
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

PRELIMINARY CLINICAL SAFETY REVIEW OF NDA

Brand Name: Xyrem

Generic Name: Sodium Oxybate

Sponsor: Orphan Medical, Inc.

Indication: Narcolepsy

NDA Number: 21196

Original Receipt Date: 10/3/00

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Table of Contents

1. REVIEW SOURCES	7
1.1 MATERIALS FROM NDA.....	7
1.2 RELATED REVIEWS, CONSULTS.....	7
1.3 OTHER REVIEWS	7
2. BACKGROUND.....	8
2.1 INDICATION	8
2.2 IMPORTANT INFORMATION FROM PHARMACOLOGICALLY RELATED AGENTS.....	8
2.3 ADMINISTRATIVE HISTORY	8
2.4 PROPOSED LABELING	8
2.5 FOREIGN MARKETING	8
2.6 MISCELLANEOUS BACKGROUND INFORMATION.....	9
3. CHEMISTRY, MANUFACTURING AND CONTROLS.....	9
4. TOXICOLOGY.....	10
5. CLINICAL DATA SOURCES.....	10
5.1 SOURCES OF ALL DATA IN INTEGRATED SUMMARY OF SAFETY.....	10
5.1.1 Study Type.....	10
5.1.2 Number Of Unique Narcoleptic Patients And Healthy Subjects In Integrated Summary Of Safety	11
5.1.3 Demographics.....	12
5.1.4 Extent of Exposures.....	13
5.2 CUT-OFF DATE FOR DATA IN INTEGRATED SUMMARY OF SAFETY	14
5.3 PRIMARY DATA SOURCES	14
5.3.1 Efficacy And Long-Term Safety Studies.....	14
5.3.2 Pharmacokinetic Studies.....	15
5.4 SECONDARY DATA SOURCES	15
5.5 OTHER DATA SOURCES	15
5.6 ADEQUACY OF HUMAN EXPERIENCE.....	16
5.7 DATA QUALITY AND COMPLETENESS.....	16
6. HUMAN PHARMACOKINETICS	16
7. TABULAR SUMMARY OF KEY EFFICACY STUDIES.....	17
7.1 STUDY OMC-GHB-2	17
7.2 SCRIMA STUDY.....	17
7.3 LAMMERS STUDY	18
7.4 STUDY OMC-SXB-21.....	18
8. INTEGRATED REVIEW OF SAFETY	18
8.1 BACKGROUND AND METHODOLOGY	18
8.2 DEATHS.....	19
8.2.1 Tabular Summary Of Deaths	19
8.2.2 Conclusions Regarding Deaths.....	19
8.3 SERIOUS ADVERSE EVENTS.....	19
8.3.1 Serious Adverse Events In Integrated Clinical Trials.....	20
8.3.2 Serious Adverse Events In Scharf Study.....	23
8.4 DROPOUTS AND "OTHER SIGNIFICANT ADVERSE EVENTS"	25
8.4.1 Adverse Event Discontinuations In Integrated Clinical Trials	26
8.4.2 Adverse Event Discontinuations In Scharf Trial.....	31

8.4.3	<i>Adverse Event Discontinuations In Integrated Pharmacokinetic Trials</i>	35
8.5	ADVERSE EVENTS INCIDENCE TABLES.....	35
8.5.1	<i>Approach to Eliciting Adverse Events</i>	35
8.5.2	<i>Adverse Events Categorization and Preferred Terms</i>	36
8.5.3	<i>Key Adverse Events Tables</i>	36
8.5.4	<i>Common and Drug-Related Side Effects</i>	41
8.5.5	<i>Additional Analyses and Explorations</i>	42
8.6	LABORATORY FINDINGS.....	56
8.6.1	<i>Extent of Laboratory Testing During Development</i>	56
8.6.2	<i>Selection of Studies for Overall Drug-Control Comparisons And Other Analyses</i>	57
8.6.3	<i>Standard Analyses and Explorations of Laboratory Data</i>	57
8.7	VITAL SIGNS.....	64
8.7.1	<i>Extent of Vital Sign Testing During Development</i>	64
8.7.2	<i>Selection of Studies for Overall Drug-Control Comparisons And Other Analyses</i>	65
8.7.3	<i>Standard Analyses and Explorations of Vital Sign Data</i>	65
8.8	ECG.....	67
8.8.1	<i>Extent of Electrocardiogram Testing During Development</i>	67
8.8.2	<i>Selection of Studies for Overall Drug-Control Comparisons And Other Analyses</i>	67
8.8.3	<i>Standard Analyses and Explorations of Electrocardiogram Data</i>	67
8.9	WITHDRAWAL PHENOMENON AND ABUSE POTENTIAL.....	70
8.9.1	<i>Background</i>	70
8.9.2	<i>Purposes For Which GHB Is Misused Or Abused</i>	70
8.9.3	<i>Clinical Psychological And Physical Dependence In Humans</i>	70
8.9.4	<i>Rebound Symptoms With GHB Withdrawal</i>	71
8.9.5	<i>Extent Of GHB Abuse In The United States</i>	72
8.9.6	<i>Pre-Clinical Studies Of Drug Abuse Potential</i>	72
8.10	HUMAN REPRODUCTION DATA.....	72
8.11	OVERDOSE.....	73
8.11.1	<i>Background</i>	73
8.11.2	<i>Clinical Presentation</i>	73
8.11.3	<i>Treatment</i>	74
9.	STUDY OMC-SXB-20	74
9.1	OBJECTIVES.....	74
9.1.1	<i>Primary</i>	74
9.1.2	<i>Secondary</i>	74
9.2	DESIGN/SUMMARY OF INVESTIGATIONAL PLAN.....	75
9.2.1	<i>Phase I</i>	75
9.2.2	<i>Phase II</i>	75
9.3	DURATION.....	75
9.4	SAMPLE SIZE.....	75
9.5	KEY INCLUSION CRITERIA.....	75
9.6	KEY EXCLUSION CRITERIA.....	76
9.7	DOSAGE.....	76
9.8	OUTCOME MEASURES.....	76
9.8.1	<i>Primary Efficacy Measures</i>	76
9.8.2	<i>Secondary Efficacy Measures</i>	77
9.8.3	<i>Safety Measures</i>	77
9.9	ANALYSIS PLAN.....	77
9.10	RESULTS.....	78
9.10.1	<i>Patient Disposition</i>	78
9.10.2	<i>Baseline And Demographic Characteristics</i>	78
9.10.3	<i>Tricyclic Antidepressants, Selective Serotonin Re-Uptake Inhibitors And Hypnotics At Baseline</i> 78	
9.10.4	<i>Protocol Deviations</i>	78
9.10.5	<i>Treatment Compliance</i>	79

9.10.6	Extent Of Exposure	79
9.10.7	Efficacy Results	79
9.10.8	Safety Results	79
9.11	REVIEWER'S COMMENTS	81
10.	SAFETY DATA FROM STUDY OMC-SXB-21	81
10.1	BRIEF SUMMARY OF STUDY PROTOCOL	81
10.1.1	Objective	81
10.1.2	Design	81
10.1.3	Duration	82
10.1.4	Sample Size	82
10.1.5	Key Inclusion Criteria	82
10.1.6	Key Exclusion Criteria	83
10.1.7	Concomitant Medications	83
10.1.8	Dosage	83
10.1.9	Schedule	83
10.1.10	Outcome Measures	84
10.1.11	Analysis Plan	84
10.2	PROTOCOL AMENDMENTS	85
10.3	ACTUAL ANALYSES PERFORMED	85
10.4	EFFICACY RESULTS	85
10.4.1	Patient Disposition	85
10.4.2	Protocol Deviations	86
10.4.3	Medication Compliance	86
10.4.4	Baseline And Other Demographic Characteristics	87
10.4.5	Primary Efficacy Analysis	87
10.4.6	Analysis Of Secondary Efficacy Measures	89
10.5	SAFETY RESULTS	89
10.5.1	Exposure	89
10.5.2	Deaths, Serious Adverse Events And Adverse Event Discontinuations	90
10.5.3	Other Adverse Events	90
10.5.4	Laboratory Data	92
10.5.5	Vital Signs	93
10.6	SPONSOR'S CONCLUSIONS REGARDING SAFETY	93
10.7	REVIEWER'S COMMENTS	93
11.	KEY INFORMATION FROM INTEGRATED SUMMARY OF SAFETY AND OMC-SXB-21	
SAFETY DATA	94	
11.1	ALL ADVERSE EVENTS	94
11.2	DEATHS	94
11.3	SERIOUS ADVERSE EVENTS	94
11.4	ADVERSE EVENT DISCONTINUATIONS	95
11.5	LABORATORY DATA	95
11.6	ELECTROCARDIOGRAMS	96
11.7	VITAL SIGNS	96
11.8	WITHDRAWAL PHENOMENA	96
12.	LITERATURE REVIEW	96
12.1	PUBLISHED STUDIES CONDUCTED IN HEALTHY INDIVIDUALS	96
12.2	PUBLISHED STUDIES CONDUCTED FOR SPECIFIC MEDICAL INDICATIONS	97
13.	120-DAY SAFETY UPDATE	98
13.1	CONTENTS	98
13.2	OUTLINE OF PROTOCOL FOR OMC-SXB-7	99
13.2.1	Objectives	99
13.2.2	Design	99

13.2.3	<i>Inclusion Criteria</i>	99
13.2.4	<i>Exclusion Criteria</i>	100
13.2.5	<i>Sample Size</i>	100
13.2.6	<i>Duration</i>	100
13.2.7	<i>Dosage</i>	100
13.2.8	<i>Concomitant Medication</i>	100
13.2.9	<i>Schedule</i>	101
13.2.10	<i>Statistical Considerations</i>	101
13.2.11	<i>Safety Monitoring</i>	101
13.3	PROTOCOL AMENDMENTS.....	101
13.4	PATIENT DISPOSITION.....	101
13.5	DEMOGRAPHICS.....	101
13.6	DOSAGE.....	102
13.7	PATIENT EXPOSURE.....	102
13.8	SAFETY RESULTS.....	103
13.8.1	<i>All Adverse Events</i>	103
13.8.2	<i>Adverse Event Tables</i>	103
13.9	DEATHS.....	104
13.10	SERIOUS ADVERSE EVENTS.....	105
13.10.1	<i>Patient # 0214</i>	105
13.10.2	<i>Patient # 0232</i>	106
13.10.3	<i>Patient # 0931</i>	106
13.10.4	<i>Patient # 1131</i>	106
13.10.5	<i>Patient # 14043</i>	106
13.10.6	<i>Patient # 2030</i>	107
13.11	ADVERSE EVENT DISCONTINUATIONS.....	107
13.11.1	<i>Patient 1305</i>	107
13.12	REVIEWER'S COMMENTS.....	108
14.	RISK MANAGEMENT PROGRAM.....	108
14.1	STRUCTURE.....	108
14.1.1	<i>Closed-Loop Distribution System</i>	108
14.1.2	<i>Drug Product Kit</i>	110
14.1.3	<i>Xyrem® Physician Success Program</i>	111
14.1.4	<i>Xyrem® Patient Success Program</i>	113
14.2	OPDRA COMMENTS.....	114
14.3	COMMENTS OF CONTROLLED SUBSTANCES STAFF.....	115
14.4	ADDITIONAL RISK MANAGEMENT RECOMMENDATIONS.....	115
15.	LABELING REVIEW.....	115
16.	OVERALL COMMENTS.....	115
16.1	CLINICAL SAFETY.....	115
16.2	CLINICAL EFFICACY.....	116
16.3	WITHDRAWAL PHENOMENA AND ABUSE POTENTIAL.....	116
16.4	RISK MANAGEMENT PROGRAM.....	117
16.5	ADDITIONAL COMMENTS.....	117
17.	STUDY SITE INSPECTIONS.....	117
18.	FINANCIAL DISCLOSURE CERTIFICATION.....	118
18.1	COMPONENTS OF CERTIFICATION.....	118
18.1.1	<i>Certification Pertinent To Dr Lawrence Scrima</i>	118
18.1.2	<i>Certification Pertinent To Other Investigators</i>	118
18.2	REVIEWER'S COMMENT.....	119

19. MAJOR AMENDMENT	119
20. ADDITIONAL COMMENTS BASED ON REVIEW OF MAJOR AMENDMENT	119
21. CONCLUSIONS.....	121
22. RECOMMENDATIONS	121

1. Review Sources

This submission contains an original New Drug Application for Xyrem® (sodium oxybate; γ -hydroxybutyrate) oral solution. The application is dated 9/30/2000 and was received by the Center for Drug Evaluation and Research of this Agency on 10/3/00.

