 3 month supply)
_____ Date: ____/____/____
Prescriber's Signature

Physician Declaration – Please initial each box To be completed at initial prescription only
☐ I have read the materials in the Xyrem Physician Success Program
☐ I verify that the patient has been educated with respect to Xyrem preparation, dosing and scheduling
☐ I understand that Xyrem is approved by FDA only for the treatment of cataplexy in patients with narcolepsy

Patient Information

Best time to contact patient: ☐ Day ☐ Evening
Day #: _____ Evening #: _____
Insurance Company Name: _____ Phone #: _____
Insured's Name: _____ Relationship to Patient: _____
Identification Number: _____ Policy/Group Number: _____
Prescription Card: ☐ No ☐ Yes If Yes, Carrier: _____ Policy #: _____ Group: _____
Please attach copies of patient's insurance cards

Statement of Medical Necessity

Anticipated Start Date: _____ (Xyrem Success Program will call to verify date)
Pertinent medical history and clinical course: _____
_____
Diagnosis: _____
Previous Treatments Tried and Failed: _____
_____

- Medication Guide

10.2.3 Video

The sponsor states that

- A storyboard and proposed text has previously been submitted to the NDA
- A prototype video has been submitted to the briefing booklet for the FDA Advisory Panel meeting
- A new video will be prepared once final labeling is arrived at and agreed upon

10.2.4 Patient Evaluation Program

This section contains the following components

10.2.4.1 Dear Doctor Letter

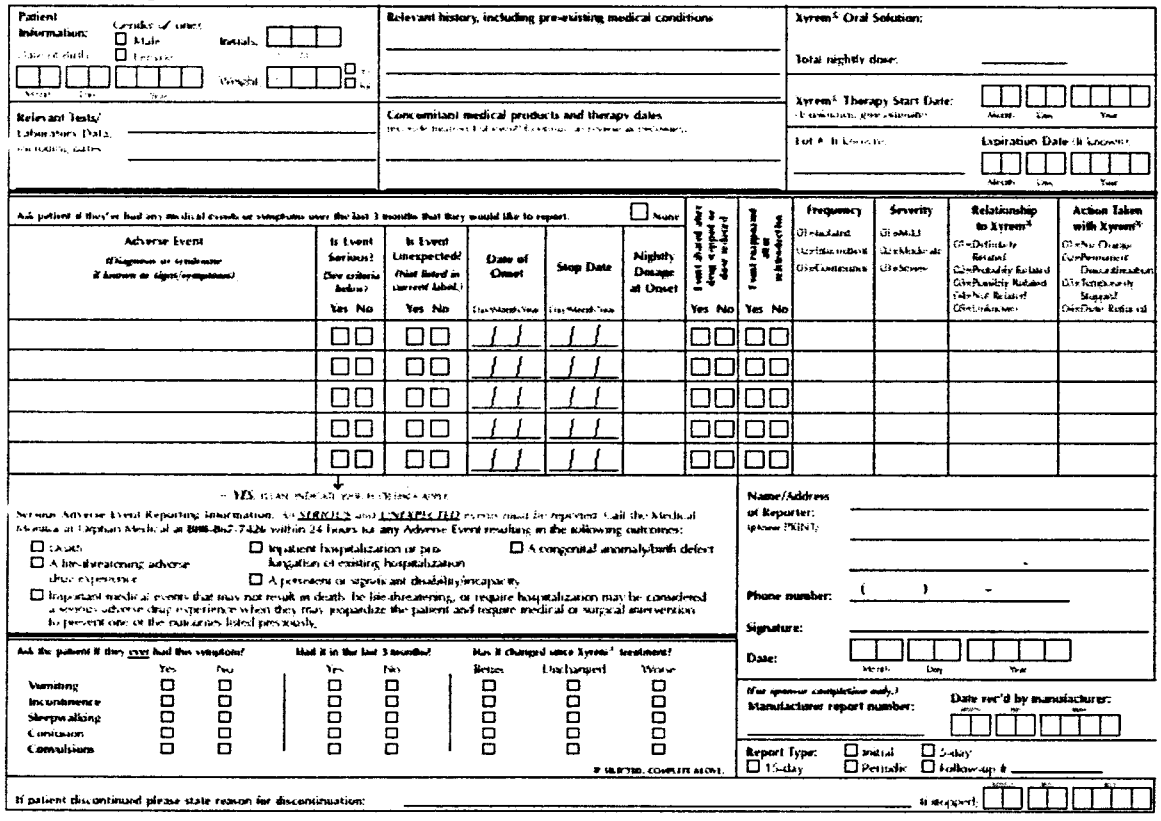
This explains

- The purpose of the Program which is fulfil a commitment made as a condition for approval to provide data on the first 6 months of Xyrem® therapy for 1000 patients to the FDA
- What the physician needs to do to fulfil this requirement: complete the Xyrem® Post-Marketing Evaluation Form at repeat visits every 6 months during the first 6 months of treatment (i.e., the form must be completed twice); and whenever any adverse event occurs

10.2.4.2 Instructions For Completion Of Xyrem® Post-Marketing Evaluation Form

10.2.4.3 Xyrem® Post-Marketing Evaluation Form

This 2-page form is copied below



Patient Information:
Gender ✓ one: ☐ Male ☐ Female
Initials:
Date of Birth:
Weight: ☐ kg ☐ lbs

Relevant history, including pre-existing medical conditions

Xyrem® Oral Solution:
Total nightly dose:

Xyrem® Therapy Start Date:

Relevant Tests/ Laboratory Data, including dates

Concomitant medical products and therapy dates

Lot #
Expiration Date (if known):

Ask patient if they've had any medical events or symptoms over the last 3 months that they would like to report. ☐ None

Adverse Event (if diagnoses or symptoms if known or signs/symptoms)	Is Event Serious? (See criteria below) Yes No	Is Event Unexpected? (Not listed in current label.) Yes No	Date of Onset	Stop Date	Nightly Dosage at Onset	Event abated after drug stopped or dose reduced? Yes No	Event reappeared after reintroduction? Yes No	Frequency ☐=Isolated ☐=Intermittent ☐=Continuous	Severity ☐=Mild ☐=Moderate ☐=Severe	Relationship to Xyrem® ☐=Definitely Related ☐=Probably Related ☐=Possibly Related ☐=Not Related ☐=Unknown	Action Taken with Xyrem® ☐=No Change ☐=Permanent Discontinuation ☐=Temporarily Stopped ☐=Dose Reduced
	☐☐	☐☐	/ /	/ /		☐☐	☐☐				
	☐☐	☐☐	/ /	/ /		☐☐	☐☐				
	☐☐	☐☐	/ /	/ /		☐☐	☐☐				
	☐☐	☐☐	/ /	/ /		☐☐	☐☐				
	☐☐	☐☐	/ /	/ /		☐☐	☐☐				

↓ YES (CLICK INDICATED TEXT TO OPEN A FAX)

Serious Adverse Event Reporting Information: All SERIOUS and UNEXPECTED events must be reported. Call the Medical Monitor at Orphan Medical at 888-867-7426 within 24 hours for any Adverse Event resulting in the following outcomes:

☐ Death
☐ A life-threatening adverse drug experience
☐ Inpatient hospitalization or prolongation of existing hospitalization
☐ A persistent or significant disability/incapacity
☐ A congenital anomaly/birth defect
☐ Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient and require medical or surgical intervention to prevent one of the outcomes listed previously.

