

**Body As A Whole**

**Cardiovascular system**

**Digestive system**

**Hemic and lymphatic system**

Anemia, ecchymosis, leukocytosis,  
lymphadenopathy, polycythemia.

**Metabolic and nutritional**

Alkaline phosphatase increased,  
hypercholesteremia,

**Musculoskeletal system**

Arthritis, arthrosis, , leg  
cramps, myopathy

***Nervous system***

Agitation,  
convulsion,

stupor.

***Respiratory system***

Apnea, epistaxis, hiccup,

***Skin and appendages***

Acne, alopecia,

rash,

***Special senses***

taste loss,

***Urogenital system***

albuminuria,

menorrhagia,

papanicolau Papanicolau smear suspicious, polyuria, prostatic disorder, testis

urine frequency,

## 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;  $\gamma$ -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<sub>x</sub> only

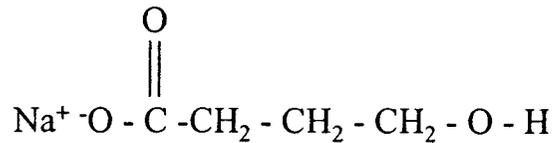
CIII

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

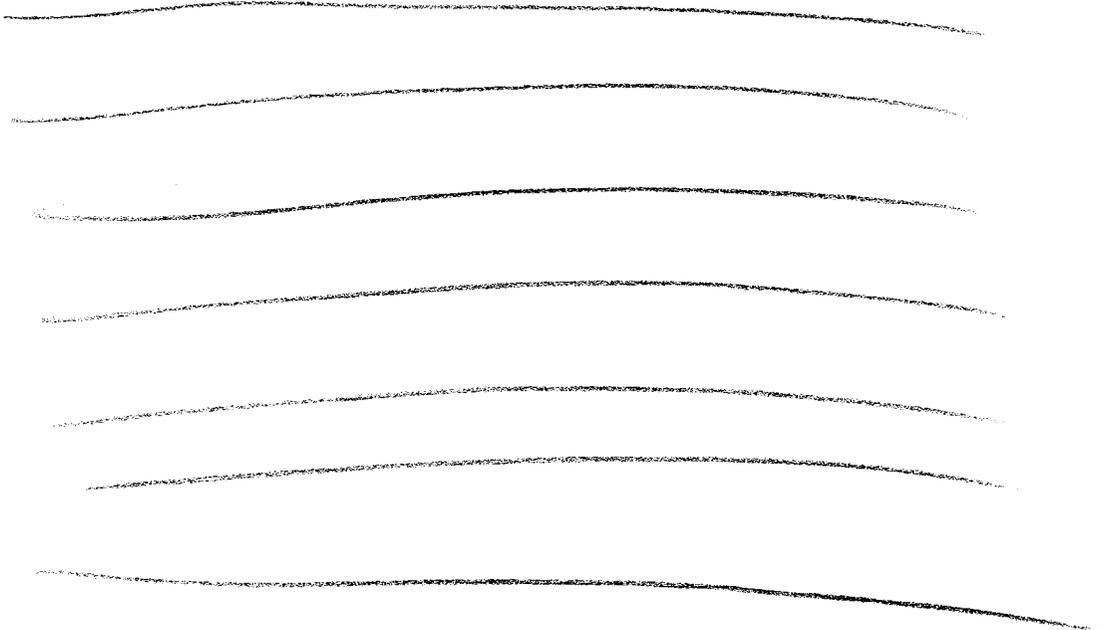
nocturnal awakenings. Xyrem is intended for oral administration. The chemical name for sodium oxybate is gamma-hydroxybutyric acid (GHB), sodium. The molecular formula is  $\text{NaC}_4\text{H}_7\text{O}_3$  and the molecular weight is 126.1 grams/mole. The chemical structure is:



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*

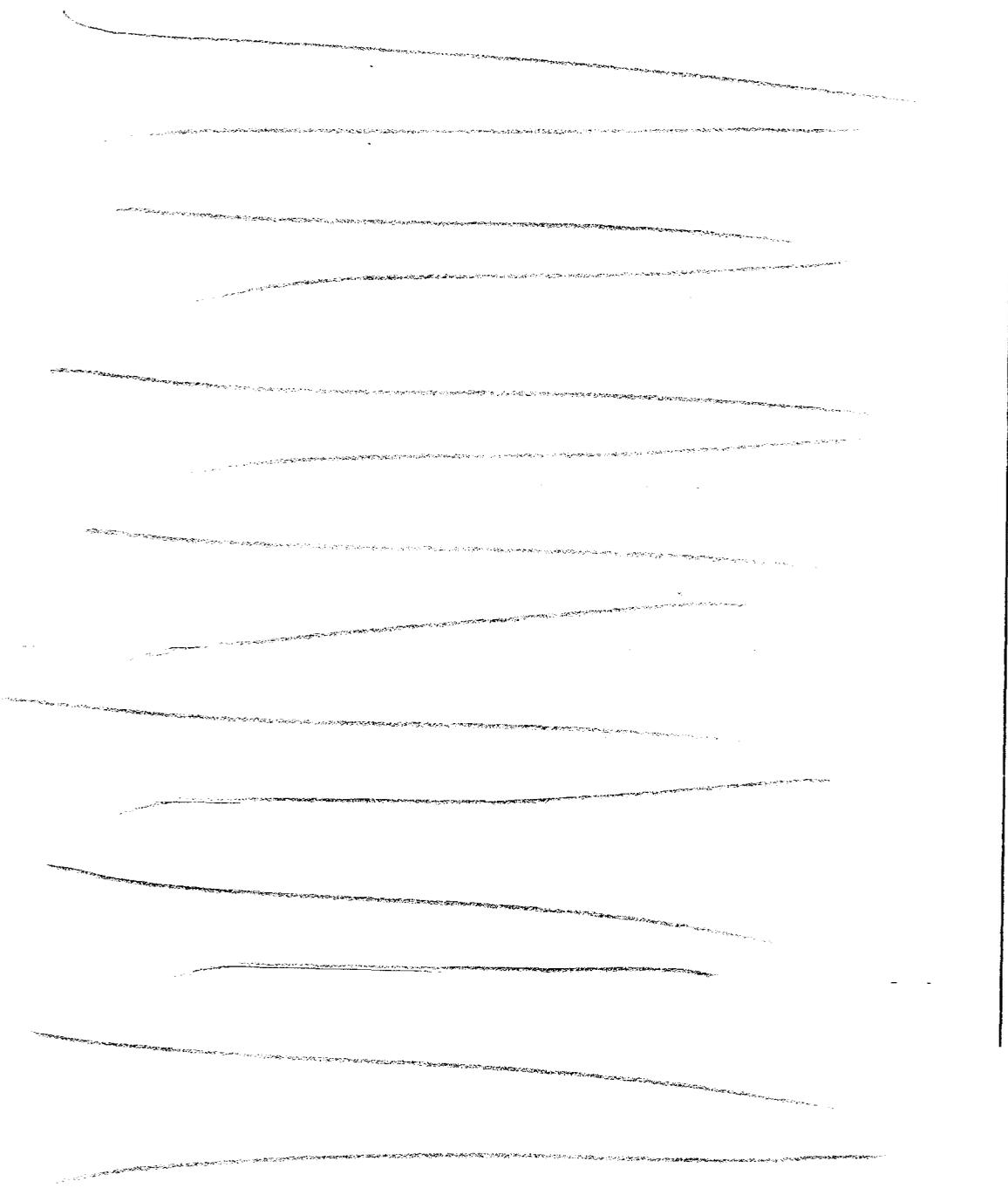
Oxybate undergoes significant presystemic (hepatic first-pass) metabolism.