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

Xyrem® has been developed by Orphan Medical, Inc. for the treatment of narcolepsy under IND # 49641 and Treatment IND # 57271. Data obtained from individual sponsor-investigator INDs #s 21654 (M. Scharf) and 19911 (L. Scrima) have also been used in support of this application.

Note that this is a preliminary, and not final review. Further editing of this review is possible.

1.1 Materials from NDA

In reviewing this application I have read the following volumes of the NDA submission of 9/30/00. These volumes have been read almost entirely in electronic format.

Volumes 1, 5, 25-34, 36-63, 100-104 and 114-122

I have also reviewed the following:

- A separate submission dated 12/16/00 containing the final reports for several clinical trials: OMC-SXB-16, OMC-SXB-20 and OMC-SXB-21
- The sponsor's responses to a number of requests for information from this reviewer
- A 120-Day Safety Update
- Risk management materials, comprising physician and patient information materials, supplied by the sponsor

1.2 Related Reviews, Consults

I have utilized the many reviews that I have done, since 1997, of submissions under IND # 49641 and Treatment IND # 57271 for details about this drug.

Consults that were obtained from other Divisions within the Agency and have been reviewed by me include reports from

- The Controlled Substances Staff
- The Office of Post-Marketing Drug Risk Assessment

1.3 Other Reviews

I have reviewed publications submitted by the sponsor as part of the NDA and the following recently published article:

Zvosec DL et al. Adverse Events, Including Death, Associated With The Use Of 1,4-Butanediol. N Engl J Med 2001;344:87-94

2. Background

2.1 Indication

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.”

Narcolepsy is a chronic neurological disorder characterized by excessive daytime sleepiness, disturbed nocturnal sleep, cataplexy, sleep paralysis and hypnagogic hallucinations. The prevalence of this condition in the United States, as per a publication cited by the sponsor, is between 0.02% and 0.07%. According to the sponsor, current treatments for this condition are limited in effectiveness and have frequent undesirable adverse events.

2.2 Important Information from pharmacologically related agents

None.

2.3 Administrative History

This drug has been developed by Orphan Medical, Inc. for the treatment of narcolepsy under IND # 49641 and Treatment IND # 57271. Data obtained from individual sponsor-investigator INDs #s 21654 (M. Scharf) and 19911 (L. Scrima) have also been used in support of this application.

This drug product has been the subject of numerous meeting and items of correspondence involving the following: the current sponsor; this Division; the Controlled Substances Staff; the Division of Anesthetic, Critical Care and Addiction Drug Products; the Division of Orphan Drug Products; and other bodies. These contacts are too numerous to summarize in this review

2.4 Proposed Labeling

The proposed labeling for this drug is reviewed separately

2.5 Foreign Marketing

Currently, this drug product has not been marketed in any country. However, according to the sponsor

- Gamma-OH® an injectable oxybate preparation is marketed as an adjuvant anesthetic and sedative in France
- Somsanit® an injectable oxybate preparation is marketed as a sedative in Germany
- Alcover® an oxybate containing oral solution (175 mg/mL) is marketed in Italy for the treatment of alcohol withdrawal
- A powdered form of GHB is sold by Biogenesis Laboratories of South Africa via the Internet, but **NOT** in the following countries: Australia, New Zealand, Norway, South Africa and the United States

For many years GHB was distributed in this country as a health food product under a variety of trade names. However, in 1990 it was removed from the market after a number of reports of adverse reactions.

2.6 Miscellaneous Background Information

In the popular media there have been many reports over the last few years of instances of overdose with illegally-manufactured GHB. A number of anecdotal single case reports/case series of a similar nature have also been published in the medical literature. There have also been similar reports linked to the use of related compounds such as gammabutyrolactone and 1,4-butanediol.

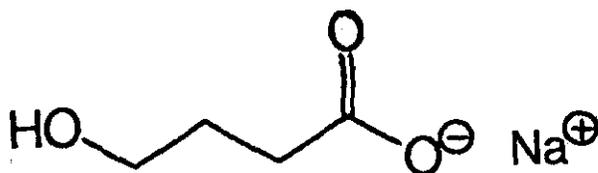
According to the sponsor, GHB users in this country derive the drug from the following sources

- Purchase from illegal vendors, including those selling the drug over the Internet
- By home manufacture: both recipes and starting materials are easily available

Public Law 106-172 (passed by the United State Congress) has allowed for the designation of GHB as a Schedule I agent, with exemption from the security requirements for the GHB drug product studied under an FDA-approved IND. Upon marketing approval from the FDA being received, the GHB drug product would become a Schedule III agent with Schedule I penalties for illicit use. All other GHB containing products would remain Schedule I agents

3. Chemistry, Manufacturing and Controls

Gamma-hydroxybutyrate is a short chain fatty acid normally found in a variety of mammalian tissues, including the human brain, where it is a metabolite of gamma-aminobutyric acid. The chemical structure of the sodium salt of this compound is as depicted below:



The drug product is a 500 mg/mL solution. It is composed of sodium oxybate, purified water, DL-malic acid, and sodium hydroxide.

The drug product is supplied in a 240 mL PET amber bottle, sealed with a child-resistant cap. Additional items supplied with the bottle include

- A Press-In-Bottle Adapter (PIBA Well)
- A dispenser (Exacta-Med®)
- 2 child-resistant dosing cups

The PIBA Well will be placed into the solution by the pharmacist dispensing the drug. The drug product, PIBA Well, dispenser and dosing cups will be packaged in a carton when supplied to the patient

4. Toxicology

Salient items that I have derived from a summary provided by the sponsor are below:

- The sponsor did not conduct any acute toxicity studies but has cited literature reports of such studies instead. The sponsor has conducted repeated-dose toxicity studies in rats and dogs, reproductive toxicity studies in rats and rabbits, and mutagenicity studies. A 104-week carcinogenicity study in rats is ongoing.
- Effects of GHB in toxicology studies included reduced activity, prostration, ataxia, emesis, reduced food consumption and weight loss/weight gain. No evidence of organ toxicity was seen based on laboratory tests, and gross as well as microscopic pathological examination.
- GHB had no evidence of reproductive toxicity or mutagenicity
- In regard to carcinogenicity
 - The carcinogenicity of gammabutyrolactone (GBL), a precursor of GHB, has been studied under the National Toxicology Program. According to the sponsor "equivocal" evidence of carcinogenicity was demonstrated in male, but not female, mice based on increased adrenal medulla hyperplasia and increases in benign and malignant pheochromocytomas at a dose of 262 mg/kg/day
 - In bridging studies with GBL in the same strain of mice studied under the National Toxicology Program the sponsor has measured plasma levels of both GHB and GBL. Based on these plasma levels the sponsor has concluded that systemic exposure to GHB is similar whether GBL or GHB is administered, and that the National Toxicology Program studies are therefore valid as an appropriate evaluation of GHB. These studies were discussed with the Agency
 - A 104-week rat carcinogenicity study is currently ongoing

5. Clinical Data Sources

5.1 Sources Of All Data In Integrated Summary of Safety

5.1.1 Study Type

A total of 15 clinical trials are included in the Integrated Summary of Safety. The sponsor has grouped these studies into 4 separate pools which are outlined below. Safety data for each of these pools are described separately by the sponsor. Note that the sponsor has not included controlled clinical trials under a separate heading

5.1.1.1 Integrated Clinical Trials

A total of 402 patients participated in these trials; some of these patients participated in more than one trial. 3/402 patients received placebo only.

Study #	Design	Number of Patients	Duration
OMC-GHB-2	Randomized, double-blind, placebo-controlled, parallel-arm	136 patients	4 weeks

OMC-GHB-3	Open-label, uncontrolled, extension study	118 patients	Up to 24 months
OMC-SXB-6	Open-label uncontrolled study	185 patients	6 months
OMC-SXB-7	Open-label uncontrolled study	145 patients	Up to 24 months
Scrima	Randomized, double-blind, placebo-controlled, cross-over	20 patients	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 naïve patients (except for a single patient previously in OMC-GHB-2 and OMC-GHB-3)
OMC-SXB-7	Extension to OMC-GHB-3 (52 patients) OMC-SXB-6 (30 patients) Scharf Study (63 patients) The numbers in parentheses in this cell refer to the number of patients entering OMC-SXB-7 from each study

5.1.1.2 Lammers Trial

25 patients participated in this randomized, double-blind, placebo-controlled, cross-over trial of 4 weeks' duration (GHB and placebo were each used for 4 weeks).

5.1.1.3 Long-Term Clinical Trial (Scharf)

This long-term open-label study involved 143 patients and has lasted about 16 years

5.1.1.4 Integrated Pharmacokinetic Trials

A total of 144 subjects/patients have been enrolled in these trials which 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 (total of 19 narcoleptic patients) all were healthy volunteers (total of 125 subjects)

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

*The 6 narcoleptic patients participating in this study also enrolled in the Scharf study

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

5.1.2 Number Of Unique Narcoleptic Patients And Healthy Subjects In Integrated Summary Of Safety

I had obtained a clarification from the sponsor regarding the numbers of unique patients and healthy subjects in the Integrated Summary of Safety. The details are below

5.1.2.1 Unique Narcoleptic Patients

The number of unique narcoleptic patients participating in clinical trials of GHB is listed in the table below

Study Grouping	Number of Patients
OMC-GHB-2/OMC-GHB-3	133
OMC-SXB-6/OMC-SXB-7	183
Scrima	20
Lammers Trial	25
Scharf Trial	143
TOTAL	504

NOTE: The narcoleptic patients who participated in the pharmacokinetic trials OMC-GHB-4 (6 patients) and OMC-SXB-10 (13 patients) also participated in the Scharf and OMC-SXB-6 trials. These patients are counted in the above table under the Scharf and OMC-SXB-6 trials

5.1.2.2 Unique Healthy Subjects

The number of unique healthy subjects participating in clinical trials of GHB are in the following table. All these trials were pharmacokinetic.