Name/Address of Reporter: (please PRINT)

Phone number: ( ) -

Signature:

Date:

Ask the patient if they ever had the symptom?	Yes	No	Had it in the last 3 months?	Yes	No	Has it changed since Xyrem® treatment?	Better	Unchanged	Worse
Vomiting	☐	☐		☐	☐		☐	☐	☐
Incontinence	☐	☐		☐	☐		☐	☐	☐
Sleepwalking	☐	☐		☐	☐		☐	☐	☐
Confusion	☐	☐		☐	☐		☐	☐	☐
Convulsions	☐	☐		☐	☐		☐	☐	☐

If SELECTED, COMPLETE ABOVE.

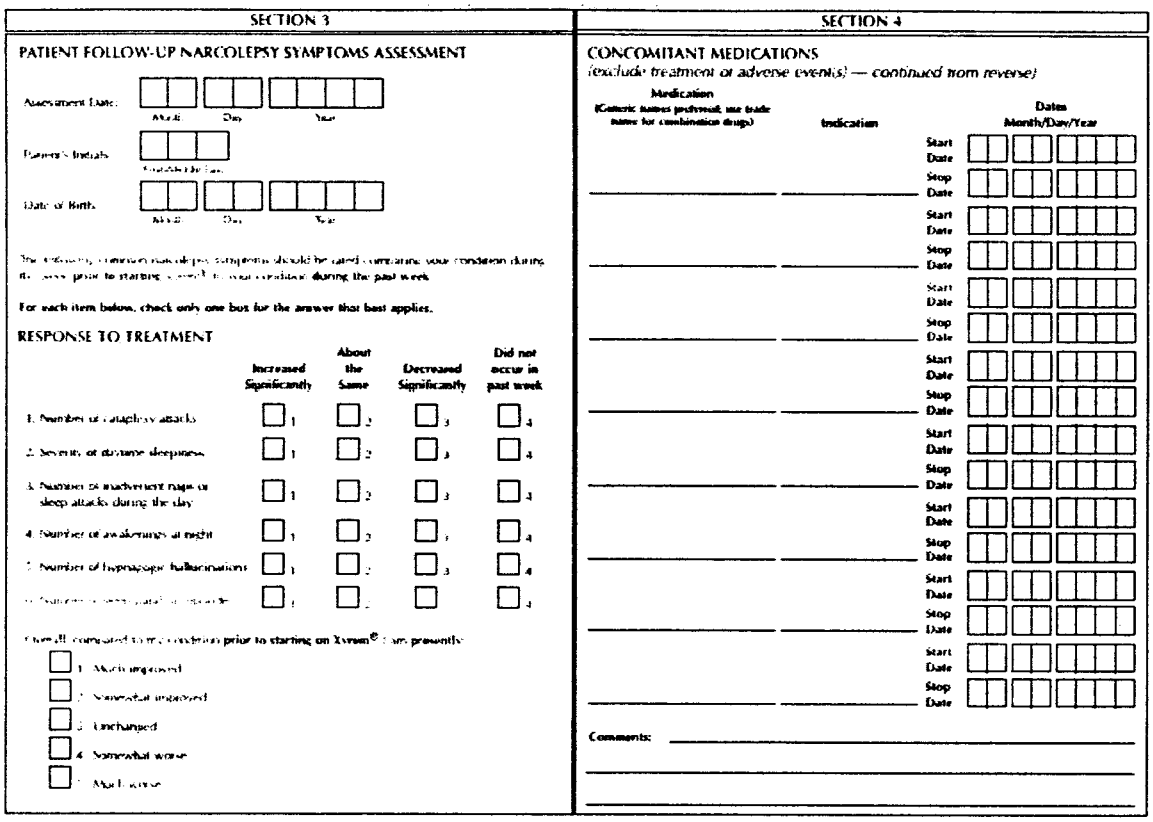
(For sponsor completion only.)
Manufacturer report number:

Date rec'd by manufacturer:

Report Type: ☐ Initial ☐ 5-day ☐ 15-day ☐ Periodic ☐ Follow-up #

If patient discontinued please state reason for discontinuation:

If stopped:



SECTION 3

PATIENT FOLLOW-UP NARCOLEPSY SYMPTOMS ASSESSMENT

Assessment Date: Month Day Year

Patient's Initials

Date of Birth: Month Day Year

For each item below, check only one box for the answer that best applies.

RESPONSE TO TREATMENT

	Increased Significantly	About the Same	Decreased Significantly	Did not occur in past week
1. Number of cataplexy attacks	1	2	3	4
2. Severity of daytime sleepiness	1	2	3	4
3. Number of inadvertent naps or sleep attacks during the day	1	2	3	4
4. Number of awakenings at night	1	2	3	4
5. Number of hypnagogic hallucinations	1	2	3	4
6.	1	2		4

Overall, compared to my condition prior to starting on Xyrem® I am presently:

1. Much improved
2. Somewhat improved
3. Unchanged
4. Somewhat worse
5. Much worse

SECTION 4

CONCOMITANT MEDICATIONS
(exclude treatment of adverse event(s) — continued from reverse)

Medication (Generic names preferred, use trade names for combination drugs)	Indication	Dates Month/Day/Year
		Start Date
		Stop Date
		Start Date
		Stop Date
		Start Date
		Stop Date
		Start Date
		Stop Date
		Start Date
		Stop Date
		Start Date
		Stop Date
		Start Date
		Stop Date
		Start Date
		Stop Date

Comments: _____

10.3 Proposed Patient Success Program

The components of this section are as follows

10.3.1 Dear Patient Letter

This outlines

- What Xyrem® is approved for
- Distinctive features of the drug
- Purpose of the Patient Success Program
- A toll-free number for the central pharmacy

10.3.2 Booklet

The main sections in this booklet are titled as follows

- How do I obtain Xyrem®?
- How do I take Xyrem®?
- Precautions needed for Xyrem® use
- Other information (sources for information on Xyrem®, narcolepsy and other sleep disorders)
- My prescription record
- At home storage and safety tips
- Traveling tips
- Reimbursement information for patients
- Medication guide
- Wallet card

10.3.3 Video

The sponsor states that

- A storyboard and proposed text has previously been submitted to the NDA
- A prototype video has been submitted to the briefing booklet for the FDA Advisory Panel meeting
- A new video will be prepared once final labeling is arrived at and agreed upon

10.4 Office Of Post-Marketing Drug Risk Assessment Comments On Risk Management Program

This submission, including the comments made in the cover letter were reviewed by Lauren Lee, Pharm. D., of the Division of Drug Risk Evaluation I. Her comments are contained in a memo dated 10/23/01 and are summarized below