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**

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



## INDICATIONS AND USAGE

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

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

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 \_\_\_\_\_ (see Pharmacokinetics  
\_\_\_\_\_  
\_\_\_\_\_

### Renal Insufficiency

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

### Gender, \_\_\_\_\_ \_\_\_\_\_ \_\_\_\_\_ \_\_\_\_\_

## Drug Interactions

In animal models, oxybate and depressant drug combinations generally greater depressant effects than 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); \_\_\_\_\_ 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%)

---

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

**Body As A Whole**

**Cardiovascular system**

**Digestive system**

**Hemic and lymphatic system**

Anemia, ecchymosis, leukocytosis,  
lymphadenopathy, polycythemia.

**Metabolic and nutritional**

Alkaline phosphatase increased,  
hypercholesteremia,

**Musculoskeletal system**

Arthritis, arthrosis, leg  
cramps, myopathy,

***Nervous system***

Agitation,  
convulsion,

stupor.

***Respiratory system***

Apnea, epistaxis, hiccup,

***Skin and appendages***

Acne, alopecia,

rash,

***Special senses***

taste loss,

***Urogenital system***

albuminuria,

menorrhagia,

papanicolaou Papanicolaou smear suspicious, polyuria, prostatic disorder, testis

urine frequency,

APPEARS THIS WAY  
ON ORIGINAL

This page is blank

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

**DRUG ABUSE AND DEPENDENCE**

**Controlled Substance Class**

Xyrem is classified as a Schedule III controlled substance by Federal law. Non-medical uses of sodium oxybate are classified under Schedule I.

**Abuse, Dependence, and Tolerance**

**Abuse**

**Dependence**

There have been \_\_\_\_\_ case reports of dependence after illicit use of \_\_\_\_\_

at frequent repeated doses (18 to 250 g/d), in excess of the therapeutic dose range. In these cases, the signs and symptoms of abrupt discontinuation included an abstinence syndrome (insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, and tachycardia. These symptoms generally abated in 3 to 14 days.

## Tolerance

tolerance to sodium oxybate has not been systematically studied in controlled clinical trials;

Clinical studies of sodium oxybate in the treatment of alcohol withdrawal suggest a potential cross-tolerance with alcohol. Because illicit use and abuse of sodium oxybate has been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of sodium oxybate (e.g. increase in size or frequency of dosing, drug-seeking behavior).

## OVERDOSAGE

### Human Experience

Information regarding overdose with sodium oxybate is derived from reports in the medical literature that describe symptoms and signs in drug-abusers individuals who have ingested the drug illicitly or for medically-unapproved purposes. In those circumstances the co-ingestion of multiple drugs and alcohol, is common, and may influence the presentation and severity of clinical manifestations of overdose.

## Signs and Symptoms

Emesis (even ~~obtund~~), diaphoresis, headache, and ~~impaired~~ psychomotor skills may be observed. ~~no~~ typical pupillary ~~changes~~ to assist in diagnosis, and pupillary reactivity to light is maintained; ~~Blurred~~ vision has been reported.

An increasing depth of ~~may be observed with higher doses.~~ Myoclonus and ~~T~~ tonic-clonic seizures have been reported. Respiration may be maintained or be compromised in rate and depth ~~Cheyne-Stokes~~ Cheyne-Stokes respiration or apnea. Bradycardia and hypothermia may accompany unconsciousness, as may muscular hypotonia, but tendon reflexes remain intact.

## Recommended Treatment of Overdose

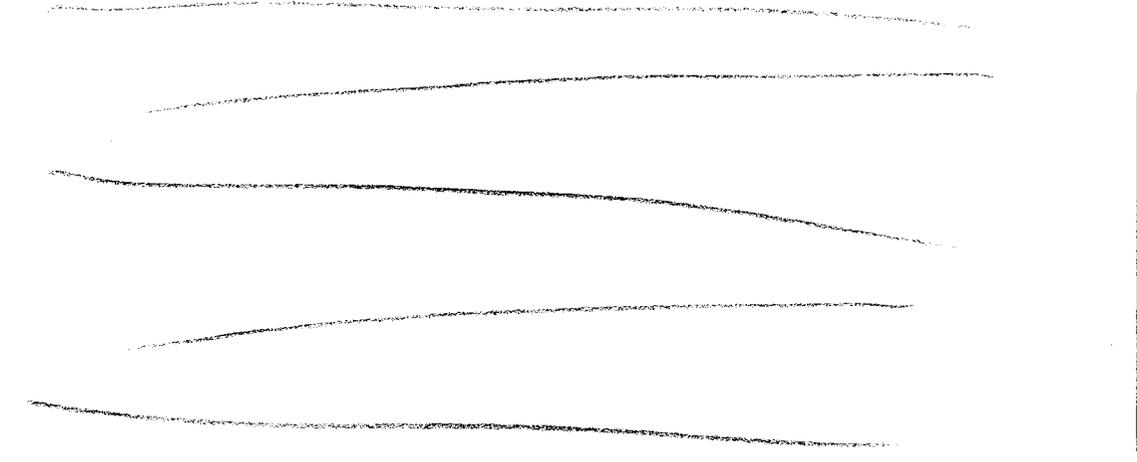
General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if coingestants are suspected. ~~emesis is a frequent symptom in the presence of~~ ~~obtundation,~~ appropriate posture (left lateral recumbent position) ~~and~~ protection of the airway by intubation ~~may be~~

## Poison Control Center

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician

blood samples for routine toxicologic screening.