Study #	Number of subjects/patients
OMC-SXB-8	36
OMC-SXB-9	13
OMC-SXB-11	36
OMC-SXB-12	15
OMC-SXB-14	12
OMC-SXB-17	13
TOTAL	125

5.1.3 Demographics

Demographics are summarized according to the study pools used by the sponsor in this summary

5.1.3.1 Integrated Clinical Trials

Demographics for all Xyrem®-treated patients are summarized below. The table is derived from one supplied by the sponsor

Variable	Number	Mean	Standard Deviation	Range
Age (years)	402	46.1	15.22	13.9-81.1
Weight (kg)	397	83.9	20.22	47.0-175.0
Height (cm)	396	170.3	10.33	129.0-206.0
Gender	402	Males 43% /Females 57%		

Demographics for the 3 patients treated exclusively with placebo are summarized below

Variable	Number	Mean	Standard Deviation	Range
Age (years)	3	37.5	14.43	26.1-53.7
Weight (kg)	3	90.0	15.72	76.0-107.0
Height (cm)	3	168.3	4.62	163.0-171.0
Gender	3	Females 100%		

5.1.3.2 Lammers Trial

The following table illustrates the demographics for all 25 patients in the study. The table is derived from one supplied by the sponsor

Variable	Number	Mean	Standard Deviation	Range
Age (years)	25	40	14	16-65
Weight (kg)	24	79	10	63-92
Height (cm)	24	175	7	157-187

Gender	25	Males 52% /Females 48%
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5.1.3.3 Scharf Trial

The following table illustrates the demographics for all 143 patients in this study. The table is derived from one supplied by the sponsor

Variable	Number	Mean	Standard Deviation	Range
Age (years)	143	45.3	14.5	13.0-75.0
Gender	143	Males 55.9% /Females 44.1%		
Race	143	Caucasian 88.8%/Afro-American 1.4%/ Unavailable 9.8%		

5.1.3.4 Integrated Pharmacokinetic Trials

The following table illustrates the demographics for all 144 subjects in these 8 studies. The table is derived from one supplied by the sponsor

Variable	Number	Mean	Standard Deviation	Range
Age (years)	144	32.3	12.24	18.0-62.0
Weight (kg)	144	73.0	11.28	50.8-114.0
Height (cm)	138	169.3	7.92	152.4-190.5
Gender	144	Males 40% /Females 60%		

5.1.4 Extent of Exposures

Total exposure and exposure by study pool (Integrated Clinical Trials, Lammers Trial, Scharf Trial and Integrated Pharmacokinetic Trials) is described below.

In all trials listed in the Integrated Summary of Safety, the number of patients and healthy subjects exposed to GHB for specified periods is illustrated in the table below

Period of Exposure to Xyrem	Number of Patients with Narcolepsy	Number of Healthy Controls
Any Exposure	504	125
≥ 6 months	354	0
≥ 1 year	179	0
≥ 2 years	127	0
≥ 5 years	79	0
≥ 10 years	46	0

Total exposure in patient-years in each of the study pools (except the pharmacokinetic trials) is listed in the next table

Pool	Exposure to Xyrem® (Patient-Years)
Integrated Clinical Trials	266.83
Lammers Trial	2.08
Scharf Trial	996.15
Total	1265.06

5.1.4.1 Integrated Clinical Trials

The cumulative duration of exposure by last dose for this group of trials is illustrated in the following table. The duration of exposure was calculated based on the 28-day month. Note that the “Any Exposure” row lists all patients who have been exposed to specific doses at any time, not just as the last dose.

Duration of Exposure	Total	Xyrem® last dose g/day				
		3.0	4.5	6.0	7.5	9.0
Any Exposure	399	94	266	290	116	118
≥ 6 months	233	5	43	88	37	60
≥ 1 year	75	3	8	25	13	26
≥ 2 years	37	1	3	12	7	14

5.1.4.2 *Lammers Trial*

25 patients were exposed to a mean Xyrem® dose of 4.75 g/day (range 3.78 to 5.52 g/day) for 28 days

5.1.4.3 *Scharf Trial*

The cumulative duration by the Xyrem® dose administered for the longest duration is in the following table

Duration of Exposure	Total	Longest-used dose of Xyrem® (g/day)				
		3.0	4.5	6.0	7.5	9.0
Any Exposure	143	5	49	62	18	9
> 6 months	121	3	41	54	14	9
> 1 year	104	2	37	45	12	8
> 2 years	90	1	32	38	12	7
> 5 years	74	1	27	30	10	6
> 10 years	46	1	12	23	7	3

Note that 63 patients in the Scharf trial were subsequently also enrolled in OMC-SXB-7

5.1.4.4 *Integrated Pharmacokinetic Trials*

Exposure data for these studies was not calculated as these were all single dose studies. As noted earlier 144 patients/subjects were exposed to Xyrem® in these studies.

The dose(s) used in each these single-dose studies is indicated in the following table

Study #	GHB Total Dose	Number of subjects/patients
OMC-GHB-4	6.0 g	6*
OMC-SXB-8	4.5 g	36
OMC-SXB-9	4.5 g or 9.0 g	13
OMC-SXB-10	4.5 g	13**
OMC-SXB-11	4.5 g	36
OMC-SXB-12	3.0 g	15
OMC-SXB-14	4.5 g	12
OMC-SXB-17	4.5 g	13

*Narcoleptic patients

Note that the total dose of GHB was administered either as a true single-dose or 2 divided doses 4 hours apart

5.2 **Cut-Off Date For Data In Integrated Summary Of Safety**

- The only ongoing trial in the Integrated Summary Of Safety is OMC-SXB-7. The cut-off date for data in this trial is 12/31/99
- All other clinical trials in the Integrated Summary Of Safety are complete as are the safety data submitted with the NDA.

5.3 **Primary Data Sources**

These are studies conducted by Orphan Medical, Inc. They include the following

5.3.1 *Efficacy And Long-Term Safety Studies*

These are listed in the following table

Study #	Design	Number of Patients	Duration
OMC-GHB-2	Randomized, double-blind, placebo-controlled, parallel-arm	136 patients	4 weeks
OMC-GHB-3	Open-label, uncontrolled,	118 patients	Up to 24 months

Study #	Design	Number of Patients	Duration
	extension study		
OMC-SXB-6	Open-label uncontrolled study	185 patients	6 months
OMC-SXB-7	Open-label uncontrolled study	145 patients	Up to 24 months

5.3.2 Pharmacokinetic Studies

These are listed in the following table

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

5.4 Secondary Data Sources

These are studies that have not been conducted by the sponsor and consist of efficacy and long-term safety studies only.

Study #	Design	Number of Patients	Duration
Scrima	Randomized, double-blind, placebo-controlled, cross-over	20 patients	4 weeks*
Lammers	Randomized, double-blind, placebo-controlled, cross-over	25 patients	4 weeks*
Scharf	Open-label extension study	143 patients	< 16 years

*GHB and placebo were each used for 4 weeks

5.5 Other Data Sources

The sponsor has also used 3 published reports of open-label studies of Xyrem® in narcolepsy to support the efficacy and safety of Xyrem®.

The outlines of these studies, including adverse event data, are summarized below. As these were open-label, uncontrolled studies, I have not summarized the efficacy data that was derived from them

Study	Scharf (1985)*	Broughton (1979)**	Broughton (1980)***
Design	Open-label, uncontrolled study	Open-label, uncontrolled study	Open-label, uncontrolled study
Maximum duration of treatment	30 weeks	20 months	7-10 days
Number of patients	30	16	14
Total nightly dose of Xyrem®	5-7 g	50 mg/kg	3.75 to 6.25 g
Adverse events	Protracted sleep paralysis (3 patients) Enuresis (1 patient) Increased sexual drive (1 patient)	"Hangover", urinary urgency, enuresis, dream-like confusional state prior to sleeping, abdominal pain, muscular weakness, left arm dysesthesia	"No serious toxic side-effects"

*Scharf MB et al. The effects and effectiveness of gamma-hydroxybutyrate in patients with narcolepsy. J Clin Psychiatry. 1985;:222-5. (Note that the patients reported in this publication are a subset of those included in the interim Scharf study report under this IND).

**Broughton R, Mamelak M. The treatment of narcolepsy-cataplexy with nocturnal gamma-hydroxybutyrate. Can J Neurol Sci. 1979;6:1-6.

***Broughton R, Mamelak M. Effects of nocturnal gamma-hydroxybutyrate on sleep/waking patterns in narcolepsy-cataplexy. Can J Neurol Sci. 1980;7:23-31.

5.6 Adequacy of Human Experience

- Xyrem® has been designated as an orphan drug product
- Based on the total number of narcoleptic patients exposed to Xyrem® in clinical trials derived from primary and secondary data sources (see Sections 5.3 and 5.4) and their duration of exposure (see Section 5.1.4)
 - The total number of unique patients exposed to this drug is below ICH guidelines
 - On the other hand the number of unique patients exposed to GHB for 6 month and 1 year periods is sufficient to meet these guidelines
- A separate review of the efficacy of Xyrem® indicates that the effective dose may range from 4.5 to 9 g/day, with the most conclusive evidence for efficacy at 9 g/day. The number of unique narcoleptic patients exposed to that dose range, and the duration for which they were exposed to that dose, is difficult to determine from the submission especially since a number of patients participated in more than one study grouping (e.g., Integrated Clinical Trials and Scharf study) and were exposed to several different doses
- The extent of human experience with this drug would not be considered adequate under ordinary circumstances, as per the ICH guidelines. However given that Xyrem® has been designated as an orphan drug, and that the narcoleptic population in this country is relatively small, a smaller safety database may be acceptable.

5.7 Data Quality and Completeness

The quality of the data available in this submission appears to be quite variable. The extent to which monitoring and data collection were systematic and accurate in the Secondary Data Source (see Section 5.4) studies is unclear.

6. Human Pharmacokinetics

The following pharmacokinetic summary is based on a summary supplied by the sponsor in this submission.

Orally administered GHB is rapidly absorbed with a t_{max} of 30 - 75 minutes and to a similar degree in narcoleptic and other patient populations; absorption characteristics are similar in males and females and are not altered by chronic dosing; t_{max} is delayed, at higher doses (suggesting a limited absorption capacity) and by the administration of food. C_{max} and $AUC_{0-\infty}$ are reduced by the administration of the drug with food. The absolute bioavailability of the drug is < 30%.

The apparent volume of distribution divided by absolute bioavailability (V_d/F) ranges between 190 and 384 mL/kg. Inter-subject variability in the volume of distribution is high as indicated by the coefficient of variation which ranges between 16% and 84%. The drug readily crosses the placental and blood-brain barriers. Protein binding has been estimated at about 1%.

Less than 5% of an oral dose of GHB is excreted unchanged in the urine. Based on a review of the scientific literature the sponsor states that the end-product of metabolism, regardless of biotransformation pathway, is carbon dioxide. 2 main biotransformation pathways have been identified:

- A β -oxidation pathway

- A pathway involving the entry of succinic acid into the tricarboxylic acid cycle, through the initial formation of succinic semialdehyde

First-pass metabolism occurs with orally administered GHB, probably through the β -oxidation pathway, resulting in an oral bioavailability of < 30%. Intermediate compounds in the metabolic pathways for GHB do not appear to be pharmacologically active

The pharmacokinetics of GHB are non-linear. Plasma clearance is dose-dependent across the therapeutic range: following a total dose of 9 g (2 doses of 4.5 g each administered 4 hours apart) the apparent elimination half-life of GHB was 0.83 hours, which was approximately 40% longer than the mean elimination half-life following a total dose of 4.5 g (2 doses of 2.25 g each administered 4 hours apart). Chronic dosing with GHB did not alter its pharmacokinetics in a clinically significant manner: treatment with this drug for 8 weeks resulted in 13% and 16% increases in AUC_{∞} and C_{max} , respectively; these increases were not considered clinically significant.

There are no significant gender differences in the pharmacokinetics of GHB. Neither are there significant differences in pharmacokinetics between healthy subjects and narcoleptic patients, and between healthy patients and those who are alcohol-dependent. Oral clearance of GHB is altered in the presence of cirrhosis with or without ascites. Renal disease is not expected to alter the pharmacokinetics of GHB; studies in that setting have therefore not been carried out.

Formal studies indicated that GHB had no interactions with protryptiline, zolpidem and modafinil. In-vitro pooled human liver microsomal studies showed that GHB did not significantly inhibit or enhance the activities of human CYP450 isoenzymes.