- Her Division is in agreement that the diagnosis of narcolepsy with cataplexy should be confirmed prior to the drug being dispensed. The sponsor's counter-proposal (see Section 4.1.1) will not result in off-label use being restricted
- Her Division agrees that the pharmacist dispensing Xyrem® could obtain telephonic (as opposed to written) confirmation that the patient has read the educational materials. OPDRA does however recommend that the Risk Management Program explicitly states that this phone call be received and recorded by the pharmacist
- The sponsor has proposed that "after completing the post-marketing surveillance program and review by the FDA any specific prescription be allowed to be extended to 6 months pursuant to normal Schedule III practices." OPDRA does not recommend that such an extension be given: the dispensing of 18 bottles of Xyrem® at a time raises safety concerns including those of secure storage of such a large quantity of Xyrem®
- According to the sponsor, Orphan Medical, Inc. has no legal right to access patient pharmacy records to actively monitor for abuse, misuse and diversion, and that the patient registry would be made available for review by the regulatory agencies charged with policing, abuse, and misuse. OPDRA recommends that a licensed pharmacist in the central pharmacy who has access to patient pharmacy records routinely monitors for over-prescribing or frequent refills
- In addition to completing the Xyrem® Post-Marketing Evaluation Form and observing the standard Agency reporting requirements for deaths and serious adverse events physicians should be encouraged to report any adverse event, serious or not, to the FDA through MEDWATCH and/or the manufacturer using Form 3500 (since the Xyrem® Post-Marketing Evaluation Form is not intended to replace Form 3500). A copy of Form 3500 should be included in the Physician Success Program packet.
- The registry created through the Xyrem® Post-Marketing Evaluation Forms should not be limited to 1000 patients or the first 6 months but should

continue to accrue patients until sufficient safety data has been obtained and presented to the FDA. OPDRA also recommends that safety data from these forms should be submitted quarterly during the "initial" phase and the need for longer term reporting be reassessed.

- The Post-Marketing Patient Evaluation Form does not provide for physician inquiry directed at evidence of abuse, misuse, or diversion of Xyrem®. OPDRA recommends revising the form to include a subsection where physicians are asked to record unusual refill requests and reports of loss/theft that would be suspicious of inappropriate drug use.
- In the column contained in the Post-Marketing Patient Evaluation Form that that records the severity of the adverse event it is unclear whether the severity is to be based on patient or physician assessment and what criteria are to be used to qualify an adverse event as mild, moderate or severe. OPDRA recommends clarifying these matters
- In the column headed "Relationship to Xyrem®" it is unclear if the relationship of the adverse event to Xyrem® is to be based on patient or physician assessment; OPDRA feels that that requires clarification as well
- The Response to Treatment section of the Post-Marketing Evaluation Form is designed to collect data on the efficacy of the drug and can be used for marketing purposes. One of the questions in this section requires assessment of the severity of daytime sleepiness and may encourage off-label use of the drug. OPDRA recommends that this section should be deleted since it does not address any safety-related issues
- OPDRA recommends that the following statement be added to the section entitled "Information you need to know about Xyrem®" in the Physician Success Program booklet

  "Educate your patients that Xyrem® should not be taken with alcohol and other medications that may cause drowsiness"
- OPDRA recommends that the following be added to the section entitled "What do I do before taking Xyrem® each night" in the Patient Success Program booklet

  A statement specifying that the each dose should be diluted with 2 oz of water (currently the directions merely state that the each dose should be diluted with water)

10.5 Reviewer's Comments

In making this summary I have also referred to the sponsor's cover letter summarized in Section 4

- The only significant change to the Risk Management Program summary outlined in the attachment to the Approvable letter is that the physician prescribing Xyrem® must verify that he/she has read the materials contained in the Xyrem® Physician Success Program prior the medication being sent to the patient.

- Based on recommendations from the Office Of Post-Marketing Drug Risk Assessment, the following should be added to the detailed Risk Management Program

  - The pharmacist who obtains telephone confirmation that the patient has read the educational materials should record this confirmation
  - Even after completing the post-marketing safety assessment program, refills should continue to be limited to a maximum of 3 months
  - A licensed pharmacist in the central pharmacy who has access to patient pharmacy records should routinely monitor for over-prescribing or frequent refills
  - A copy of Form 3500 should be included in the Physician Success Program packet.
  - The registry created through the Xyrem® Post-Marketing Evaluation Forms should not be limited to 1000 patients or the first 6 months but should continue to accrue patients until sufficient safety data has been obtained and presented to the FDA as well as reviewed by the Agency.
  - The Post-Marketing Patient Evaluation should include a subsection where physicians are asked to record unusual refill requests and reports of loss/theft that would be suspicious of inappropriate drug use.
  - The following statement be added to the section entitled "Information you need to know about Xyrem®" in the Physician Success Program booklet:

    "Educate your patients that Xyrem® should not be taken with alcohol and other medications that may cause drowsiness"
  - A statement specifying that the each nightly dose of Xyrem® should be diluted with 2 oz of water should be added to the section entitled "What do I do before taking Xyrem® each night" in the Patient Success Program booklet

11. Interaction Of GHB With Human Hepatic Microsomal CYP450 Isoenzymes

This study is summarized below. Please see the Biopharmaceutics review for full details

- The purpose of the study was to evaluate the in-vitro inhibitory potential of GHB towards specific isoenzymes of human hepatic cytochrome P450 using selective probe substrates for each isoenzyme

- A mixed pool of human hepatic microsomes was used

- Each assay was performed at a single concentration of the probe substrate approximating the K_m value for human hepatic microsomes. Each assay was performed in the presence and absence of GHB. GHB concentrations used were 300, 1000 and 3000 μM

- The substrates used, isoenzymes assessed and IC50 values for each assay are in the following table which I have copied from the submission.

Assay	P450 Isoenzyme	IC_{50} (μM)
7-Ethoxyresorufin O-deethylase	CYP1A2	>3000
Tolbutamide 4-methyl hydroxylase	CYP2C9	>3000
S-Mephenytoin 4'-hydroxylase	CYP2C19	>3000
Dextromethorphan O-demethylase	CYP2D6	>3000
p-Nitrophenol hydroxylase	CYP2E1	>3000
Erythromycin N-demethylase	CYP3A	>3000

- The sponsor has concluded that GHB at concentrations of 300, 1000 and 3000 μM did not inhibit the following CYP450 isoenzymes: 1A2, 2C9, 2C19, 2D6, 2E1, and 3A

12. Chemistry, Manufacturing And Controls

I have confirmed with the Chemistry reviewer of this application, Dr Thomas Oliver, that [redacted], was found acceptable (on 11/6/01) for the manufacture of Xyrem®.

13. Proposed Labeling

This is reviewed in a separate document

14. Proposed Patient Medication Guide

14.1 Contents

The 9-page medication guide contains sections entitled as follows

14.1.1 What is the most important information I should know about Xyrem®?

This section is copied verbatim below

[redacted]

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

prescribers about the restricted distribution program, prescribing of Xyrem and the illicit use of GHB, are in the professional insert."