## DOSAGE AND ADMINISTRATION



### Preparation and Administration Precautions

Bottles of Xyrem are provided with a child resistant cap and child resistant dosing cups.

Care should be taken to prevent access to this medication by children:

See \_\_\_\_\_ for a complete description.



**APPEARS THIS WAY  
ON ORIGINAL**

## HOW SUPPLIED

resistant cap.

NDC 62161-008-20: Each tamper evident single unit carton contains one 180 mL bottle (500 mg/mL) of Xyrem<sup>®</sup>, one press-in-bottle-adaptor , one oral syringe, and two dosing cups with child resistant cap.

## HANDLING AND DISPOSAL

Xyrem is a Schedule III drug under the Controlled Substances Act. Xyrem should be handled according to state and federal regulations. It is safe to dispose of Xyrem oral solution down the sanitary sewer.

**Rx only**

**Distributed By**  
Orphan Medical Inc.  
Minnetonka, Minnesota 55305

For questions of a medical nature or to order Xyrem call the Xyrem Patient Success Program at 1-XXX-XXX-XXXX..

US Patents Pending

Rev. 12/15/2000  
Part No.

## **Comments**

The following major changes have been made to specific sections of the sponsor's draft label

### **Clinical Trials**

- Descriptions of, and all data from, the Scrima and Lammers studies (Trials 2 and 3 in the sponsor's version of the label) have been deleted as the evidence for efficacy in these studies is marginal or questionable (see NDA Efficacy Review for full details)
- All information about open-label, uncontrolled studies has also been deleted from the label as such studies cannot be used to support the efficacy of Xyrem®
- Data pertaining to secondary efficacy measures have also been deleted. For a number of reasons, described in greater detail in the Efficacy Review, these measures cannot be used to support the efficacy of Xyrem®

### **Indications And Usage**

- The indication has been limited to the treatment of cataplexy. As further described in the NDA Efficacy Review, the evidence that Xyrem® is effective in treating daytime sleepiness accompanying narcolepsy is questionable

### **Warnings**

- The text of this section of the label has been altered so as to be more clearly informative.
- A description of the special safety concerns associated with GHB, and the risk management program has been added to this section
- A statement indicating that convulsions have been noted in clinical trials of Xyrem® has been added

### **Precautions**

- The text of this section has been made more accurate

### **Adverse Reactions**

- Tables depicting adverse event data from the Lammers and Scrima studies have been deleted. These studies were cross-over in design, enrolled a small number of patients only, and the adverse events noted did not differ materially from those in the larger controlled Trial 1
- The text of this section has been reorganized
- In the section entitled "Adverse Events In All Clinical Trials", adverse events of unclear meaning (e.g., "reaction unevaluable") have been deleted
- The description of positive antinuclear antibody tests in the Scharf study has been altered so as to be more consistent with the actual data

### **Overdosage**

- The text of this section has been made more compact
- A recommendation that physostigmine be used for the treatment of overdosage with GHB has been deleted as the recommendation is based on very limited anecdotal evidence.

### **Dosage And Administration**

- This section has been made consistent with the conclusion that was made in the NDA Efficacy Review that the most clearly effective dose of GHB was 9 g/day, but that some evidence of efficacy was also present in the dose range 6-9 g/day

\_\_\_\_\_  
Ranjit B. Mani, M.D.  
Medical Reviewer

J. Feeney, M.D. \_\_\_\_\_

rbm 6/14/01  
cc:  
HFD-120  
NDA 21196 (000)  
Homonnay

NDA (Serial Number)	21196
Sponsor:	Orphan Medical, Inc.
Drug:	Xyrem
Proposed Indication:	Narcolepsy
Material Submitted:	Major Amendment
Correspondence Date:	3/23/01
Date Received / Agency:	3/26/01
Date Review Completed	6/14/01
Reviewer:	Ranjit B. Mani, M.D.

## 1. Table Of Contents

1. TABLE OF CONTENTS.....	1
2. BACKGROUND .....	5
3. ORGANIZATION OF CLINICAL TRIALS IN INTEGRATED SUMMARY OF SAFETY.....	6
4. DEFICIENCIES IN SCHARF STUDY DATA REVEALED AT INITIAL SITE INSPECTION 7	
4.1 OUTLINE OF SCHARF STUDY.....	7
4.2 PRELIMINARY RESULTS OF INSPECTION .....	7
4.3 DIVISIONAL RECOMMENDATIONS FOR ADDRESSING DEFICIENCIES IN SCHARF STUDY .....	8
5. AGENCY QUESTIONS ABOUT ORPHAN-SPONSORED CLINICAL TRIALS.....	8
5.1 EXPOSURE TABLE .....	9
5.2 SERIOUS ADVERSE EVENTS.....	9
5.3 LABORATORY DATA .....	9
5.3.1 <i>Table Of Interest</i> .....	9
5.3.2 <i>Questions About Table</i> .....	11
5.4 ADDITIONAL QUESTIONS .....	11
5.5 ADDITIONAL REQUEST.....	12
6. CONTENTS OF SUBMISSION.....	12
7. DISPOSITION OF SCHARF STUDY PATIENTS WHO DID NOT ENTER STUDY OMC-SXB-7.....	12
7.1 BACKGROUND.....	12
7.2 SPONSOR'S METHODS.....	13
7.3 DISPOSITION OF SCHARF STUDY PATIENTS WHO DID NOT ENTER OMC-SXB-7.....	13
7.4 DISCONTINUATIONS DUE TO ADVERSE EVENTS .....	14
7.4.1 <i>Deaths</i> .....	14
7.4.2 <i>Non-Fatal Adverse Events Leading To Discontinuation</i> .....	15
7.5 REVIEW OF INDIVIDUAL NARRATIVES AND CASE REPORT FORMS.....	16
7.5.1 <i>Source Of Case Report Forms</i> .....	16
7.5.2 <i>Structure Of Case Report Forms</i> .....	16
7.5.3 <i>Deficiencies In Structure Of Case Report Forms And Additional Related Concerns</i> .....	17
7.5.4 <i>Deaths And Adverse Event Discontinuations</i> .....	18
7.5.5 <i>Patients Discontinued From Scharf Study For Non-Compliance</i> .....	18
7.5.6 <i>Discontinuations On Account Of Protocol Deviations</i> .....	21
7.5.7 <i>Discontinuations On Account Of Medication Cost, Medication Cost, Lack Of Efficacy, And Transfer To Another Study</i> .....	22
7.5.8 <i>Patients Continuing In Scharf Study</i> .....	22
7.5.9 <i>Patients Subjected To Recent Attempts At Follow-Up</i> .....	23
7.5.10 <i>Unresolved Adverse Events Of Concern</i> .....	24