7. Tabular Summary Of Key Efficacy Studies

4 studies have been used in this submission to support the efficacy of Xyrem® in the treatment of narcolepsy. These are summarized in tabular form below. For full details please refer to the NDA Efficacy Review

7.1 Study OMC-GHB-2

Study #	OMC-GHB-02 Orphan Medical			
Design	Randomized, double-blind, placebo-controlled, parallel-arm			
Duration	4 weeks			
Dosage	9 g	6 g	3 g	Placebo
Number randomized	35	33	34	34
Number completed	28	29	30	33
Main inclusion criteria	Narcolepsy for at least 6 months with both excessive daytime sleepiness and cataplexy			
Primary outcome measures	Total number of cataplexy attacks			
Main efficacy analysis (statistically significant results)	9 g dose superior to placebo, based on ANCOVA (p = 0.0008)			

7.2 Scrima Study

Study #	Scrima	
Design	Randomized, double-blind, placebo-controlled, cross-over	
Duration	4 weeks	
Dosage	50 mg/kg/day	Placebo
Number randomized	20	20
Number completed		
Main inclusion criteria	Excessive daytime sleepiness, a history of cataplexy with ≥ 10 cataplexy attacks over the 2 week baseline period and ≥ 2 REM onsets and a sleepiness index of ≥ 75 on the a multiple sleep latency test	
Primary outcome measures	Total number of cataplexy attacks per day	
Main efficacy analysis (statistically significant results)	GHB superior to placebo (p = 0.013)	

7.3 Lammers Study

Study #	N -1 (R 55 667 082) Lammers et al	
Design	Randomized, double-blind, placebo-controlled, cross-over	
Duration	4 weeks	
Dosage	4.75 g *	Placebo
Number randomized	25	25
Number completed	25 **	25 **
Main inclusion criteria	Excessive daytime sleepiness and at least one of the following: cataplexy, hypnagogic hallucinations, and sleep paralysis	
Primary outcome measures	Total number of cataplexy attacks Global therapeutic impression (patient) Global clinical impression (clinician)	
Main efficacy analysis (statistically significant results)	GHB superior to placebo on first two of above measures, numbered as above p = 0.002 (ANCOVA)*** p = 0.001 (McNemar's test) Not measured	

*This dose is the mean of the protocol-specified dose of 60 mg/kg/day (range 3.78 to 5.52 g/day)

** The number included in the efficacy analysis was 24 for reasons which are described below in a more detailed review of the study

***This was not the protocol specified analysis. The ANCOVA was performed by the current sponsor several years after the study blind was broken and after the initial report of this study was published. The protocol-specified analysis (which was cited in the publication) was the Wilcoxon Signed Rank Test which yielded a p-value of 0.42, but which may have been an inappropriate analysis.

7.4 Study OMC-SXB-21

Study #	OMC-SXB-21 Orphan Medical	
Design	Randomized, double-blind, placebo-controlled, parallel-arm, RANDOMIZED WITHDRAWAL study after long-term open label treatment	
Duration	2 weeks (withdrawal phase)	
Study Arms	GHB	Placebo
Number receiving study drug	26	29
Number completed	26	29
Main inclusion criteria	Continuous treatment with GHB for narcolepsy for 6 months to 3.5 years	
Primary outcome measures	Total number of cataplexy attacks	
Main efficacy analysis (statistically significant results)	GHB superior to placebo, based on ANCOVA (p < 0.001)	

8. Integrated Review of Safety

8.1 Background and Methodology

The 15 clinical trials included in the Integrated Summary of Safety consist of the following groupings which I have already tabulated in greater detail in Section 5.1.1, but which are also listed in the table below

Study Grouping	Number of Patients/Subjects
Integrated Clinical Trials	402
Lammers Trial	25
Scharf Trial	143
Integrated Pharmacokinetic Trials	144

The patients/subjects participating in these trials comprised

- 504 unique patients with narcolepsy
- 125 unique healthy subjects

2 separate integrated analyses were performed: one for the Integrated Clinical Trials and the second for the Integrated Pharmacokinetic Trials.

Additional analyses were performed separately on the Lammers and Scharf trials for the following reasons, as stated by the sponsor

- The Scharf study was not included on account of its design and history
- The Lammers study had a “simplified method of data collection”

8.2 Deaths

8.2.1 Tabular Summary Of Deaths

11 deaths occurred, all in the Scharf study. These are tabulated below: the table was provided by the sponsor.

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

As the table above indicates only 5/11 deaths are listed by the sponsor as having occurred within 30 days of the last dose of study drug. In the case of one death (patient # 200) the exact date of death is not stated in the Case Report Form and presumably other source documents were used to document that the patient’s death occurred within 30 days of the last dose of study drug

8.2.2 Conclusions Regarding Deaths

The listed cause of death (and a detailed review by me of patient narratives, and of Case Report Forms when needed), for all 11 patients do not suggest that their deaths could be causally related to use of GHB. Intercurrent unrelated illnesses and, in one instance, an accident appear to have been responsible

8.3 Serious Adverse Events

A total of 72 patients experienced serious adverse events. Their distribution by study grouping is as follows.

Study Grouping	Total number of patients/subjects in grouping	Number (%) of patients/subjects with serious adverse events
Integrated Clinical Trials	402	18 (4.5%)
Scharf Study	143	54 (37.8%)
Lammers Study	25	0
Integrated Pharmacokinetic Trials	144	0

These serious adverse events are further discussed under the 2 study groupings in which they occurred

8.3.1 Serious Adverse Events In Integrated Clinical Trials

As noted above 18 patients had serious adverse events in the Integrated Clinical Trials. These are tabulated below using investigator terms.

Patient ID Initials Study #	Gender Age (years)	GHB Dose At Onset Of Adverse Event (g/day)	Study Day When Adverse Event Began	Study Day When Adverse Event Ended	Adverse Event	Action Taken	Outcome Of Serious Adverse Event
0123 (b) OMC-GHB-2	F 22.1	3.0	30	31	Removal of left ovarian cyst and ovary	Study drug temporarily stopped	Resolved
0181 (b) OMC-GHB-2	F 60.1	0	-30	-29	Somniloquy	None	Resolved
0207 (b) OMC-GHB-2	F 53.2	6.0	7	9	Acute confusional state	Study drug permanently discontinued	Resolved
0214 (b) OMC-SXB-7	M 42.9	9.0	877	None	Abnormal liver function tests	Study drug permanently discontinued	Unresolved
0231 (b) OMC-SXB-6	M 67.9	9.0	119	119	Dizziness, confusion, nausea, vomiting, vertigo, weakness	Study drug permanently discontinued	Resolved
0238 (b) OMC-SXB-6	M 64.3	4.5	170	171	Altered mental status, unresponsive, respiratory failure	Study drug permanently discontinued	Resolved
0801 (b) (6)----GHB-3	M 40.6	9.0 Carry-forward dose	181	186	Myocardial infarction	None	Resolved
0814 (b) (6)-----HB-3	M 55.7	4.5	172	255	Breast carcinoma	None	Resolved
0932 (b) (6)----SXB-6	F 24.4	6.0	84	99	Auditory hallucinations	None	Resolved
0936 (b) (6)----SXB-6	F 50.9	6.0	79	83	Kidney stone	None	Resolved
1030 (b) OMC-SXB-6	F 34.8	6.0	32	None	Arthralgia	Study drug temporarily stopped	Unresolved
1032 (b) OMC-SXB-6	F 41.7	None	-7	-6	Injury to toe	No change	Resolved
1305 (b) OMC-GHB-3	F 73.6	9.0 Carry-forward dose	670	679	Agitation	Study drug temporarily stopped	Resolved
1433 (b) OMC-SXB-6	F 57.0	6.0	18	18	Body aches after automobile accident	Study drug temporarily stopped	Resolved
1509 (b) (6)----SXB-7	M 70.6	6.0	748	749	Gastroenteritis	Study drug temporarily stopped	Resolved
1630 (b) OMC-SXB-6	M 59.7	6.0	54	57	Lower back pain	Study drug temporarily stopped	Resolved
1735 (b)	F 26.8	6.0	108	108	Miscarriage	Study drug permanently	Resolved

Patient ID Initials Study #	Gender Age (years)	GHB Dose At Onset Of Adverse Event (g/day)	Study Day When Adverse Event Began	Study Day When Adverse Event Ended	Adverse Event	Action Taken	Outcome Of Serious Adverse Event
OMC-SXB-6						discontinued 6 weeks prior to adverse event	
(b)(6)--- OMC-SXB-6	F 65.3	6.0	160	163	Pancreatitis Cholelithiasis	Study drug permanently discontinued	Resolved

In regard to the above list the sponsor has drawn attention to the following:

- 2 patients (#s 0181 and 1032) had serious adverse events prior to beginning GHB
- In 2 patients (#s 0181 and 0123) their “serious adverse events” were subsequently considered not to have been serious

Note that no serious adverse events occurred in placebo-treated patients in this grouping.

I have read the narratives, and where necessary the Case Report Forms, for the above patients. A further description is warranted in the following patients

8.3.1.1 Patient 0238 (Initials)(b)(6)

This 65 year old man, participating in OMC-SXB-6, had been taking Xyrem® 4.5 g daily for 5 months. He had a background history of hypertension.

Immediately after his wife heard a loud noise, he was found comatose, flaccid, incontinent, bradycardic and hypoventilating. No convulsive movements had been witnessed. He required intubation and artificial ventilation. However the same day he awoke, was extubated and returned home. An EEG was normal; an echocardiogram showed ventricular hypertrophy with posterolateral wall hypokinesia, but with a satisfactory ejection fraction. A “cardiac event” was proposed as a cause for his symptoms by the hospital staff caring for him. However the Principal Investigator, after reviewing his hospital records considered the possibility that an inadvertent overdose with GHB was responsible for the episode was responsible for the episode. Study medication was permanently discontinued. Further information is not available.

8.3.1.2 Patient 0207 (Initials)(b)(6)

This 53 year old woman participating in OMC-GHB-2 received Xyrem® 6 g daily. On Day 4 of treatment she developed nausea. Beginning Day 5 she became very talkative with pressured speech, and the next day was noted to be disoriented, agitated and to sleep poorly. Xyrem® was discontinued, the patient was treated with haloperidol and by the next day her confusion had resolved. An EEG was normal and a CT scan of the head showed minor temporal lobe asymmetry. The study drug was permanently discontinued.

8.3.1.3 Patient 0932 (Initials)(b)(6)

This 24 year old woman who participated in OMC-SXB-6 had a history of depression dating back to 1994. Her dose of Xyrem® was increased from 4.5 g daily to 6 g daily. On Day 84 she experienced auditory hallucinations for which she was hospitalized and treated with olanzapine. Her dose of Xyrem® was then reduced to 4.5 g daily. Her hallucinations resolved and she was discharged after 14 days continuing with GHB for

the remainder of the trial. Hospital discharge records indicated to her investigator that for the previous 5 years she had experienced repeated auditory hallucinations and had 2 psychiatric hospitalizations

8.3.1.4 Patient 1030 (Initials)(b)(6)

This 34 year old woman participating in OMC-SXB-6 had a preceding history of lower back and knee pain for which she received acetaminophen. Her back pain was believed to be related to herniated intervertebral discs; further descriptions of her back and knee pain are unavailable. She was begun on Xyrem® in a dose of 4.5 g/day. On Day 4 of the study she complained of knee pain and on Day 31 reported generalized joint pain. At that point Xyrem® was stopped temporarily (it is uncertain for how long) but was then resumed in a dose of 6 g/day. On Day 68 on account of continued generalized joint pain, she was referred to a rheumatologist (details of this consultation are unavailable); treatment with diclofenac 100 mg/day was begun. On Day 131 the patient was stated to have patello-femoral syndrome (presumably she had knee pain at that point). Study medication was then stopped for 3 days, resumed and continued until Day 185. Her generalized arthralgia and knee pain were apparently continuing at her last visit.

8.3.1.5 Patient 1735 (Initials)(b)(6)

This 26 year old woman participating in OMC-SXB-6 initially took Xyrem® 4.5 g/day for 13 days, followed by 6 g/day for 52 days. On Day 66 she was discontinued from the study on account of her becoming pregnant, a protocol violation. She had a miscarriage on Day 108.