15.2 Reviewer's Comments

The advertisement contains the following statement

Xyrem is a known neuromodulator of brain dopamine and serotonin

The relevance of this statement to the role of Xyrem® in treating cataplexy is unclear. The statement should be deleted.

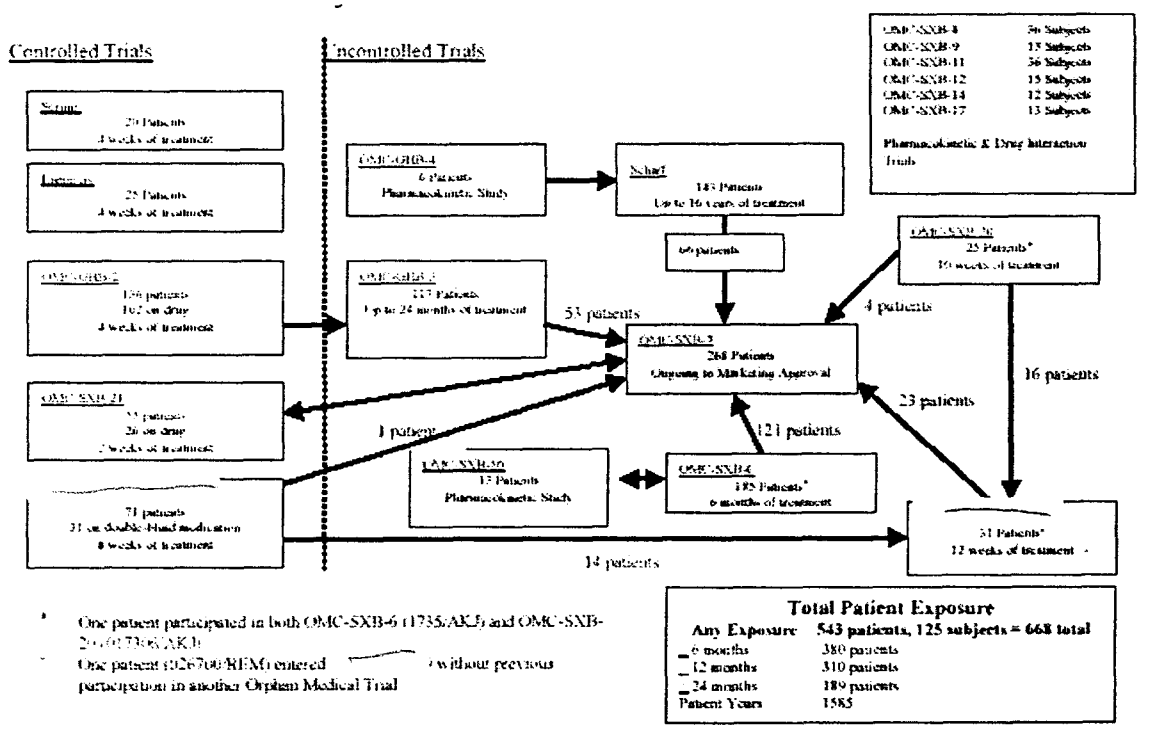
16. Updated Exposure Data

At the request of this reviewer the sponsor submitted on 2/18/02 updated exposure tables for Xyrem®. Similar tables were submitted with the Major Amendment dated 3/23/01 and were reviewed at that time.

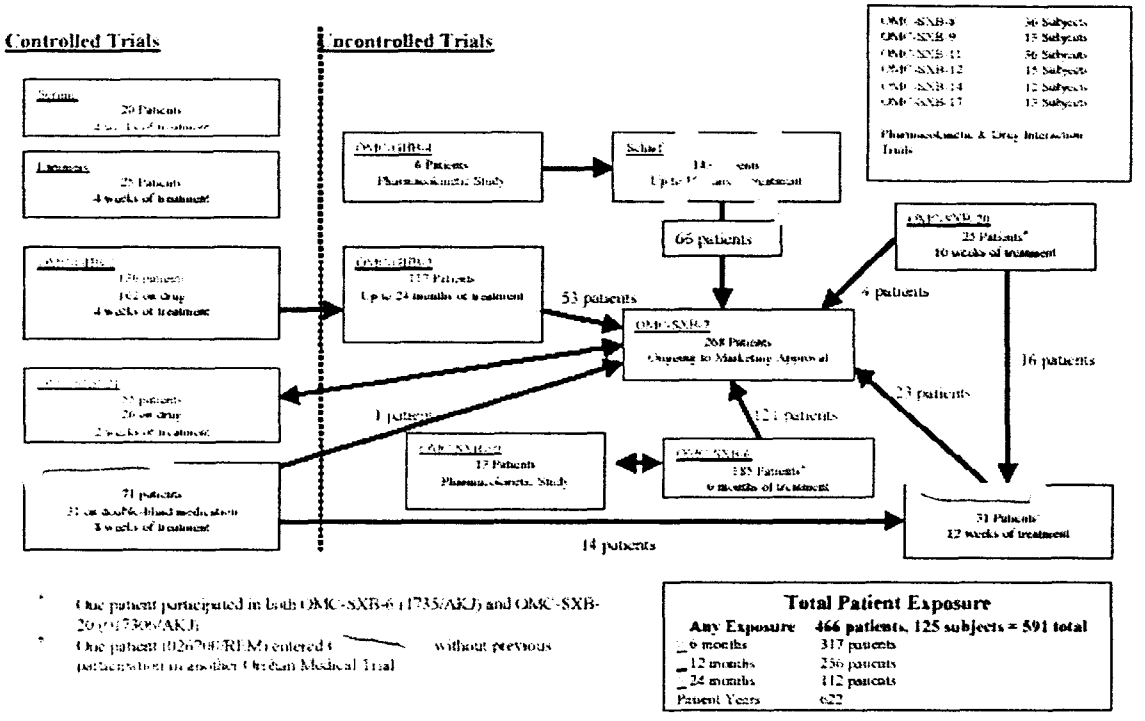
16.1 Overall Schematics For Clinical Trials In Narcoleptic Patients Included In NDA

The submission contains 2 schematics

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



16.1.2 Schematic For Clinical Trials Sponsored By Orphan Medical Alone



16.2 Tables

16.2.1 Sponsor's Methods For Creating Tables

Tables were created for 2 different groups of patients

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

The sponsor used the following methods for creating these tables

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

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

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

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

16.2.2 Tables

The sponsor has presented tables for different durations of exposure

16.2.2.1 Duration of Exposure ≥ 6 Months

The sponsor's table is presented below

Patients	3.0 g/d	4.5 g/d	6.0 g/d	7.5 g/d	9.0 g/d	Overall
ISS Only	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
ISS + Scharf	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

16.2.2.2 Duration of Exposure ≥ 12 Months

The sponsor's table is presented below

Patients	3.0 g/d	4.5 g/d	6.0 g/d	7.5 g/d	9.0 g/d	Overall
ISS Only	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
ISS + Scharf	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