7.6	REVIEWER'S COMMENTS.....	26
8.	<b>NARRATIVE FOR PATIENT 01-064 PARTICIPATING IN SCHARF STUDY.....</b>	<b>26</b>
8.1	NARRATIVE.....	26
8.2	REVIEWER'S COMMENTS.....	27
9.	<b>"REACTION UNEVALUABLE" ADVERSE EVENTS IN SCHARF TRIAL.....</b>	<b>27</b>
9.1	BACKGROUND.....	27
9.2	CATEGORIES OF "UNEVALUABLE" ADVERSE EVENTS.....	28
9.3	SERIOUS "UNEVALUABLE" ADVERSE EVENTS.....	28
9.4	ALL "UNEVALUABLE" ADVERSE EVENTS.....	28
9.5	REVIEWER'S COMMENTS.....	29
10.	<b>ANALYSIS OF URINARY AND FECAL INCONTINENCE IN SCHARF TRIAL.....</b>	<b>29</b>
10.1	BACKGROUND.....	29
10.2	SPONSOR'S METHODS.....	29
10.3	TABULAR SUMMARY OF CASES IDENTIFIED BY SPONSOR.....	30
10.4	NARRATIVES FOR SELECTED PATIENTS IN ABOVE TABLE.....	30
10.4.1	<i>Patient # 01-048.....</i>	<i>30</i>
10.4.2	<i>Patient # 01-247.....</i>	<i>31</i>
10.4.3	<i>Patient # 01-255.....</i>	<i>32</i>
10.4.4	<i>Patient # 01-257.....</i>	<i>32</i>
10.5	PATIENTS WITH SLEEPWALKING AND INCONTINENCE.....	33
10.6	SPONSOR'S CONCLUSIONS.....	33
10.7	REVIEWER'S COMMENTS.....	34
11.	<b>ADVERSE EVENTS CODED AS "CONFUSION" IN SCHARF STUDY.....</b>	<b>35</b>
11.1	BACKGROUND AND METHODS.....	35
11.2	OVERALL SUMMARY.....	35
11.3	VERBATIM INVESTIGATOR TERMS.....	36
11.4	TABULAR SUMMARY.....	36
11.5	NARRATIVE FOR PATIENT WITH CONFUSION AS A SERIOUS ADVERSE EVENT.....	36
11.5.1	<i>Patient 01-012 (Initials) —.....</i>	<i>36</i>
11.6	NARRATIVES FOR ADDITIONAL PATIENTS WITH CONFUSION.....	37
11.6.1	<i>Patient 01-016 (Initials) —.....</i>	<i>37</i>
11.6.2	<i>Patient 01-027 (Initials) —.....</i>	<i>37</i>
11.6.3	<i>Patient 01-048 (Initials) —.....</i>	<i>37</i>
11.6.4	<i>Patient 01-215 (Initials) —.....</i>	<i>37</i>
11.6.5	<i>Patient 01-235 (Initials) —.....</i>	<i>38</i>
11.6.6	<i>Patient 01-248 (Initials) —.....</i>	<i>38</i>
11.6.7	<i>Patient 01-251 (Initials) —.....</i>	<i>38</i>
11.7	REVIEWER'S COMMENTS.....	38
12.	<b>NEUROPSYCHIATRIC ADVERSE EVENTS IN SCHARF STUDY.....</b>	<b>38</b>
12.1	BACKGROUND.....	38
12.2	OVERALL SUMMARY.....	39
12.3	DISTRIBUTION OF INDIVIDUAL NEUROPSYCHIATRIC ADVERSE EVENTS.....	39
12.4	SPECIFIC NEUROPSYCHIATRIC ADVERSE EVENTS.....	40
12.4.1	<i>Depression.....</i>	<i>40</i>
12.4.2	<i>Emotional Lability.....</i>	<i>40</i>
12.4.3	<i>Thinking Abnormal.....</i>	<i>42</i>
12.4.4	<i>Depersonalization.....</i>	<i>43</i>
12.4.5	<i>Hostility.....</i>	<i>43</i>
12.4.6	<i>Stupor.....</i>	<i>44</i>
12.4.7	<i>Neurosis.....</i>	<i>45</i>
12.4.8	<i>Overdose.....</i>	<i>46</i>
12.4.9	<i>Suicide Attempt.....</i>	<i>46</i>

12.4.10	Hallucinations	46
12.4.11	Paranoid Reaction	46
12.5	NARRATIVES FOR SERIOUS NEUROPSYCHIATRIC ADVERSE EVENTS, AND DISCONTINUATIONS DUE TO NEUROPSYCHIATRIC ADVERSE EVENTS	47
12.5.1	Patient 01- 019 (Initials)	47
12.5.2	Patient 01-259 (Initials)	47
12.5.3	Patient 01-012 (Initials)	47
12.5.4	Patient 01-017 (Initials)	47
12.5.5	Patient 01-267 (Initials)	48
12.6	ADDITIONAL NARRATIVE	48
12.6.1	Patient 01-006 (Initials)	48
12.7	PSYCHOPATHOLOGY IN NARCOLEPSY	49
12.8	REVIEWER'S COMMENTS	49
13.	ADVERSE EVENTS CODED AS "CONVULSIONS" IN SCHARF STUDY	49
13.1	BACKGROUND AND METHODS	49
13.2	RESULTS OF ANALYSIS	50
13.2.1	Number And Distribution Of Patients With "Convulsion(s)"	50
13.2.2	Investigator Terms	50
13.3	NARRATIVES FOR PATIENTS WITH NON-CATAPLECTIC CONVULSIONS	52
13.3.1	Patient # 01-048	52
13.3.2	Patient # 01-064	52
13.3.3	Patient # 01-247	53
13.3.4	Patient # 01-255	54
13.3.5	Patient # 01-257	54
13.4	REVIEWER'S COMMENTS	55
14.	ADVERSE EVENTS CODED AS "CONFUSION" IN INTEGRATED CLINICAL TRIALS	55
14.1	BACKGROUND AND METHODS	55
14.2	OVERALL SUMMARY	55
14.3	VERBATIM INVESTIGATOR TERMS	56
14.4	TABULAR SUMMARY	56
14.5	"CONFUSION" IN STUDY OMC-GHB-2	57
14.6	NARRATIVES FOR PATIENTS WITH CONFUSION AS A SERIOUS ADVERSE EVENT	57
14.6.1	Patient 0207 (Initials)	57
14.6.2	Patient 0231 (Initials)	57
14.7	NARRATIVES FOR PATIENTS WITH CONFUSION AS AN ADVERSE EVENT WARRANTING PERMANENT DISCONTINUATION OF GHB	58
14.7.1	Patient 0207 (Initials)	58
14.7.2	Patient 0231 (Initials)	58
14.7.3	Patient # 0702 (Initial)	58
14.8	REVIEWER'S COMMENTS	58
15.	NEUROPSYCHIATRIC ADVERSE EVENTS IN INTEGRATED CLINICAL TRIALS	59
15.1	BACKGROUND	59
15.2	OVERALL SUMMARY	59
15.3	DISTRIBUTION OF INDIVIDUAL NEUROPSYCHIATRIC ADVERSE EVENTS	60
15.4	SPECIFIC NEUROPSYCHIATRIC ADVERSE EVENTS	60
15.4.1	Depression	60
15.4.2	Hallucinations	61
15.4.3	Stupor	61
15.4.4	Suicide Attempt	62
15.4.5	Paranoia	63
15.4.6	Coma	63
15.4.7	Psychosis	64
15.4.8	Manic Depressive Reaction	64
15.4.9	Personality Disorder	65