8.3.1.6 Patient 0214 (Initials (b)(6))

This 42 year old man participating in OMC-SXB-7, was noted to have abnormal liver function tests at the Month 6 (Day 196) visit; he was taking 9 g/day of Xyrem® at that time. At that time he had a tremor and diaphoresis. His concomitant medications at that time included ascorbic acid, multivitamins, methylphenidate, acetaminophen and pseudoephedrine; earlier he had also taken a butalbital-aspirin combination, zolpidem, tramadol, alprazolam, fluoxetine and paroxetine for unknown periods of time, and modafinil for about 5 months. At that time (Day 196) his liver function studies were as follows: total protein 7.3 g/dl; albumin 4.2 g/dl; total bilirubin 0.6 mg/dl; alkaline phosphatase 135 U/L AST 189 IU/L; ALT 362 IU/L. A further 9 days later (Day 205) his liver functions were: total protein 7.0 g/dl; albumin 4.1 g/dl; total bilirubin 0.4 mg/dl; alkaline phosphatase 112 U/L; AST 141 IU/L; ALT 271 IU/L.

His past medical history was remarkable for migraine, hay fever, a right nephrectomy and known hepatitis C infection.

At the time of his entry into the OMC-SXB-7 study his serum liver function tests were as follows: total protein 7.2 g/dl; albumin 4.2 g/dl; total bilirubin 0.4 mg/dl; alkaline phosphatase 63 U/L AST 27 IU/L; ALT 41 IU/L (all well within normal limits)

On Study Day 205 Xyrem® was permanently discontinued. Results of follow-up liver functions, if any, are not available. It is unclear based on the Case Report Form, if his abnormal liver functions were associated with any symptoms.

8.3.1.7 Patient 0231 (Initials (b)(6))

This 67 year old man participating in Study OMC-SXB-6 took Xyrem® in a dose of 4.5 g/day for 12 days and 9 g/day for 106 days. He was reported to experience nausea,

vomiting, dizziness, confusion and generalized weakness. His past medical history was remarkable for a stomach ulcer, gastroesophageal reflux disease, and a cholecystectomy. Concomitant medications included clomipramine, methylphenidate, paroxetine, imipramine and modafinil.

Xyrem® was permanently discontinued. Within 24 hours the adverse event had resolved.

8.3.1.8 Patient 1305 (Initials (b))

This 73 year old woman participating in Study OMC-GHB-3 became agitated, frightened and restless after taking GHB for 670 days. Her dose of Xyrem® at that time was not recorded; her last recorded dose was 9 g/day and this dose was carried forward. Xyrem® was temporarily stopped, and she was treated at an emergency room with diphenhydramine and lorazepam injections. She was discharged home having apparently recovered, and was able to complete the study (study medication was resumed but it is unclear for how long and in what dose it was administered).

8.3.2 Serious Adverse Events In Scharf Study

54 patients had serious adverse events in the Scharf study. 51 of these patients had serious adverse events that occurred after they started to receive study drug: these adverse events are tabulated below.

	Number Of Patients	Percentage of Patients Participating In Study
Total Number With Serious Adverse Events	51	35.7
Asthenia	5	3.5
Cellulitis	3	2.1
Fever	1	0.7
Headache	1	0.7
Infection	2	1.4
Accidental injury	7	4.9
Neoplasm	1	0.7
Overdose	2	1.4
Pain	6	4.2
Abdominal pain	7	4.9
Back pain	3	2.1
Chest pain	10	7.0
Substernal chest pain	1	0.7
Unevaluated reaction	11	7.7
Angina pectoris	1	0.7
Vascular anomaly	2	1.4
Arrhythmia	1	0.7
Cerebrovascular accident	1	0.7
Coronary artery disease	1	0.7
Right-sided heart failure	1	0.7
Hypertension	1	0.7
Hypotension	1	0.7
Myocardial infarction	3	2.1
Ventricular tachycardia	1	0.7
Anorexia	1	0.7
Gastrointestinal carcinoma	1	0.7
Cholecystitis	3	2.1
Cholelithiasis	2	1.4
Diarrhea	2	1.4
Gastroenteritis	1	0.7
Gastrointestinal hemorrhage	1	0.7
Rectal hemorrhage	1	0.7
Melena	1	0.7
Nausea	2	1.4
Rectal disorder	1	0.7
Duodenal ulcer	1	0.7

Vomiting	3	2.1
Diabetes mellitus	2	1.4
Anemia	1	0.7
Leukocytosis	1	0.7
Rheumatoid arthritis	1	0.7
Anxiety	1	0.7
Coma	1	0.7
Confusion	1	0.7
Convulsion	1	0.7
Depression	1	0.7
Dizziness	2	1.4
Hypesthesia	1	0.7
Stupor	2	1.4
Apnea	3	2.1
Asthma	1	0.7
Lung carcinoma	2	1.4
Dyspnea	9	6.3
Pulmonary embolism	1	0.7
Hemoptysis	1	0.7
Hypoventilation	1	0.7
Lung disease	2	1.4
Pharyngitis	3	2.1
Pneumonia	2	1.4
Respiratory diseases	2	1.4
Skin carcinoma	4	2.8
Melanoma of skin	1	0.7
Skin disease	1	0.7
Skin disorder	3	2.1
Sweating	3	2.1
Bladder calculus	1	0.7
Carcinoma bladder	1	0.7
Carcinoma breast	1	0.7
Urinary incontinence	2	1.4
Unintended pregnancy	1	0.7
Prostate disorder	1	0.7
Urinary frequency	1	0.7
Enlarged uterine fibroid	1	0.7

I have read through the narratives, and Case Report Forms where needed, for the above patients. Serious adverse events that warrant further description are listed below.

8.3.2.1 Patient 012 (Initials (b))

This man was 74 years old at the time of study entry. He had a past history of cardiomyopathy, left bundle branch block and sleep apnea. About 2 years after beginning GHB and while taking a dose of 7.5 g daily he had an episode of disorientation, stupor and weakness that necessitated hospitalization and a reduction in dose of GHB to 6 g daily for one day. The episode resolved and did not recur despite the patient continuing to take 7.5 g daily.

8.3.2.2 Patient 017 (Initials (b))

This 63 year old man had a history of narcolepsy and sleep apnea. as well as hypertension. Initial physical examination is reported to have shown a “mild-to-moderate degree of oropharyngeal compromise.”

He began taking GHB in a dose of 4.5 g daily. About 11 months after enrolling in an incident attributed to possible sleepwalking he ingested an additional estimated 9 g of GHB in addition to his first nightly 3 g dose of the drug. He drove himself to an emergency room, where he was administered ipecac and slept for 2 hours

Approximately 1 ½ years after enrolling in the study he was hospitalized after an overdose of GHB 18 g, again attributed to sleepwalking. At the time of hospitalization he was comatose and unresponsive. He needed intubation and artificial ventilation, and awoke 6 hours later. He continued in the study.

Other significant items of information regarding this patient are as follows

- He had many episodes of sleep walking and multiple episodes of urinary incontinence.
- In 2 instances episodes of sleep walking and urinary incontinence are listed in the Case Report Form as occurring on the same day although there is no evidence presented that they occurred at the same time.
- On the days when both incontinence and sleep walking are listed as having occurred, the patient's prescribed dose was 7.5 g/day
- As noted above this had multiple episodes of sleep walking that did not occur on the same days as his episodes of incontinence.
- He also reported muscle jerks over the front of his trunk over a period of several years while taking GHB. These were stated to be most prominent when lying in bed in the morning as the last dose of GHB was wearing off; they could be controlled voluntarily and would disappear with ambulation, returning when at rest.
- He developed congestive heart failure during the study and died about 5 years after study entry. While participating in the study he underwent a thoracotomy for a right lung nodule that was confirmed to be a squamous cell carcinoma.

8.3.2.3 Patient 019 (Initials (b))

This 41 year old man with a past history of depression and suicidal ideation was begun on treatment with GHB in a dose of 5.3 g/day. 6 months later he was hospitalized for treatment of depression at a time when he was taking GHB in a dose of 6 g/day; that medication was interrupted for a day and then resumed at 9 g/day. About 2 years after first beginning the drug he was hospitalized after a suicide attempt that consisted of taking an overdose of GHB. At that time he was dropped from the study

8.3.2.4 Patient 257 (Initials (b))

This 32 year old man with a past history of a whiplash injury with numbness and paresthesia in his hands was begun on treatment with GHB 4.5 g daily while concomitantly taking protryptiline. About 3 months later he was seen at a hospital emergency room on account of complaints of chills, sweating, blurred vision, memory loss, and shaking as well as vibrating sensations. A further 6 months later shaking and vibrating sensations occurred again at which time he was also recorded as having attacks of cataplexy at least one of which resulted in a fall. 2 further years later he was hospitalized overnight after an unspecified adverse reaction that was attributed to ingesting too much GHB.

After an additional 2 years on GHB the patient fell on a long butcher knife, and perforated his colon. During the peri-operative period GHB was stopped for 10 days. About 2 months after surgery he was hospitalized on account of hypoxemia and required intubation and mechanical ventilation. Further details are unavailable. GHB was apparently not stopped at the time.

8.4 Dropouts and "Other Significant Adverse Events"

A total of 63 GHB-treated patients permanently discontinued treatment on account of adverse events. Their distribution by study grouping, according to the sponsor, is as follows.

Study Grouping	Total number of patients/subjects in grouping	Number (%) of patients/subjects with adverse events leading to discontinuation
Integrated Clinical Trials	402	44 (10.9%)
Scharf Study	143	19 (13.3%)*
Lammers Study	25	0
Integrated Pharmacokinetic Trials	144	2 (1.4%)

*Note that the sponsor has counted 7 deaths as discontinuations due to adverse events. The actual adverse event discontinuation rate is 12/143 or 8.4%.

A single placebo-treated patient (# 0818; initials(b)(6) participating in OMC-GHB-2 discontinued treatment 1 month after study entry on account of insomnia (see Section 8.4.1)

These adverse event discontinuations are further discussed under the 3 study groupings in which they occurred.

8.4.1 Adverse Event Discontinuations In Integrated Clinical Trials

44 patients discontinued treatment on account of adverse events in this grouping

Of the 44 patients who discontinued treatment in the Integrated Clinical Trials Grouping, 10 discontinued treatment in the 3 controlled clinical trials; all 10 participated in OMC-GHB-2. The adverse events that led to treatment discontinuation in OMC-GHB-2 (n = 136) were as follows

Nausea 2.9%

Somnolence 2.2%

Confusion 1.5%

Amnesia, asthenia, chest pain, dizziness, dyspnea, hyperkinesia, fecal incontinence, insomnia, paranoid reaction, thinking abnormal, vertigo, and vomiting each 0.7%.

A listing of patients who discontinued treatment in OMC-GHB-2 is as follows; as the table indicates these adverse events were dose-related. Also note, however, that individual doses were not titrated in this study.

Patient Number	Preferred term [investigator term]
Placebo	
818	Insomnia [insomnia]
3g GHB	
901	Nausea [nausea], somnolence [lethargy], pain chest [chest pressure]
6g GHB	
207	Confusion [acute confusional state]
509	Hyperkinesia [restless leg increased], headache [headache]
9g GHB	
221	Somnolence [increased sleepiness], dizziness [dizzy], nausea [nauseated], and asthenia [weakness (had difficulty standing)]
605	Somnolence [daytime sedation feeling; "drugged feeling"], thinking abnormal [poor concentration]
702	Confusion [confusion], hallucinations [hallucinations], amnesia [forgetfulness], nausea [nausea], paranoid reaction [paranoia]
824	Dyspnea [difficulty breathing]
1201	Incontinence fecal [patient lost bowel control while asleep]
1504	Nausea [nausea], vertigo [vertigo], vomit [vomiting]

The following table, supplied by the sponsor, provides a summary for 38 out of 44 patients who discontinued treatment on account of an adverse event in the entire Integrated Clinical Trials grouping. In these 38 patients discontinuation was considered to be treatment-related by the investigator.