16.2.2.3 Duration of Exposure ≥ 24 Months

The sponsor's table is presented below

Patients	3.0 g/d	4.5 g/d	6.0 g/d	7.5 g/d	9.0 g/d	Overall
ISS Only	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
ISS + Scharf	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

16.2.2.4 Sponsor's Comments About Above Tables

The sponsor has drawn attention to the following:

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

16.3 Sponsor's Overall View Of Adequacy Of Exposure

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

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

Study Pool	Integrated Clinical Trials Plus Scharf		Integrated Clinical Trials Only	
	Patients	Healthy Subjects*	Patients	Healthy Subjects*
Exposure				

*Healthy subjects were exposed to single doses only

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

16.4 Additional Request For Information From Sponsor

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

16.4.1 Request For Information

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

- Integrated Clinical Trials
- Integrated Clinical Trials plus Scharf Study

16.4.2 Sponsor's Response

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

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

The sponsor used the following methods for creating this table

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

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

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

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

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

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

16.5 Reviewer's Comments

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

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

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

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

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

17. Comments

17.1 Safety Update

- The spectrum of adverse events seen in the safety update included in this submission 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

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

- 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.

17.3 Sleepwalking

- In most instances of sleepwalking in GHB clinical trials, a detailed description of patient behavior during that adverse event is not available; in the absence of adequate clinical descriptions in most instances it is unclear what the investigator term "sleepwalking" represents as a clinical entity, or whether it refers to single or multiple entities. The basis of these episodes has not been further elucidated by the current analysis.
- Regardless of what the term "sleepwalking" means in the context of this NDA, it is clear that such episodes are common; almost one-third of patients participating in the long-term Scharf safety study did have one or more such occurrences, and a single patient is recorded as having as many as 346 episodes.
- The few clinical descriptions of this adverse event that are available in this NDA suggest that during at least a few such episodes patients may be confused and may act in a manner that could be seriously prejudicial to their own safety and to that of others.
- It is possible that sleepwalking as seen in the context of this application, was causally related to GHB use

- Similar adverse events appear to be uncommon in narcoleptic patients who have not been treated with GHB.
- Although the incidence of this adverse event was only slightly higher than that of placebo in controlled clinical trials of GHB, these were of short duration (≥ 1 month). The highest incidence was seen in the long-term Scharf study

- The sponsor has not supplied any evidence other than a single anecdote which suggests that preventive measures are of value in reducing the adverse consequences of such episodes

17.4 Respiratory Data In Study OMC-SXB-20

- This small open-label uncontrolled dose-escalation polysomnogram-based study was intended primarily to determine the effects of sodium oxybate on sleep architecture and not its effects on respiration
- As discussed earlier in this review, this study must be considered inconclusive, not providing evidence whether or not GHB has a respiratory depressant effect
- A study specifically intended to assess the effects of GHB on respiration in pulmonary-compromised patients is planned post-approval, as earlier agreed to by this Division.

17.5 Stimulant Use In Clinical Trials Of Xyrem®

- The vast majority of patients (82%) participating in clinical trials of Xyrem® were concurrently receiving stimulant drugs for the treatment of narcolepsy
- 93% of the person-time exposure to Xyrem® in clinical trials occurred in patients who were concomitantly receiving stimulant drugs for the treatment of narcolepsy.
- There is some support in the medical literature for the view that methylphenidate exerts a stimulant effect on respiration (see abstract below)

Dodson ME, Fryer JM. Postoperative effects of methylphenidate. Br J Anaesth 1980;52:1265-70
A double-blind study is described in which the analgesic and analeptic properties of methylphenidate were investigated in 63 patients following surgery. No effect of methylphenidate on postoperative pain was observed. However, methylphenidate reduced sedation up to 30 min after operation, and improved respiratory function up to 180 min in patients receiving halothane. No conclusive evidence of improvement in mood was obtained, and occasional undesirable behavioural effects of methylphenidate were seen.

- Based on data submitted under this NDA, the margin of safety between doses that are clinically effective and those that have serious central nervous system toxicity may be very narrow, or even non-existent, in some patients. Given that ~ 80% of the total exposure to Xyrem® in this NDA occurred in patients who were concomitantly using stimulants, the possibility cannot be excluded 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)
- Given the high frequency of concomitant stimulant medication use in the 2 pivotal efficacy trials of Xyrem® (OMC-GHB-2 and OMC-SXB-21) it might

also be reasonable to state that the efficacy of Xyrem® in treating cataplexy in patients not taking stimulants is yet to be established.

- As agreed to in a meeting with the sponsor held on 9/19/01
  - The initial statement in the Indications section of the label read as follows

    [redacted] as proposed in the labeling accompanying the approvable letter]

    Xyrem® (sodium oxybate) oral solution is indicated for the treatment of cataplexy in patients with narcolepsy.
  - A subsequent sentence in the Indications section could state that ~ 80% of the total exposure to Xyrem® in the data reviewed occurred in patients who were concomitantly using stimulants and could refer to more detailed explanations in the boxed warning and Clinical Trials sections of the label.

17.6 Summary Of Risk Management Program

In making this summary I have also referred to the sponsor's cover letter summarized in Section 4

- The only significant change to the Risk Management Program summary outlined in the attachment to the Approvable letter is that the physician prescribing Xyrem® must verify that he/she has read the materials contained in the Xyrem® Physician Success Program prior the medication being sent to the patient.
- Based on recommendations from the Office Of Post-Marketing Drug Risk Assessment, the following should be added to the detailed Risk Management Program

  - The pharmacist who obtains telephone confirmation that the patient has read the educational materials should record this confirmation
  - Even after completing the post-marketing safety assessment program, refills should continue to be limited to a maximum of 3 months
  - A licensed pharmacist in the central pharmacy who has access to patient pharmacy records should routinely monitor for over-prescribing or frequent refills
  - A copy of Form 3500 should be included in the Physician Success Program packet.
  - The registry created through the Xyrem® Post-Marketing Evaluation Forms should not be limited to 1000 patients or the first 6 months but should continue to accrue patients until sufficient safety data has been obtained and presented to the FDA as well as reviewed by the Agency.
  - The Post-Marketing Patient Evaluation should include a subsection where physicians are asked to record unusual refill requests and reports of loss/theft that would be suspicious of inappropriate drug use.
  - The following statement be added to the section entitled "Information you need to know about Xyrem®" in the Physician Success Program booklet:

    "Educate your patients that Xyrem® should not be taken with alcohol and other medications that may cause drowsiness"
  - A statement specifying that the each nightly dose of Xyrem® should be diluted with 2 oz of water should be added to the section entitled "What do I do before taking Xyrem® each night" in the Patient Success Program booklet

- A statement specifying that the each dose should be diluted with 2 oz of water (currently the directions merely state that the each dose should be diluted with water)