15.5	NARRATIVES FOR DEATHS ASSOCIATED WITH NEUROPSYCHIATRIC ADVERSE EVENTS, SERIOUS NEUROPSYCHIATRIC ADVERSE EVENTS, AND DISCONTINUATIONS DUE TO NEUROPSYCHIATRIC ADVERSE EVENTS	65
15.5.1	Patient # 0932 (Initials)	65
15.5.2	Patient # 0531 (Initials)	65
15.5.3	Patient # 0936 (Initials)	66
15.5.4	Patient # 1131 (Initials)	66
15.5.5	Patient # 14043 (Initials)	66
15.5.6	Patient # 0232 (Initials)	67
15.5.7	Patient # 0238 (Initials)	67
15.5.8	Patient # 2030 (Initials)	67
15.5.9	Patient # 0931 (Initials)	67
15.5.10	Patient # 0204 (Initials)	68
15.5.11	Patient # 0213 (Initials)	68
15.5.12	Patient # 0702 (Initials)	68
15.5.13	Patient # 1101 (Initials)	68
15.6	EXPERIENCE WITH NEUROPSYCHIATRIC ADVERSE EVENTS IN CONTROLLED CLINICAL TRIAL OMC-GHB-2	68
15.7	PSYCHOPATHOLOGY IN NARCOLEPSY	69
15.8	REVIEWER'S COMMENTS	70
16.	ADVERSE EVENTS CODED AS "CONVULSIONS" IN INTEGRATED CLINICAL TRIALS	70
16.1	BACKGROUND	70
16.2	RESULTS OF ANALYSIS	70
16.2.1	Number And Distribution Of Patients With "Convulsion(s)"	70
16.2.2	Investigator Terms	71
16.2.3	Narrative For Patient # 0814 (Initials)	72
16.3	REVIEWER'S COMMENTS	72
17.	ABNORMALITIES OF BLOOD GLUCOSE AND TRANSAMINASES IN INTEGRATED CLINICAL TRIALS	72
17.1	ABNORMALITIES OF BLOOD GLUCOSE	72
17.1.1	Background And Sponsor's Methods	72
17.1.2	Hypoglycemia	73
17.1.3	Hyperglycemia	75
17.1.4	Teleconference With Sponsor: 4/6/01	76
17.1.5	Dr James Knudsen's Review Of Hypoglycemia	76
17.1.6	Reviewer's Comments	77
17.2	ABNORMALITIES OF TRANSAMINASES	78
17.2.1	Background	78
17.2.2	Sponsor's Description Of Individual Cases	78
17.2.3	Sponsor's Comments	80
17.2.4	Reviewer's Comments	80
18.	PATIENT 0231	80
18.1	BACKGROUND	80
18.2	NARRATIVE	80
18.3	REVIEWER'S COMMENTS	80
19.	DRUG-INDUCED LUPUS IN INTEGRATED CLINICAL TRIALS	80
19.1	BACKGROUND	80
19.2	SPONSOR'S METHODS	81
19.3	SPONSOR'S CONCLUSIONS	82
19.4	REVIEWER'S COMMENTS	82
20.	EXPOSURE TABLES	82

20.1	OVERALL SCHEMATIC FOR CLINICAL TRIALS IN NARCOLEPTIC PATIENTS INCLUDED IN NDA	82
20.2	TABLES.....	83
20.2.1	<i>Sponsor's Methods For Creating Tables</i> .....	83
20.2.2	<i>Tables</i> .....	84
20.3	SPONSOR'S OVERALL VIEW OF ADEQUACY OF EXPOSURE.....	84
20.4	REVIEWER'S COMMENTS.....	85
21.	REVIEWER'S SUMMARY OF "SLEEPWALKING".....	86
21.1	BACKGROUND.....	86
21.2	INCIDENCE OF "SLEEPWALKING" IN XYREM® NDA.....	86
21.2.1	<i>Controlled Clinical Trial OMC-GHB-2</i> .....	86
21.2.2	<i>Integrated Clinical Trials</i> .....	87
21.2.3	<i>Scharf Trial</i> .....	87
21.3	CHARACTERIZATION OF "SLEEPWALKING" EPISODES.....	87
21.4	CONSEQUENCES OF "SLEEPWALKING" IN XYREM® NDA.....	88
21.4.1	<i>Patient 01-215 (Initials)</i> .....	88
21.4.2	<i>Patient 01-017 (Initials)</i> .....	88
21.4.3	<i>Patient 01-267 (Initials)</i> .....	89
21.4.4	<i>Patient 01-206 (Initials)</i> .....	89
21.5	REVIEWER'S COMMENTS.....	89
22.	SCHARF STUDY RE-INSPECTION.....	90
23.	OVERALL COMMENTS.....	90
24.	CONCLUSIONS.....	93
25.	RECOMMENDATIONS.....	93

## 2. Background

This submission is a major amendment to the New Drug Application for Xyrem® which was originally submitted on 9/30/2000.

Please refer to my original NDA Safety and Efficacy Reviews for full details about Xyrem®.

Through the original application and amendment, the sponsor wishes to pursue the following claim:

**"Xyrem® (sodium oxybate) oral solution is indicated to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy."**

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

The primary purpose of this amendment is to address concerns raised by this Division about the validity of data in the original NDA that were derived from the long-term, open-label, individual-investigator Scharf Study. These concerns were

raised by an Agency inspection of the study site, conducted in February 2001. Further details of these concerns are in Section 4 below.

An additional goal of this amendment is to answer questions from this Division regarding the safety data from several Orphan-sponsored clinical trials which were submitted with the original NDA.