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day ^a		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0204	OMC-GHB-3	6.0	33	51	Insomnia	Insomnia	No	Moderate
0207	OMC-GHB-2	6.0	7	9	Acute confusional state	Confusion	Yes	Severe
0213	OMC-GHB-3	9.0	90	135	Depressed mood	Depression	No	Moderate
		9.0	90	135	Excessive tiredness	Asthenia	No	Moderate
0221	OMC-GHB-2	9.0	13	15	Dizzy	Dizziness	No	Moderate
		9.0	13	15	Increased sleepiness	Somnolence	No	Moderate
		9.0	13	15	Nauseated	Nausea	No	Moderate
		9.0	13	15	Weakness (had trouble standing)	Asthenia	No	Moderate
0231	OMC-GHB-3	3.0	30	108	Lethargic all day	Somnolence	No	Mild
	OMC-SXB-6	9.0	119	119	Dizziness	Dizziness	Yes	Severe
0231	OMC-SXB-6	9.0	119	119	Confusion	Confusion	Yes	Severe
		9.0	119	119	Nausea	Nausea	Yes	Severe
		9.0	119	119	Vomiting	Vomiting	Yes	Severe
		9.0	119	119	Vertigo	Vertigo	Yes	Severe
		9.0	119	119	Weakness	Asthenia	Yes	Severe
		9.0	119	119	Weakness	Asthenia	Yes	Severe
0238	OMC-SXB-6	4.5	170	170	Respiratory failure	Apnea	Yes	Severe
		4.5	170	170	Non-responsive	Coma	Yes	Severe
0409	OMC-GHB-3	9.0	61		Weight loss	Weight loss	No	Mild
0509	OMC-GHB-2	6.0	1	2	Restless leg syndrome increased	Hyperkinesia	No	Severe
0533	OMC-SXB-6	4.5	10		Swelling in legs	Peripheral edema	No	Severe
0605 ^b	OMC-GHB-2	9.0	9	12	Daytime sedation feeling; "drugged feeling"	Somnolence	No	Mild
		9.0	9	12	Poor concentration	Thinking abnormal	No	Mild
0637	OMC-SXB-6	7.5	93 ^c		Restless legs	Hyperkinesia	No	Moderate
		7.5	93 ^c		Anxiety	Anxiety	No	Moderate

(continued)

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day ^a		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0701	OMC-GHB-3	6.0 ^a	32		Decreased sexual libido	Libido decreased	No	Moderate
		6.0 ^b	32		Decreased initiative to start any activity by gradual progression	Apathy	No	Mild
0702	OMC-GHB-2	9.0	20	25	Confusion	Confusion	No	Moderate
		9.0	20	25	Forgetfulness	Amnesia	No	Moderate
		9.0	20	23	Hallucinations	Hallucinations	No	Moderate
		9.0	21	21	Nausea	Nausea	No	Mild
		9.0	22	24	Paranoia	Paranoid reaction	No	Mild
0801	OMC-GHB-3	9.0	147	178	Chest pain, patient on drug, no hospitalization, no concomitant medication	Chest pain	No	Moderate
0802	OMC-GHB-3	9.0	49	55	Nervousness	Nervousness	No	Moderate
		9.0	49	51	Metallic taste	Taste perversion	No	Mild
		9.0	49	51	Upset stomach	Dyspepsia	No	Moderate
0809	OMC-GHB-3	3.0	332	332	Inability to control body 1 h after taking medicine	Incoordination	No	Mild
0818	OMC-GHB-2	Placebo	23		Insomnia	Insomnia	No	Moderate
0821	OMC-GHB-3	6.0	39	51	Headaches	Headache	No	Moderate
		6.0	40	51	Irritable	Nervousness	No	Moderate
0824	OMC-GHB-2	9.0 ^a	5	5	Difficulty breathing	Dyspnea	No	Severe
	OMC-GHB-3	3.0	25	29	Difficulty breathing	Dyspnea	No	Moderate
0836 ^c	OMC-SXB-6	4.5	1		Headache	Headache	No	Moderate
0844	OMC-SXB-6	4.5	1	42	Nausea	Nausea	No	Moderate
		4.5	1	42	Vomiting	Vomiting	No	Moderate
		4.5	1	42	Headaches	Headache	No	Severe

(continued)

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day ^a		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0901	OMC-GHB-2	3.0	2	18	Lethargy	Somnolence	No	Mild
			2	18	Nausea	Nausea	No	Moderate
			3	18	Chest pressure	Chest pain	No	Mild
1101 ^f	OMC-GHB-3	4.5	156		Acute psychosis ^g	Psychosis	No	Moderate
1134	OMC-SXB-6	4.5	3		Urinary incontinence	Urinary incontinence	No	Moderate
1142	OMC-SXB-6	7.5	31	34	Left eye exposure keratitis	Keratitis	No	Mild
1201	OMC-GHB-2	9.0	5	5	Patient lost bowel control while asleep	Incontinence, fecal	No	Moderate
1504	OMC-GHB-2	9.0	2	2	Nausea	Nausea	No	Severe
			2	2	Vertigo	Vertigo	No	Severe
			2	2	Vomiting	Vomiting	No	Severe
1631	OMC-SXB-6	6.0	23	59	Sleepwalking	Sleep disorder	No	Moderate
			44	59	Fragmented sleep	Sleep disorder	No	Severe
			44	60	Involuntary limb movements in sleep	Sleep disorder	No	Moderate
1735 ^h	OMC-SXB-6	6.0	108 ^h	108 ^h	Miscarriage	Abortion	Yes	Mild
2532 ^a	OMC-SXB-6	4.5	16	43	Sleepwalking	Sleep disorder	No	Mild
			16	43	Dizziness	Dizziness	No	Mild
			39	43	Arms and legs numb	Paresthesia	No	Mild
2533 ^a	OMC-SXB-6	4.5	25	81	Nausea	Nausea	No	Moderate
			74	81	Morning grogginess	Somnolence	No	Moderate
2537 ^a	OMC-SXB-6	4.5	12		Increased headaches	Headache	No	Moderate
2633	OMC-SXB-6	4.5	2	4	Increased awakenings	Sleep disorder	No	Mild
			2	4	Tongue paresthesia	Paresthesia	No	Mild
2933	OMC-SXB-6	4.5	29		"Phlegm/knot" in throat	Pharyngitis	No	Moderate
3231	OMC-SXB-6	6.0	56		Exacerbation of colitis (Crohn's disease)	Colitis	No	Moderate

(continued)

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day ^a		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
3830	OMC-SXB-6	7.5	52	62	Nausea	Nausea	No	Moderate
			58	58	Vomiting	Vomiting	No	Moderate
3831	OMC-SXB-6	3.0	12	24	Itching and swelling of extremities	Pruritus	No	Moderate
			12	24	Itching and swelling of extremities	Edema	No	Moderate
3930	OMC-SXB-6	4.5	2	3	Sleep paralysis	Sleep disorder	No	Moderate

^a Day relative to start of treatment.

^b Patient 0605 was not listed as discontinued on the end-of-trial page of the case report form, but had an AE action of "permanently discontinued" on the AE page.

^c Whole or partial data imputed from start of trial medication.

^d Dosage carried forward.

^e Patients 0836, 2532, 2533, and 2537 were listed as discontinuing due to a lack of efficacy on the end-of-trial page of the case report form, but had an AE action of "permanently discontinued" on the AE page.

^f After subsequent analysis by the principal investigator, the AE of psychosis for patient 1101 was determined to be not related to trial medication.

^g Patient 1735 discontinued trial medication on Day 66, due to a presumed protocol violation (pregnancy).

Of the patients listed in the table above, short narratives have already been provided under the discussion of Serious Adverse Events above for the following: #s 0207, 0231, 0238 and 1735. Brief narratives are provided for the following additional patients. Narratives for more patients do not appear to be needed based on a review of the data provided by the sponsor.

8.4.1.1 Patient 0221 (Initials (b)(6))

This 57 year old woman was enrolled in the OMC-GHB-2 trial and was begun on GHB in a dose of 9 g/day. 12 days later she complained of increased sleepiness along with dizziness, nausea and weakness (with difficulty maintaining an upright posture). GHB was discontinued and her symptoms resolved. She was next enrolled in OMC-GHB-3 during which her most common dose of GHB was 6 g/day; while taking a dose of 3 g/day, her initial dose, she reported excessive somnolence from the first day in the trial onward. After about 1.5 months of participation in OMC-GHB-3, the study drug was stopped permanently with resolution of this adverse event

8.4.1.2 Patient 3831 (Initials(b)(6))

This 31 year old woman with a previous history of eczema was enrolled in OMC-SXB-6. She took Xyrem® 4.5 g/day for 10 days followed by 3 g/day for 2 days; she then experienced itching and swelling of her extremities leading to discontinuation of GHB on Day 13. By Day 24 both itching and extremity swelling had resolved.

The 6 remaining patients who discontinued study drug permanently on account of adverse events and are not listed above are summarized in the table below. In these patients the adverse events that lead to treatment discontinuation were not considered to be drug-related

Patient ID Initials Study #	Gender Age (years)	GHB Dose At Onset Of Adverse Event (g/day)	Study Day When Adverse Event Began	Study Day When Adverse Event Ended	Adverse Event	Outcome After Study Drug Discontinuation
0123 (b)(6)-----HB-2	F 22.1	6.0	42	None	Unintended pregnancy	“Unresolved”
0208 (b)(6)-----OMC-GHB-3	M 26.7	9.0	43	525	Twitching	Resolved
(b)(6)-----HB-3	F 44.4	6.0	30	352	Memory loss	Resolved
0214 (b)(6)-----OMC-SXB-7	M 42.9	9.0	877	None	Abnormal liver function tests	Unresolved
(b)(6)-----XB-6	F 51.2	4.5	38	None	Sinusitis Generalized edema	Unresolved
(b)(6)-----XB-6	M 52.6	9.0	86	None	Apnea (sleep apnea)	Unresolved

A narrative for Patient # 0214 has already been provided under the discussion of Serious Adverse Events. Narratives are provided below for 2 additional patients

8.4.1.3 Patient 0504 (Initials(b)(6))

This 45 year old woman participated first in OMC-GHB-2 and then in OMC-GHB-3 for a total period in these trials of 10 months. While taking Xyrem® in a dose of 6 g/day in

OMC-GHB-3 she was reported to have lapses of memory each afternoon. Xyrem® was stopped and this adverse event resolved.

8.4.1.4 Patient 3533 (Initials(b)(6)

This 52 year old man participating in OMC-SXB-6 had no significant past medical history. At entry into the study he was begun on GHB in a dose of 4.5 g/day. This dose was gradually increased in steps to 9 g/day. After 4 days on the last dose and after 86 days of treatment with GHB he was noted to have sleep apnea which was judged to be severe and lead to Xyrem® being stopped. The adverse event did not resolve after the study drug was stopped

8.4.2 Adverse Event Discontinuations In Scharf Trial

According to the sponsor, 19 patients withdrew from this study because of adverse events. They are listed in the following table which I have copied from the submission. Note that of the 19 patients listed, 7 patients were “withdrawn” because of death; ordinarily such patients would not be considered as having withdrawn due to adverse events. **An eighth patient (# 064; Initials (b)(is incorrectly listed in this table as having died**

Pt No.:	Age ¹	Sex	Duration of Exposure (yr) ¹	Reason for patient withdrawal (as provided by the site)
001 ²	51	M	5.7	Death due to metastatic colon carcinoma
005	53	F	4.7	Increased difficulty sleeping, hospital admission to assess suspected psychiatric problem
009 ²	68	M	10.0	Died (2/95) last recorded dose gamma was 11/94. Death due to arteriosclerotic cardiovascular disease
014 ²	49	M	8.6	Death due to cardiac arrhythmia
019	43	M	2.0	Patient attempted suicide (unsuccessfully)
032 ²	74	F	10.2	Death due to lung cancer
053 ²	57	M	10.4	Died 10-10-94, heart attack
064 ²	15	F	1.8	Increased seizure activity
066	50	F	6.1	Repeated high ANA tests (antinuclear antibodies)
200 ²	71	M	5.4	Patient expired from lung cancer
232 ²	69	M	4.8	Death due to bladder cancer; CAD, and cardiac arrest
238	47	M	1.9	Decrease in short term memory
243 ²	63	M	4.7	Weight loss
244	56	F	0.9	Elevated ANA, possible Lupus Syndrome
247	34	F	0.8	Seizure
254	63	F	1.2	Interstitial infiltrate possible, pulmonary toxicity
259	41	F	0.1	Complains of feeling like zombie, stiffness in legs
271	46	M	0.5	Swelling
273	60	F	0.9	Weight loss

¹Age and duration of exposure were based on the time of the last change in the dosage of study medication.