17.7 Interaction Of GHB With Human Hepatic Microsomal CYP450 Isoenzymes

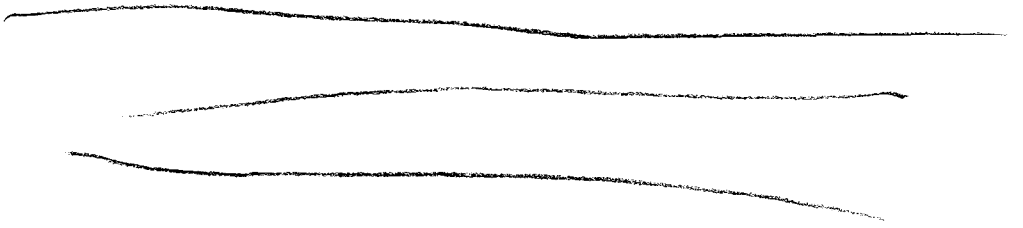
- The sponsor appears to have concluded that therapeutically relevant concentrations of GHB do not inhibit key CYP450 isoenzymes in vitro
- Biopharmaceutics review of this study is awaited

17.8 Chemistry, Manufacturing And Controls

_____ has been found acceptable by the Agency for the manufacture of Xyrem®.

17.9 Proposed Patient Medication Guide

This will need extensive revision by Agency staff.



17.11 Proposed Labeling

This has been reviewed in a separate document.

17.12 Updated Exposure Data

- The size of the Xyrem® NDA database (with the 120-Day Safety Update included) does meet ICH guidelines for drug exposure for 6 months and a minimum of 1 year if one assumes that the effective dose ranges from 3 to 9 grams/day. The ICH guidelines are met even if the Scharf study is excluded
- However, if one concludes (from the efficacy studies) that the 9 g/day dose is the only effective dose and is that to be recommended for general use the number of those exposed to Xyrem® at that dose for ≥ 6 months and ≥ 12 months does not meet ICH guidelines. If it is concluded from the efficacy studies that the effective dose of Xyrem® ranges from 6-9 g/day, the number of those exposed at that dose range for ≥ 6 months falls somewhat short of that specified in the ICH guidelines, whereas the number exposed for 12 months does not.
- The extent of exposure to GHB in patient-years is reduced by about 61% once the Scharf study data are eliminated. Admittedly, the ICH guidelines do not specifically address the issue of desirable exposure in patient-years.
- There are no ICH guidelines that address exposure requirements for orphan drugs. The total number of patients exposed to Xyrem® may be appropriate for an orphan drug used for an orphan indication (i.e., cataplexy in narcolepsy); that may be especially true if the sponsor's estimate that the

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

18. Advisory Committee Meeting

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

The overall agenda for the meeting was as follows:

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

A full transcript of the meeting 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

18.1 Key Items Voted On

18.1.1 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*

18.1.2 Question #2

The original question posed to the committee was as follows:

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

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

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

18.1.3 Question #3

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

Yes = 8 *No = 1*

18.2 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

18.3 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.

19. Risk-Benefit Equation And Overall Conclusions

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

- **Xyrem® is effective for treating cataplexy, a chronic and 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. Moreover, about 61% of the exposure (in patient-years) to Xyrem® contained in this application is derived from the Scharf study, irregularities in the conduct of which lead to the issuance of a Warning Letter by the Agency; the Division of Scientific Investigations recommended that data from this study not be used in support of the application.

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

- In clinical trials, adverse events of concern that could be causally attributed to Xyrem®, and have occurred at therapeutic doses are almost entirely related to the effects of the drug on the central nervous system. These have included confusion, sleepwalking, somnolence, depressed respiration, and urinary as well as fecal incontinence. The incidence of these events has been low, and they have almost always been reversible. However, such events have had at even more serious consequences in some instances (as evidenced in some patients with sleepwalking). The margin of safety between doses that are clinically effective and those that have serious 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 potential for Xyrem® to cause respiratory depression, especially in those with pre-existing respiratory compromise (e.g., those with chronic obstructive pulmonary disease or sleep apnea; the latter disorder may frequently co-exist with narcolepsy) has not been satisfactorily assessed so far in a formal study.

- The abuse of illicitly manufactured and distributed GHB appears to be widespread in this country and increasing; it has been extensively highlighted not merely in the popular media, but also in the peer-reviewed medical literature . Such abuse has been associated with many reports of central nervous system toxicity, including fatalities, at widely varying (estimated) doses; however, many such reports have been confounded by the co-ingestion of alcohol and of other drugs with effects on the central nervous system. There have also been reports of the development of a dependence syndrome and of addictive behavior in individuals taking high and frequent (round-the-clock) doses of GHB from the same sources, although not with Xyrem® used in clinical trials included in this NDA; however the exposure to GHB in clinical trials has not been extensive. The abuse potential of GHB has yet to be specifically evaluated in a human clinical trial, although only minimal symptoms that might be attributable to withdrawal were seen in the small randomized withdrawal efficacy study #OMC-SXB-21

- GHB has been proposed in the scientific literature as well as in lay publications as a treatment for a variety of conditions known or presumed to have a medical basis including insomnia, alcohol and opiate withdrawal, fibromyalgia, diseases causing weight loss such as AIDS, as well as other entities (see full list below). 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 some of which are known or perceived to be common. Under such circumstances it is also likely to be prescribed by physicians with much less familiarity with Xyrem® than those who specialize in sleep disorders.

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

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

The full list of "off-label" entities for which GHB use has been proposed is as follows:

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

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

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

- In summary, therefore, while there is evidence that Xyrem® is effective for the treatment of cataplexy and while there is a clear medical need for the drug for treating that specific indication, the small clinical trial safety database, the narrow margin of safety, and the risks of abuse and misuse all 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 must include

  - Dispensing of the drug exclusively to patients with a diagnosis of cataplexy confirmed by their physicians [the sponsor is opposed to such a provision (see Section 4.1.1) and has proposed alternatives (see Section 4.1.1)] but these alternatives will not limit off-label use]
  - 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, and 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

    [The sponsor had previously indicated a willingness to accept the imposition of the provisions of Section 314.520 (relating to restricted distribution) only, as long as it was made explicit that the other provisions of Subpart H did not apply. The sponsor stated that the main concern about the imposition of Subpart H related to the requirement that all promotional materials submitted after the 120-day approval period needed to be provided to the Agency 30 days prior to dissemination. It is unclear to this reviewer whether individual provisions of Subpart H can be selectively applied]

- Overall, this application can be considered to have provided sufficient evidence for the efficacy and safety of Xyrem® to justify approval on condition that the full risk management plan described by me above is adopted. Critical to this plan is the dispensing of the drug exclusively to patients with cataplexy and approval under Subpart H of the Accelerated Approval Regulations. **As a corollary, I would very strongly urge that this drug not be approved for marketing if off-label use is not prohibited or the Subpart H regulations are not applied.**

20. Recommendations

I would recommend 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.