With this submission the sponsor has requested a 90-day extension to the Prescription Drug User Fee Act deadline (4/2/01) for the original NDA submission.

This review was completed with the assistance of Drs Tarek Hammad and James Knudsen, of the Division's Safety Team.

### 3. Organization Of Clinical Trials In Integrated Summary Of Safety

In the original NDA the clinical trials were organized in the following manner.

- A total of 15 clinical trials were included in the Integrated Summary of Safety.
- The sponsor had grouped these studies into 4 separate pools which are listed here and further outlined below.
  - Integrated Clinical Trial
  - Lammers Trial
  - Scharf Trial
  - Integrated Pharmacokinetic Trials
- Safety data for each of these pools were described separately by the sponsor.
- Note that the sponsor did not include randomized controlled clinical trials under a separate pool

#### 3.1.1.1 Integrated Clinical Trials

With the exception of the Scrima trial, all other studies in this grouping were conducted by the sponsor

Study #	Design	Duration
OMC-GHB-2	Randomized, double-blind, placebo-controlled, parallel-arm	4 weeks
OMC-GHB-3	Open-label, uncontrolled, extension study	Up to 24 months
OMC-SXB-6	Open-label uncontrolled study	6 months
OMC-SXB-7	Open-label uncontrolled study	Up to 24 months
Scrima	Randomized, double-blind, placebo-controlled, cross-over	4 weeks*

\*GHB and placebo were each used for 4 weeks

Further details about the above extension studies are below

Study #	Comments
OMC-GHB-3	Extension to OMC-GHB-2.
OMC-SXB-6	Treatment naive patients (except for a single patient previously in OMC-GHB-2 and OMC-GHB-3)
OMC-SXB-7	Extension to OMC-GHB-3 OMC-SXB-6 Scharf Study

### **3.1.1.2 Lammers Trial**

This was a non-IND, individual investigator-conducted, randomized, double-blind, placebo-controlled, cross-over trial of 4 weeks' duration (GHB and placebo were each used for 4 weeks).

### **3.1.1.3 Long-Term Clinical Trial (Scharf)**

This long-term open-label individual investigator study lasted about 16 years

### **3.1.1.4 Integrated Pharmacokinetic Trials**

These trials which were conducted by Orphan Medical, Inc., are listed in the table below. All were single dose-studies. With the exception of those enrolled in Studies OMC-GHB-4 and OMC-SXB-10, all were healthy volunteers

OMC-GHB-4  
OMC-SXB-8  
OMC-SXB-9  
OMC-SXB-10  
OMC-SXB-11  
OMC-SXB-12  
OMC-SXB-14  
OMC-SXB-17

## **4. Deficiencies In Scharf Study Data Revealed At Initial Site Inspection**

### **4.1 Outline Of Scharf Study**

This is a long-term open-label study of sodium oxybate (GHB) for patients in narcolepsy conducted under individual investigator IND # — (Martin Scharf, Ph.D., Cincinnati, Ohio).

143 patients were enrolled in this study which was conducted over a > 16-year period.

A full report of this study, with a cut-off date of 5/31/99, was included in the original NDA

### **4.2 Preliminary Results Of Inspection**

At the request of this Division, the Center's Division of Scientific Investigations carried out an inspection of the Scharf study. This inspection was requested after the Agency was informed that the Institutional Review Board for Dr Martin Scharf's sponsor-investigator IND # — 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 reportedly 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

#### **4.3 Divisional Recommendations For Addressing Deficiencies In Scharf Study**

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. The recommendations were in part based on review of safety data for this study that were contained in the original NDA

The recommendations were as follows:

- Obtaining as much information as possible about the status of the 80 patients in the Scharf study who did not enter the Orphan-sponsored 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

The sponsor was also asked to provide arguments as to whether, even in the absence of any data at all from the Scharf study, the NDA database might be considered adequate to support an orphan drug.

#### **5. Agency Questions About Orphan-Sponsored Clinical Trials**

The Division made a written request to the sponsor (on 3/7/01) for the following items of information related to the Integrated Clinical Trials database contained in the Integrated Summary of Safety of the original NDA.

**5.1 Exposure Table**

The following table in the Integrated Summary of Safety provides cumulative exposure data by last dose

**Table 3.8.14 Cumulative Duration of Exposure, by Last Dosage — Integrated Clinical Trials**

Duration of Exposure*	Total	Sodium Oxybate Last Dosage (g/d)				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	333	54	224	250	224	216
≥ 6 mo (180 d)	233 (88.0%)	5 (11.3%)	45 (20.2%)	65 (26.2%)	39 (17.5%)	50 (23.3%)
≥ 1 y (330 d)	75 (28.6%)	3 (3.2%)	6 (3.0%)	25 (10.6%)	13 (11.2%)	26 (22.0%)
≥ 2 y (672 d)	37 (9.3%)	1 (1.1%)	3 (1.1%)	12 (4.1%)	7 (6.0%)	14 (11.9%)

\* Duration was calculated based on a 28 day month. Duration of exposure was not calculated for the 3 patients who received placebo only.

Data Source: Section 16.1, Data Listing 4.

Could the sponsor provide a table that details cumulative exposure to all doses? An example of such a table is below.

Duration of Exposure	Total	Xyrem® dose g/day				
		≥3.0	≥4.5	≥6.0	≥7.5	≥9.0
Any Exposure	X	X	X	X	X	X
≥ 6 months	X	X	X	X	X	X
≥ 1 year	X	X	X	X	X	X
≥ 2 years	X	X	X	X	X	x

**5.2 Serious Adverse Events**

This question concerns Patient 0231 (Initials — ) participating in Study OMC-SXB-6. This patient developed nausea, vomiting, confusion and generalized weakness after taking GHB for 120 days, last in a dose of 9 g/day.

Was this patient hospitalized?

**5.3 Laboratory Data**

**5.3.1 Table Of Interest**

The following table is in the Integrated Summary of Safety.