² Patients (n = 8) who died after withdrawing from the study. See Table 15 - Deaths.

After reading through the sponsor-supplied narratives, and Case Report Forms (when needed) for the above patients further details are provided for the following patients. Patient # 019 has already been described in the discussion of Serious Adverse Events.

8.4.2.1 Patient 005 (Initials (b))

This 53 year old woman was reported to have developed anger, hostility and suspiciousness, while taking dextroamphetamine and other stimulants, prior to study entry. She was begun on GHB in a dose of 5.3 g/day; concomitant medications include clomipramine as well as caffeine tablets. After taking GHB for 4.7 years that drug was discontinued when the patient had difficulty sleeping and "psychiatric problems" that were considered similar to those that occurred when she was taking stimulants. She required a psychiatric hospitalization, the outcome of which and her subsequent course are unknown.

8.4.2.2 Patient 064 (Initials (b))

This 15 year old girl had a previous history of a left frontal lobe lesion, previous burr hole placement after a "concussion" and headaches. Concomitant medications at study entry included protriptyline and methylphenidate. She received treatment with GHB for 1.8 years at a mean dose of 6 g/day. While on treatment she was reported to have "increased seizure activity" (no details of the seizures are provided; it is not clearly stated that she had seizures prior to study entry), increased urinary frequency, headache, vomiting, dyslexia, an increased appetite and shortness of breath. The increased seizures reportedly led to hospitalization and to discontinuation from the study, although the last date of medication administration is listed as being unknown. No further details are provided.

8.4.2.3 Patient 066 (Initials(b))

This 50 year old woman had a past medical history of hypertension, occasional chest pain, a dry skin rash, penicillin allergy, a hysterectomy and weight gain of 45 kg over 9 years. Concomitant medications at study entry included triamterene-hydrochlorothiazide, clorazepate and methylphenidate. She took GHB for a total of about 6 years, most commonly in a dose of 7.5 g/day. After a little less than 6 years of treatment she was noted to have an anti-nuclear antibody titer of 1:640 (this test was not performed earlier in the study). Over the next 3 months successive antinuclear antibody titers were 1:1280 and >1:2560, respectively. GHB was stopped; over the next 11 months follow-up antinuclear antibody titers were always > 1:160 (in a range of 1:160 to 1:1280). A diagnosis of drug-induced lupus was apparently considered. Antihistone antibody testing was not done.

The above summary is based on information obtained from the Case Report Form and sponsor narrative. However the sponsor has also supplied the following documents

- An abstract published by Dr Scharf in 1993 indicated that the same patient (whose identity was confirmed separately by Dr Scharf) developed "clinical symptoms suggestive of arthritis" after having received GHB for 68 months
- A letter to the sponsor from Dr Scharf dated 7/24/98, had been on GHB for 72 months at which time she was diagnosed to have rheumatoid arthritis was diagnosed

This diagnosis appears to have been made a few months before her first, positive antinuclear antibody test. Further clinical details are unavailable.

Also see “Elevated Antinuclear Antibodies” in Section

8.4.2.4 Patient 238 (Initials)(b)(6)

About 6 months after this 47-year old man began taking GHB he was first reported to have impaired short-term memory. Over the next 1.5 years further such reports occurred leading to the dose of drug being reduced from 9 g/day, the most commonly used dose, to 3.75 g/day and to the drug’s discontinuation a short while later after a total of about 2 years of treatment. Concomitant medications included methylphenidate and methamphetamine. No information is provided about his clinical course after study drug discontinuation.

8.4.2.5 Patient 244 (Initials (b)(6)

This 56-year old women had taken GHB for 1 year when the drug was discontinued on account of an antinuclear antibody titer of 1:80; there is no record of a similar test having been done previously or subsequently. The test was requested on account of back and leg pain. Antihistone antibody testing was not done. Her records indicate that she had consulted an orthopedic surgeon on account of back pain even prior to beginning GHB, and was recommended a spinal fusion. Prior included protriptyline, dextroamphetamine and meclufenamate. Her course after GHB was discontinued is unclear

Also see “Elevated Antinuclear Antibodies” in Section 8.5.5.2

8.4.2.6 Patient 247 (Initials)(b)(6)

This 34-year old woman had taken GHB for about 9 months in a dose of 6 g/day when she had a seizure that reportedly consisted of “continuous jerking all over her body”. At that time GHB was discontinued. Her narcolepsy was diagnosed 4 years before she entered this trial. Her previous medical history was also remarkable for incontinence, obesity and an unspecified psychiatric illness. Her only concomitant medication was fluoxetine. Prior medications for narcolepsy included L-tyrosine, methylphenidate, protriptyline, dextroamphetamine, imipramine, temazepam and alprazolam. No further details are available

8.4.2.7 Patient 254 (Initials)(b)(6)

This 61 year old woman had been diagnosed with narcolepsy at age 34. Her medical history was also remarkable for “Hashimoto goiter”, and episodes of sleep apnea. Previous medications for narcolepsy included dextroamphetamine, methylphenidate, and imipramine. Concomitant medications included natural thyroid 2 g/day and calcium supplementation. 11 months after beginning GHB in a dose of 3.8 g/day she was hospitalized with shortness of breath, fever and cyanosis. Chest x-ray revealed evidence of an interstitial pneumonia and she was treated with oxygen. GHB was discontinued at that time: her last dose was 4.5 g/day. These symptoms appear to have resolved based on a letter from the patient to the study center written 5 months after the event, but no further details are available; earlier in the study she was reported to have ankle swelling.

8.4.2.8 Patient 259 (Initials)(b)(6)

This 41-year old woman was diagnosed to have narcolepsy 4 years prior to study entry. Her medical history was otherwise unremarkable. Concomitant medications included methylphenidate and estrogen. GHB was begun in a dose of 5.3 g/day. 3 days later the patient reported that she felt like a zombie, and had stiffness in her legs and chest together with excessive crying. Her dose of GHB was reduced to 3 g/day that day, to 1.5 g/day the next day, was omitted once a further day later and was then resumed at 1.5

g/day. A further 8 days later the dose was reduced to 0.8 g/day. As her symptoms had not resolved a month later the drug was stopped. No additional information is available; it is unclear if her symptoms eventually resolved.

8.4.3 Adverse Event Discontinuations In Integrated Pharmacokinetic Trials

2 subjects discontinued study participation on account of adverse events. They are summarized in the table below:

Subject ID Initials Study #	Gender Age (years)	GHB Dose At Onset Of Adverse Event (g/day)	Study Day When Adverse Event Began	Study Day When Adverse Event Ended	Adverse Event	Outcome After Study Drug Discontinuation
ID # 012 (b) (6)-----XB-9	F 30	4.5*	After initial dose	Unclear	Headache, nausea and diarrhea	Adverse events resolved
ID # 003 (b) OMC-SXB-11	F 39	4.5**	After initial dose	5 hours after onset	Dizziness, nausea, vomiting, apneic episodes and fecal incontinence***	Adverse events resolved

*Administered in 2 divided doses of 2.25 g each, 4 hours apart

**Administered in a single dose of 4.5 g

***2 hours after her initial and only dose of GHB this subject began experiencing dizziness, nausea and vomiting. At the same time or shortly afterward the patient also experienced a single 2-minute period of apnea, a generally depressed depth of respiration and fecal incontinence. She was treated by rolling her over on her side, and administering oxygen by mask for several minutes on 2 occasions. All adverse events resolved over a period of about 5 hours after they first began. This summary is based on a review of the sponsor-supplied narrative and Case Report Form

In a further communication dated 2/23/01 the sponsor had, at my request, submitted further information about subject # 003 (initials:(b)(6)-participating in Study # OMC-SXB-11. The information is as follows:

- This p-----eighed 137 lbs (62.3 kg) and was 63 inches in height
- She received a single 4.5 g dose of GHB after a 10 hour fast
- 30 minutes after dosing she reported dizziness
- One hour after dosing and while asleep in the supine position she had labored, "decreased" respiration with inspiratory stridor. She did not improve with repositioning and was then apneic briefly before the episode resolved on stimulation and application of an oxygen mask
- After stimulation she awoke and vomited once.
- She then fell asleep again. 1 further hour later, and 2 hours after dosing her she vomited twice and then had a further episode of stridor (when lying on her side) and a brief pause in spontaneous respiration that again responded to stimulation and the use of an oxygen mask. At the same time she was fecally incontinent, but had her eyes open, could respond to verbal commands and was not observed to have any "seizure-like movements"
- 2 further hours later she was able to consume most of the offered lunch.
- Pulse and blood pressure remained normal throughout

The sponsor further stated that this food-effect pharmacokinetic study confirmed that exposure (based on C_{max} and AUC) was significantly increased, and t_{max} delayed, in the fasted state

8.5 Adverse Events Incidence Tables

8.5.1 Approach to Eliciting Adverse Events

Approaches used differed based on the clinical trial grouping, as discussed below.

8.5.1.1 Integrated Clinical Trials

In this clinical study grouping the following approach was used.

- Adverse events that occurred during the trial and up to 10 days after the last dose of study medication were recorded in detail on the appropriate page of the Case Report Form
- The frequency, severity, seriousness and relationship to study medication was recorded. A serious adverse event was defined using standard criteria. Serious adverse events were not recorded in the Scrima trial

- Medication dosage at which the adverse event began was also recorded

8.5.1.2 Lammers Trial

Only the incidence of adverse events was recorded. Serious adverse events were not recorded.

8.5.1.3 Integrated Pharmacokinetic Trials

The frequency, severity, seriousness and relationship to study medication were each recorded in a variable number of studies

8.5.1.4 Scharf Trial

The following is stated

- Adverse events were recorded retrospectively on Case Report Forms from information recorded by patients in daily diaries and from investigator-maintained medical records.
- The seriousness, severity and relationship to study medication of these adverse events was also recorded.
- A serious adverse event was defined using standard criteria

8.5.2 Adverse Events Categorization and Preferred Terms

Adverse events were initially entered in Case Report Forms using investigator terms, but were tabulated in the Integrated Summary of Safety and in the majority of study reports using

8.5.3 Key Adverse Events Tables

Key adverse event tables are grouped as follows

8.5.3.1 Controlled Clinical Trials

The following table, copied from the Integrated Summary of Safety, presents the number of adverse events that occurred in $\geq 5\%$ of patients in each treatment group in the following controlled clinical trials, combined: OMC-GHB-2, Lammers and Scrima.