Ranjit B. Mani, M.D.
Medical Reviewer

J. Feeney, M.D. _____

rbm 3/4/02
cc:
HFD-120
NDA
Homonnay 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
3/19/02 10:22:12 AM
MEDICAL OFFICER

John Feeney
3/30/02 03:36:08 PM
MEDICAL OFFICER
Noted. See my review for my conclusions.

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/Draft Label**
Correspondence Date:	**10/5/01**
Date Received / Agency:	**10/9/01**
Date Review Completed	**2/22/02**
Reviewer:	**Ranjit B. Mani, M.D.**

Background

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

The only part of the submission which is reviewed here is the proposed labeling. The rest of the submission has been reviewed separately.

The edited draft labeling is below, followed by my comments on each section

Draft Label

R_x only

CIII

Xyrem® (sodium oxybate) oral solution

Black Box Warning
!WARNING: CENTRAL NERVOUS SYSTEM DEPRESSANT WITH ABUSE

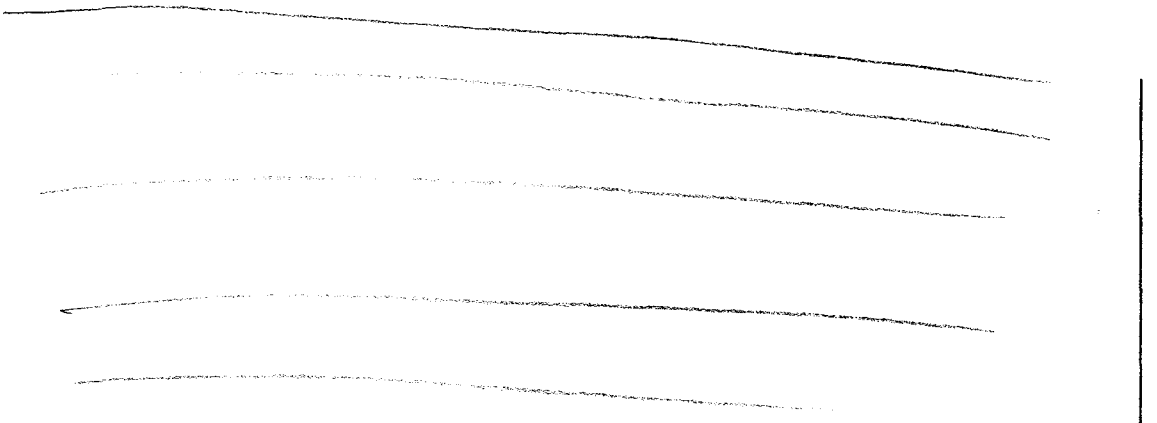
1 page(s) of revised draft labeling has been redacted from this portion of the review.

DESCRIPTION

Xyrem® (sodium oxybate) is a central nervous system depressant with anti-cataplectic activity in patients with narcolepsy. Sodium oxybate is intended for oral administration. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is $C_4H_7NaO_3$ and the molecular weight is 126.09 grams/mole. The chemical structure is:

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

CLINICAL PHARMACOLOGY



Pharmacokinetics

Sodium oxybate is rapidly but incompletely absorbed after oral administration; absorption is delayed and decreased by a high fat meal. It is eliminated mainly by metabolism with a half-life of 0.5-1 hour. Pharmacokinetics are nonlinear with blood levels increasing 3.7 fold as dose is doubled from 4.5 to 9 grams. The pharmacokinetics are not altered with repeat dosing.

Absorption and Distribution

Sodium oxybate is absorbed rapidly following oral administration with an absolute bioavailability of about 25%. The average peak plasma concentrations (1^{st} and 2^{nd} peak) following administration of a 9 g daily dose divided into two equivalent doses given four hours apart were 78 and 142 micrograms/ml respectively. The average time to peak plasma concentration (T_{max}) ranged from 0.5 to 1.25 hours in eight pharmacokinetic studies. Following oral administration, the plasma levels of sodium oxybate increased more than proportionally with increasing dose. Single doses greater than 4.5 grams have not been studied. Administration of sodium oxybate immediately after a high fat meal resulted in delayed absorption (average T_{max} increased from 0.75 hr to 2.0 hr) and a reduction in peak plasma level (C_{max}) by a mean of 58% and of systemic exposure (AUC) by 37%. Sodium oxybate is a hydrophilic compound with an apparent volume of distribution averaging 190-384 ml/kg. At sodium oxybate concentrations ranging from 3 to 300 micrograms/ml, less than 1% is bound to plasma proteins.

Metabolism and Elimination

Animal studies indicate that metabolism is the major elimination pathway for sodium oxybate, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by beta-oxidation. Carbon dioxide is eliminated by respiration. The primary pathway involves a cytosolic $NADP^+$-linked enzyme, GHB dehydrogenase, that catalyses the conversion of sodium oxybate to succinic semialdehyde, which is then biotransformed to succinic acid by the enzyme succinic semialdehyde dehydrogenase.

Special Populations

Geriatric

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

Pediatric

The pharmacokinetics of sodium oxybate in pediatric patients under the age of 18 years have 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.

Race

There are insufficient data to evaluate any pharmacokinetic differences among races.

Renal Disease

Because the kidney does not have a significant role in the excretion of sodium oxybate, no pharmacokinetic study in patients with renal dysfunction has been conducted; no effect of renal function on sodium oxybate pharmacokinetics would be expected.

Hepatic Disease

Sodium oxybate undergoes significant presystemic (hepatic first-pass) metabolism. The kinetics of sodium oxybate in 16 cirrhotic patients, half without ascites, (Child's Class A) and half with ascites (Child's Class C) were compared to the kinetics in 8 healthy adults after a single oral dose of 25 mg/kg. AUC values were double in the cirrhotic patients, with apparent oral clearance reduced from 9.1 in healthy adults to 4.5 and 4.1 ml/min/kg in Class A and Class C patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control subjects (mean $T_{½}$ of 59 and 32 versus 22 minutes). It is prudent to reduce the starting dose of sodium oxybate by one-half in patients with liver dysfunction (see Dosage and Administration).

Drug-Drug Interaction

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, and modafinil. However, pharmacodynamic interactions with these drugs cannot be ruled out.

CLINICAL TRIALS

The effectiveness of sodium oxybate as an anti-cataplectic agent was established in 2 randomized, double-blind, placebo-controlled trials (Trials 1 and 2) in patients with narcolepsy, 85% and 80%, respectively, of whom were also being treated with CNS stimulants. In each trial, the treatment period was 4 weeks and the total daily doses ranged from 3 to 9 grams, with the daily dose divided into 2 equal doses. The first dose each night was taken at bedtime and the second dose was taken 2.5 to 4 hours later. There were no restrictions on the time between food consumption and dosing. Trial 1 was a multi-center, double-blind, placebo-controlled, parallel-group trial that enrolled 136 narcoleptic patients with moderate to severe cataplexy (median of 21 cataplexy attacks per week) at baseline. Prior to randomization, medications with possible effects on cataplexy were withdrawn, but stimulants were continued at stable doses. Patients were randomized to receive placebo, sodium oxybate 3g/day, sodium oxybate 6g/day, or sodium oxybate 9g/day. Trial 2 was a multi-center, double-blind, placebo-controlled, parallel-group, randomized withdrawal trial that enrolled 55 narcoleptic patients who had been taking open-label sodium oxybate for 7 to 44 months. To be included, patients were required to have a history of at least 5 cataplexy attacks per week prior to any treatment for cataplexy. Patients were randomized to continued treatment with sodium oxybate at their stable dose or to placebo. Trial 2 was designed specifically to evaluate the continued efficacy of sodium oxybate after long-term use. The primary efficacy measure in each clinical trial was the frequency of cataplexy attacks.