**APPEARS THIS WAY  
 ON ORIGINAL**

**Table 8.8.21 Potentially Clinically Significant Changes in Laboratory Values from Baseline to Post-Baseline by Last Sodium Oxybate Oral Solution Dosage — Integrated Clinical Trials**

Laboratory Parameter (clinically significant range)		Last Sodium Oxybate Dosage (g/d)	Baseline	Post-Baseline	
Patient Number	Trial <sup>m</sup>			Study Day <sup>m</sup>	Result
<b>Hematology (N = 1)</b>					
<b>Hemoglobin (&gt; 3 g/dL decrease and absolute values &lt; 12.6 g/dL)</b>					
0914	ONC-OXB-3	4.5	16.6	393	11.5
<b>Clinical Chemistry (N = 26)</b>					
<b>ALT (SGPT) (≥ 100% increase and absolute values &gt; 75 IU/L)</b>					
0202	ONC-SXB-7	6.0	29	948	262
0214	ONC-SXB-6	9.0	50	877	362
0507	ONC-OXB-3	7.5	39	416	109
		7.5	39	710	86
	ONC-SXB-7	7.5	39	710	86
1610	ONC-OXB-3	9.0	26	395	248
1709	ONC-OXB-3	4.5	29	366	76
<b>AST (SGOT) (≥ 100% increase and absolute values &gt; 75 IU/L)</b>					
0214	ONC-SXB-6	9.0	43	477	188
1610	ONC-OXB-3	9.0	26	395	76
<b>Creatinine (≥ 66% increase and absolute values &gt; 1.5 mg/dL)</b>					
0127	ONC-OXB-3	9.0	0.8	241	1.4
0507	ONC-OXB-3	7.5	1	220	1.7
1901	ONC-OXB-3	3.0	1	720	1.9
		ONC-SXB-7	3.0	1	720
1905	ONC-OXB-3	6.0	0.6	650	1.7
		ONC-SXB-7	6.0	0.6	650
<b>Glucose (≥ 33% decrease and absolute values &lt; 70 mg/dL; ≥ 75% increase and absolute values &gt; 200 mg/dL)</b>					
0108	ONC-OXB-3	6.0	225	424	198
0215	ONC-OXB-3	9.0	104	638	217
0410	ONC-OXB-3	7.5	178	201	107
0804	ONC-OXB-3	4.5	66	273	52
0826	ONC-SXB-7	6.0	111	208	45
0850	ONC-SXB-6	6.0	68	210	56
0858	ONC-OXB-3	9.0	74	206	49

(continued)

BEST POSSIBLE COPY

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

**Table 8.8.21 Potentially Clinically Significant Changes in Laboratory Values from Baseline to Post-Baseline by Last Sodium Crybate Oral Solution Dosage — Integrated Clinical Trials**

Laboratory Parameter (clinically significant range)		Last Sodium Crybate Dosage (g/d)	Baseline	Post-Baseline	
Patient Number	Trial <sup>a</sup>			Study Day <sup>b</sup>	Result
<b>Clinical Chemistry (N = 26) (continued)</b>					
<b>Glucose (continued)</b>					
0808	DMC-GHB-3	3.0	62	102	54
0810	DMC-GHB-3	4.5	87	138	12
0814	DMC-GHB-3	4.5	101	205	34
		4.5	101	716	66
0815	DMC-GHB-2	4.5	101	716	66
		4.5	101	903	65
0815	DMC-GHB-2	3.0	67	33	24
0820	DMC-GHB-2	6.0	42	17	16
		6.0	42	331	15
0844	DMC-SXB-6	3.0	92	53	58
1505	DMC-GHB-3	6.0	168	278	286
		6.0	168	650	403
1706	DMC-GHB-3	6.0	144	650	49
		6.0	144	650	49
2134	DMC-SXB-6	6.0	107	176	68
2841	DMC-SXB-6	3.0	124	163	50
<b>Total bilirubin (2 100% increase and absolute values &gt; 1.5 mg/dL)</b>					
0202	DMC-GHB-3	9.0	1.1	2.2	2.5
0517	DMC-GHB-3	4.5	0.4	3.5	1.4
1610	DMC-GHB-3	6.0	0.5	1.5	2.1

<sup>a</sup> Trial during which post-baseline value was obtained.

<sup>b</sup> Day relative to start of treatment (trial duration).

Data Source: Appendix Section 16.1, Patient Data Listings 4, 12, and 33.

BEST POSSIBLE COPY

### 5.3.2 Questions About Table

- Patients 0810, 0815 and 0820 had exceptionally low post-baseline blood glucose estimations (ranging from 12 to 24 mg/dL).  
 Are these results accurate?  
 Is there an explanation for their apparent hypoglycemia?  
 What were their symptoms, if any, when hypoglycemic?
- A number of patients had hyperglycemia (mainly post-baseline). Were they known diabetics or are there any other explanations for their hyperglycemia?
- Patients 0202, 0517, 1610 and 1709 had post-baseline elevations in ALT and/or AST. To what extent were these patients followed up after these elevations were detected? Did these abnormalities resolve?

### 5.4 Additional Questions

- 10 patients are listed as having had “convulsions” (preferred term) in the Integrated Clinical Trials  
 Please identify these patients  
 What were the investigator terms used in these instances?  
 What additional information is available about these episodes?
- While patients participating in the Scharf trial had antinuclear antibody testing done, patients in the Integrated Clinical Trials did not.  
 To what extent were symptoms suggestive of drug-induced lupus looked for in the Integrated Clinical Trials?

### **5.5 Additional Request**

In addition to the above written request, the Division had also requested the sponsor to characterize the following in clinical trials sponsored by Orphan Medical, and in the Scharf Trial.

- Adverse events coded using the preferred term "confusion"
- Neuropsychiatric adverse events

### **6. Contents Of Submission**

The main sections of this submission cover the following areas

- The disposition of 80 patients enrolled in the Scharf trial who did not enter the OMC-SXB-7 trial
- Adverse events coded under the "reaction unevaluable" term in the Scharf trial
- Instances of urinary and fecal incontinence in the Scharf trial
- Adverse events coded under the term "confusion" in updated Integrated Clinical Trials only
- Neuropsychiatric adverse events in updated Integrated Clinical Trials only
- Adverse events coded as "convulsions" in Integrated Clinical Trials
- A narrative for Patient 0231 (initials: I—)
- Response to questions about patients in Integrated Clinical Trials with abnormalities of blood glucose and transaminases
- Symptoms suggestive of drug-induced lupus in Integrated Clinical Trials
- Patient exposure in Integrated Clinical Trials and Scharf study

The submission also includes the following SAS datasets

- The Scharf dataset provided in the original NDA submission
- An updated Integrated Summary of Safety dataset combining the datasets included in the original NDA submission with that furnished in the 120-Day Safety Update

An additional later submission dated 4/12/01, made in response to a specific request from the Division, contains characterizations of the following

- Adverse events coded under the term "confusion" in the Scharf study
- Neuropsychiatric adverse events in the Scharf study
- Adverse events coded as "convulsions" in the Scharf study

### **7. Disposition Of Scharf Study Patients Who Did Not Enter Study OMC-SXB-7**

#### **7.1 Background**

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

Study OMC-SXB-7 began early in 1999.

The sponsor was requested by the Division to characterize the 80 patients who entered the Scharf study, and did not subsequently enroll in Study OMC-SXB-7.

The Division was especially, but not solely, interested in

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

### **7.2 Sponsor's Methods**

The sponsor reports undertaking the following

- A review of source documents, Case Report Forms and data listings for all 80 patients who did not enter the OMC-SXB-7 study under treatment IND # \_\_\_\_\_
- Where necessary present day follow-up was sought in some patients to obtain further information such as the reason for withdrawal, the patient's medical history prior to enrollment, and whether adverse events continued after drug withdrawal. Such follow-up information was requested for 19 patients and collected by site personnel for 10 patients.

**Follow-up information was not felt to be needed for patients whose source documents indicated that their adverse events were unrelated to study drug, and the documentation of their reason for discontinuation was devoid of latent adverse event or severe disease**

- Based on the review a narrative was prepared for each of the 80 patients including the following: demography, GHB dosing information (date of commencement of treatment, date of last dose, last dose), previous medical history, concomitant medications, electrocardiogram history during study, treatment compliance, a summary of adverse event history and reason for discontinuation. Assessment of the extent of patient compliance with GHB dosing was based on daily diary recordings

Included in this submission are

- Individual narratives for all 80 patients
- Case Report Forms for all 80 patients: note that the Case Report Forms had been created earlier from source documents by an organization contracting with Orphan Medical, and were not created by the investigator
- Relevant supporting source documents

### **7.3 Disposition Of Scharf Study Patients Who Did Not Enter OMC-SXB-7.**

Of the 80 patients enrolled in the Scharf study who did not enter OMC-SXB-7

- 71 patients had discontinued from the Scharf trial prior to the cut-off date of 5/31/99
- 8 patients continued to participate in the Scharf trial
- 1 patient was a screening failure; this patient did not receive study drug.

For the 71 patients who discontinued from the Scharf trial, the reasons for discontinuation were in the categories outlined in the following table which I have copied from the submission.

Reason	Number of Patients
<b>Adverse Events</b>	<b>23</b>
(Death [coded as an SAE])	(10)
(Other adverse event)	(13)
<b>Non-compliance</b>	<b>24</b>
(Failure to provide diaries)	(22)
(Failure to follow dosing instructions)	(2)
<b>Cost of medication</b>	<b>13</b>
<b>Patient request/i.e., withdrawal of consent</b>	<b>5</b>
<b>Lack of efficacy</b>	<b>4</b>
<b>Protocol deviation</b>	<b>1</b>
<b>Other</b>	<b>1</b>
(Transfer to fibromyalgia study)	
<b>TOTAL</b>	<b>71*</b>

\* Of the remaining 9 unaccounted patients, 8 patients continued in the Scharf study after the 5/31/99 cutoff date and 1 was a screen failure patient who did not receive study drug.

#### 7.4 Discontinuations Due To Adverse Events

The 23 patients listed in the table in Section 7.3 as having discontinued due to adverse events consisted of

- 10 deaths
- 13 non-fatal adverse events

Tabular summaries of these patients are below

Also see Section 7.5.4 for further details about deaths and adverse event discontinuations.

##### 7.4.1 Deaths

The following table copied from the submission lists patients who died during the Scharf study. Those listed in the table were listed in the original NDA as having died during this study. An additional patient (#01-202) was listed in the original NDA but not in the following table; this patient died in a boating accident 4 months after discontinuing from the Scharf study.

APPEARS THIS WAY  
ON ORIGINAL

Patient No.	Pt Initials	Sex	Age at Trial Entry (yrs)	Date Started GHB Treatment	Date of Last Dose	Reason for Discontinuation	Comments
01-001	✓	M	46	11/17/1983	7/31/1985	Adverse Event - Patient Death	Metastatic colon carcinoma
01-009	✓	M	58	11/28/1984	11/30/1994	Adverse Event - Patient Death	Arteriosclerotic cardiovascular disease
01-014	✓	M	41	4/13/1987	10/31/1995	Adverse Event - Patient Death	Cardiac arrhythmia and severe coronary atherosclerosis
01-017	✓	M	62	2/7/1989	2/28/1995	Adverse Event - Patient Death	Cardiopulmonary arrest due to atherosclerotic disease
01-032	✓	F	64	7/25/1984	10/19/1994	Adverse Event - Patient Death	Lung Cancer
01-053	✓	M	47	3/29/1984	7/31/1994	Adverse Event - Patient Death	Myocardial infarction
01-200	✓	M	66	5/22/1985	9/30/1990	Adverse Event - Patient Death	Lung Cancer
01-232	✓	M	64	6/16/1987	3/13/1992	Adverse Event - Patient Death	Myocardial infarction secondary to bladder carcinoma
01-241	✓	M	55	2/27/1985	5/26/1989	Adverse Event - Patient Death	Small Cell Carcinoma of the lung
01-243	✓	M	58	6/20/1984	2/28/1989	Adverse Event - Patient Death	Myocardial infarction

The next table which I have copied from my safety review of the original NDA submission, and which includes Patient # 01-202, indicates the time that elapsed between drug discontinuation and death

Pt #	Age	Sex	Cause of Death	Prior History	Time on Drug (yrs)	Last Dose of Test Drug	Date of Death
001	51	M	Colon Carcinoma	None	5.7	7/31/89	9/89
009	68	M	Cardiovascular disease and diabetes	Cardiovascular disease and diabetes	10.0	11/30/94	1/2/95
014*	49	M	Cardiac arrhythmia	Coronary atherosclerosis	8.6	10/31/95	11/26/95
017*	68	M	Cardiopulmonary arrest	Atherosclerotic heart disease	6.1	2/28/95	3/6/95
032*	74	F	Lung cancer	Persistent cold symptoms	10.2	10/19/94	10/26/94
053	57	M	Heart attack	Hypertension, left ventricular hypertrophy	10.4	7/31/94	10/10/94
200*	71	M	Metastatic carcinoma	Lung cancer	5.4	9/30/90	1990
202	56	M	Boating accident	None	1.2	3/8/86	7/10/86
232*	69	M	Bladder carcinoma	Bladder carcinoma (1981)	4.8	3/13/92	3/14/92
241	59	M	Lung cancer (small cell)	None	3.9	1/31/89	5/26/89
243	63	M	Heart Attack	Left branch block, left ventricular dysfunction	4.7	3/1/89	7/89

\*Death occurred within 30 days of last dose of study drug

#### 7.4.2 Non-Fatal Adverse Events Leading To Discontinuation

The next table lists those who discontinued from the Scharf study on account of adverse events. The table is copied from the submission.

APPEARS THIS WAY  
 ON ORIGINAL