Table

Summary of Outcomes in Clinical Trials Supporting the Efficacy of Sodium Oxybate

Trial/ Dosage Group (n)	Baseline	Median Change From Baseline	Comparison to Placebo p-value

CATAPLEXY ATTACKS

Trial 1

		(median attacks/wk)	
Placebo (33)	20.5	-4	
3.0 g/d (33)	20.0	-7	
6.0 g/d (31)	23.0	-10	
9.0 g/d (33)	23.5	-16	

Trial 2

		(median attacks/two weeks)	
Placebo (29)	4.0	21	
Sodium oxybate (26)	1.9	0	<0.001

In Trial 1, the 9 g/day dose gave a statistically significant (reduction in the frequency of cataplexy attacks. The 3 g/day had little effect. In Trial 2, following the discontinuation of long-term open-label sodium oxybate therapy, patients randomized to placebo experienced a significant increase in cataplexy ($p<0.001$), providing evidence of long-term efficacy of sodium oxybate. In Trial 2, the response was numerically similar for patients treated with doses of 6-9 g/day, but there was no significant effect seen in patients treated with doses less than 6 g/day.

INDICATIONS AND USAGE

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

In Xyrem clinical trials approximately 80% patients maintained concomitant stimulant use (see BLACK BOX WARNINGS).

CONTRAINDICATIONS

Sodium oxybate is contraindicated in patients being treated with sedative-hypnotic agents,

Sodium oxybate is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency. This rare disorder is an inborn error of metabolism.

WARNINGS

SEE BOXED WARNING

Due to the rapid onset of its CNS depressant effects, sodium oxybate should only be ingested at bedtime, and while in bed. For at least 6 hours after ingesting sodium oxybate, patients must not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery, driving a motor vehicle, or flying an airplane.

Central Nervous System Depression/Respiratory Depression

Sodium oxybate is a CNS depressant with the potential to impair respiratory drive, especially in patients with already-compromised respiratory function.

APPEARS THIS WAY
ON ORIGINAL

Confusion/Neuropsychiatric Adverse Events

During clinical trials, 7% of patients treated with sodium oxybate experienced confusion. than 1% of patients discontinued the drug because of confusion.

Confusion was reported at all recommended doses from 6-9g/day.

In a controlled trial where patients were randomized to fixed total doses of 3, 6, and 9g/day or placebo, a dose-response relationship for confusion was demonstrated with 17% of patients at 9g/day experiencing confusion.

In all cases, the confusion resolved soon after termination of treatment

Other neuropsychiatric events included psychosis, paranoia, hallucinations, and agitation. The emergence of thought disorders and/or behavior abnormalities when patients are treated with sodium oxybate requires careful and immediate evaluation.

Depression

In clinical trials, 6% of patients treated with sodium oxybate reported depressive symptoms

In the controlled clinical trial where patients were randomized to fixed doses of 3, 6, 9g/day or placebo, there was a single event of depression at the 3g/day dose.

patients with previous history of depressive psychiatric disorder, there were 2 suicides and 1 attempted suicide recorded in the 448 patient dataset;

The emergence of depression when patients are treated with Xyrem requires careful and immediate evaluation. Patients with a previous history a depressive and/or suicide attempt should be monitored especially carefully for the emergence of depressive symptoms while taking Xyrem.

APPEARS THIS WAY
ON ORIGINAL

This page is blank

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

PRECAUTIONS

Incontinence

During ——clinical trials, 9% of narcoleptic patients treated with sodium oxybate experienced either a single episode or sporadic nocturnal urinary incontinence and <1% experienced a single episode of nocturnal fecal incontinence. Less than 1% of patients discontinued as a result of incontinence. Incontinence has been reported at all doses tested.

In a controlled trial where patients were randomized to fixed total doses of 3, 6, and 9g/day or placebo —— a dose-response relationship for urinary incontinence was demonstrated with 14% of patients at 9g/day experiencing urinary incontinence. In the same trial one patient experienced fecal incontinence at a dose of 9 g/day and discontinued the trial as a result.

[redacted]

—— Sleepwalking

The term "sleepwalking" [redacted] behavior, occurring at night, and at times associated with wandering. It is unclear some or all of these episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder

In controlled trials of up to 4 weeks duration, the incidence of —— (sleepwalking) was 1% in both placebo and sodium oxybate-treated patients.

—— Sleepwalking was reported —— patients treated . —— with sodium oxybate [redacted] <1% discontinued due to —— sleepwalking.

Sleepwalking was reported by 32% of patients treated with sodium oxybate for periods up to 16 years in an independent uncontrolled trial. than 1% of the patients discontinued due to sleepwalking.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Patients should be instructed that they should not take alcohol or sedative hypnotics with sodium oxybate. For additional information, patients should see the Medication Guide for Xyrem.

Laboratory Tests

Laboratory tests are not required to monitor patient response or adverse events resulting from sodium oxybate administration.

In an open-label trial of long-term exposure to sodium oxybate, which extended as long as 16 years for some patients, 30% (26/87) of patients tested had at least one positive anti-nuclear antibody (ANA) test. Of the 26, 17 patients had multiple positive ANA tests over time. The clinical course of these patients was not always clearly recorded, but one patient was clearly diagnosed with rheumatoid arthritis at the time of the first recorded positive ANA test.

Drug Interactions

Interactions between sodium oxybate and three drugs commonly used in patients with narcolepsy (zolpidem tartrate, protriptyline HCl, and modafinil) have been evaluated in formal studies. Sodium oxybate, in combination with these drugs, produced no significant pharmacokinetic changes for either drug (see **Pharmacokinetics and Metabolism**). However, pharmacodynamic interactions cannot be ruled out. Nonetheless, sodium oxybate should not be used in combination with sedative hypnotics or other CNS depressants.

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

Carcinogenicity, Mutagenicity, Impairment of Fertility

Oral carcinogenicity studies have been conducted in rats and mice with gamma-butyrolactone, a compound that is metabolized to oxybate *in vivo,* with no clear evidence of carcinogenic potential. Plasma levels (AUC) of sodium oxybate achieved in these studies were estimated to be approximately ½ (mice and female rats) and $^1/_{10}$ (male rats) those seen in humans receiving the maximum recommended daily dose of sodium oxybate.

Sodium oxybate was negative in the Ames microbial mutagen test, an *in vitro* chromosomal aberration assay in CHO cells, and an *in vivo* rat micronucleus assay.