Body System COSTART Preferred Term	Total ^a	Placebo	Sodium Oxybate
Number of patients	226 (100%)	79 (100%)	147 (100%)
Patients with ≥ 1 AE	130 (58%)	39 (49%)	101 (69%)
Body as a Whole	79 (35%)	24 (30%)	60 (41%)
Headache	39 (17%)	12 (15%)	29 (20%)
Infection	11 (5%)	1 (1%)	10 (7%)
Pain	19 (8%)	3 (4%)	17 (12%)
Cardiovascular System	11 (5%)	2 (3%)	9 (6%)
Digestive System	46 (20%)	9 (11%)	37 (25%)
Dyspepsia	14 (6%)	5 (6%)	9 (6%)
Nausea	28 (12%)	4 (5%)	24 (16%)
Vomiting	10 (4%)	1 (1%)	9 (6%)
Musculoskeletal System	9 (4%)	1 (1%)	8 (5%)
Nervous System	80 (35%)	17 (22%)	66 (45%)
Confusion	12 (5%)	1 (1%)	11 (7%)
Dizziness	36 (16%)	2 (3%)	34 (23%)
Nervousness	12 (5%)	6 (8%)	7 (5%)
Sleep disorder	15 (7%)	2 (3%)	13 (9%)
Somnolence	24 (11%)	7 (9%)	17 (12%)
Respiratory System	20 (9%)	6 (8%)	14 (10%)
Skin	15 (7%)	4 (5%)	11 (7%)
Special Senses	10 (4%)	3 (4%)	7 (5%)
Urogenital System	24 (11%)	7 (9%)	18 (12%)
Incontinence, urine	8 (4%)	0	8 (5%)

^a Two of the trials (Scrima and Lammers) were crossover trials, with patients in both the placebo and sodium oxybate groups.

As the above table indicates

- The proportion of patients with adverse events was higher in those treated with GHB than in those treated with placebo
- The most common adverse events in those treated with GHB were headache, nausea and dizziness. All 3 were more common in those treated with GHB than in those treated with placebo; nausea and dizziness were > 3-fold more common in the GHB group

8.5.3.2 Integrated Clinical Trials

The following table, copied from the Integrated Summary of Safety, presents the number of adverse events that occurred in ≥ 5% of patients in each treatment group in all studies in the Integrated Clinical Trials grouping. The dose listed is that at onset of the adverse event.

Body System COSTART Preferred Term	Total*	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total*	3.0	4.5	6.0	7.5	9.0
Number of patients	402 (100%)	54 (100%)	399 (100%)	94 (100%)	266 (100%)	290 (100%)	116 (100%)	118 (100%)
Body as a Whole	200 (50%)	25 (46%)	196 (49%)	38 (40%)	76 (29%)	94 (32%)	28 (24%)	47 (40%)
Abdominal pain	23 (6%)	1 (2%)	22 (6%)	4 (4%)	6 (2%)	8 (3%)	3 (3%)	3 (3%)
Accidental injury	27 (7%)	0	27 (7%)	4 (4%)	5 (2%)	15 (5%)	3 (3%)	4 (3%)
Asthenia	31 (8%)	1 (2%)	30 (8%)	4 (4%)	5 (2%)	16 (6%)	4 (3%)	8 (7%)
Back pain	27 (7%)	2 (4%)	25 (6%)	2 (2%)	5 (2%)	10 (3%)	5 (4%)	8 (7%)
Chest pain	18 (4%)	0	18 (5%)	2 (2%)	3 (1%)	7 (2%)	3 (3%)	4 (3%)
Flu syndrome	34 (8%)	2 (4%)	32 (8%)	4 (4%)	7 (3%)	13 (4%)	7 (6%)	5 (4%)
Headache	107 (27%)	12 (22%)	103 (26%)	17 (18%)	39 (15%)	38 (13%)	11 (9%)	21 (18%)
Infection	25 (6%)	1 (2%)	24 (6%)	5 (5%)	1 (0%)	10 (3%)	3 (3%)	5 (4%)
Malaise	8 (2%)	3 (6%)	7 (2%)	1 (1%)	1 (0%)	1 (0%)	3 (3%)	2 (2%)
Pain	65 (16%)	4 (7%)	64 (16%)	11 (12%)	18 (7%)	31 (11%)	6 (5%)	14 (12%)
Viral infection	35 (9%)	0	35 (9%)	2 (2%)	4 (2%)	17 (6%)	5 (4%)	10 (8%)
Cardiovascular System	37 (9%)	2 (4%)	35 (9%)	6 (6%)	3 (1%)	13 (4%)	5 (4%)	9 (8%)
Digestive System	143 (36%)	9 (17%)	136 (34%)	23 (24%)	38 (14%)	60 (21%)	17 (15%)	37 (31%)
Diarrhea	29 (7%)	1 (2%)	28 (7%)	3 (3%)	3 (1%)	14 (5%)	5 (4%)	7 (6%)
Dyspepsia	31 (8%)	5 (9%)	26 (7%)	7 (7%)	8 (3%)	7 (2%)	2 (2%)	6 (5%)
Nausea	89 (22%)	4 (7%)	85 (21%)	9 (10%)	21 (8%)	30 (10%)	11 (9%)	27 (23%)
Vomiting	29 (7%)	1 (2%)	28 (7%)	1 (1%)	5 (2%)	12 (4%)	2 (2%)	9 (8%)
Metabolic and Nutritional System	45 (11%)	2 (4%)	45 (11%)	6 (6%)	8 (3%)	17 (6%)	10 (9%)	11 (9%)
Musculoskeletal System	63 (16%)	2 (4%)	61 (15%)	8 (9%)	16 (6%)	31 (11%)	4 (3%)	9 (8%)

(continued)

Body System COSTART Preferred Term	Total*	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total*	3.0	4.5	6.0	7.5	9.0
Number of patients	402 (100%)	54 (100%)	399 (100%)	94 (100%)	266 (100%)	290 (100%)	116 (100%)	118 (100%)
Nervous System	196 (49%)	17 (31%)	190 (48%)	31 (33%)	61 (23%)	98 (34%)	23 (20%)	54 (46%)
Abnormal dreams	20 (5%)	0	20 (5%)	2 (2%)	8 (3%)	7 (2%)	4 (3%)	1 (1%)
Confusion	29 (7%)	1 (2%)	28 (7%)	4 (4%)	6 (2%)	10 (3%)	6 (5%)	9 (8%)
Depression	26 (6%)	1 (2%)	25 (6%)	4 (4%)	2 (1%)	12 (4%)	3 (3%)	6 (5%)
Dizziness	72 (18%)	2 (4%)	70 (18%)	16 (17%)	13 (5%)	32 (11%)	9 (8%)	20 (17%)
Emotional lability	13 (3%)	3 (6%)	10 (3%)	2 (2%)	2 (1%)	2 (1%)	1 (1%)	3 (3%)
Nervousness	35 (9%)	6 (11%)	31 (8%)	3 (3%)	9 (3%)	13 (4%)	2 (2%)	8 (7%)
Sleep disorder	46 (11%)	2 (4%)	44 (11%)	4 (4%)	15 (6%)	22 (8%)	4 (3%)	10 (8%)
Somnolence	55 (14%)	8 (15%)	49 (12%)	11 (12%)	13 (5%)	21 (7%)	3 (3%)	12 (10%)
Respiratory System	105 (26%)	6 (11%)	103 (26%)	15 (16%)	29 (11%)	54 (19%)	13 (11%)	14 (12%)
Cough increased	24 (6%)	2 (4%)	22 (6%)	5 (5%)	6 (2%)	9 (3%)	2 (2%)	1 (1%)
Pharyngitis	42 (10%)	3 (6%)	41 (10%)	5 (5%)	7 (3%)	22 (8%)	7 (6%)	1 (1%)
Rhinitis	30 (7%)	1 (2%)	29 (7%)	4 (4%)	11 (4%)	10 (3%)	5 (4%)	2 (2%)
Sinusitis	21 (5%)	0	21 (5%)	4 (4%)	4 (2%)	11 (4%)	2 (2%)	3 (3%)
Skin	52 (13%)	4 (7%)	49 (12%)	4 (4%)	8 (3%)	23 (8%)	4 (3%)	14 (12%)
Sweating	17 (4%)	0	17 (4%)	2 (2%)	2 (1%)	6 (2%)	1 (1%)	9 (8%)
Special Senses	48 (12%)	3 (6%)	45 (11%)	8 (9%)	9 (3%)	15 (5%)	7 (6%)	9 (8%)
Urogenital System	78 (19%)	6 (11%)	74 (19%)	6 (6%)	16 (6%)	34 (12%)	8 (7%)	21 (18%)
Incontinence urine	8 (2%)	0	8 (2%)	0	0	2 (1%)	0	6 (5%)
Urinary incontinence	24 (6%)	0	24 (6%)	2 (2%)	7 (3%)	7 (2%)	5 (4%)	5 (4%)

* Patients are counted only once in each category.

The above table confirms that

- The most common adverse events in those treated with GHB were headache, pain, nausea and dizziness.
- A dose response could be seen, at least in the case of the 9 g dose, in the case of nausea.

8.5.3.3 Lammers Trial

Only a few adverse events were seen in this study as summarized by the following table taken from the Lammers study report. Note that

- Only 3 patients had adverse events while taking GHB
- Adverse events seen in this study have also been included in the Controlled Clinical Trials grouping above

Patient number	Treatment	Investigator term
8	GHB	terrible dreaming dry mouth paralysis in legs and arms anxious insecure
15	Placebo	kidney problems urination problems (stranguria)
2	GHB	severe perspiration influenza (common cold), sore throat headache frequent micturition
5	GHB	infection bladder sore throat flickering in the eyes
9	Wash out	frequent headache
17	Wash out	severe dreaming

8.5.3.4 Integrated Pharmacokinetic Trials

The following table, copied from the Integrated Summary of Safety, presents the number of adverse events that occurred in $\geq 5\%$ of subjects in the Integrated Pharmacokinetic Trials Grouping

Body System COSTART Preferred Term	Sodium Oxybate ^a
Number of Subjects	144 (100%)
Body as Whole	21 (15%)
Headache	18 (13%)
Digestive System	44 (31%)
Nausea	37 (26%)
Vomiting	27 (19%)
Nervous System	40 (28%)
Confusion	7 (5%)
Dizziness	26 (18%)

^a Subjects are counted only once in each category.

As the above table indicates the most common adverse events in this grouping as well are headache, nausea, vomiting and dizziness.

8.5.3.5 Scharf Trial

Given the duration of this study, adverse events were common and at least 1 adverse event was experienced by 95.1% of those participating in this trial. Adverse events that occurred in $\geq 5\%$ of patients in the study are in the following table

Adverse Event (COSTART)	Number of patients	% of Patients
Allergic reaction	13	9.1
Asthenia	32	22.4
Chills	19	13.3
Fever	38	26.6
Flu syndrome	55	38.5
Headache	75	52.4
Infection	16	11.2
Infection viral	81	56.6
Injury accidental	60	42.0
Malaise	33	22.1
Neoplasm	12	8.4
Pain	69	48.3
Pain abdominal	38	26.6
Pain back	29	20.3
Pain chest	33	20.1
Pain neck	15	10.5
Reaction unevaluable	33	23.1
Arrhythmia	15	10.5
Ventricular extrasystoles	10	7.0
Hypertension	21	14.7
Tachycardia	11	7.7
Vasodilatation	11	7.7
Periodontal abscess	8	5.6
Colitis	6	4.2
Constipation	8	5.6
Diarrhea	40	28.0
Dry mouth	12	8.4
Dyspepsia	36	25.2
Gastroenteritis	20	14.0
Nausea	58	40.6
Tooth disease	18	12.6
Vomiting	29	20.3
Peripheral edema	18	12.6
Arthralgia	16	11.2
Arthritis	26	18.2
Leg cramps	11	7.7
Joint disease	15	10.5
Myalgia	15	10.1
Anxiety	10	7.0
Ataxia	9	6.3
Confusion	9	6.3
Convulsion	8	5.6
Depression	19	13.3
Dizziness	39	27.3
Emotional lability	8	5.6
Hypertonia	13	9.1
Hypesthesia	12	8.4
Insomnia	10	7.0
Nervousness	20	14.0
Neuralgia	8	5.6
Paresthesia	17	11.9
Sleep disorder	45	31.5
Somnolence	15	10.5
Tremor	9	6.3
Apnea	19	13.3
Bronchitis	32	22.4
Increased cough	49	34.3
Dyspnea	27	18.9
Epistaxis	10	7.0
Lung disease	13	9.1
Pharyngitis	54	37.8
Pneumonia	9	6.3
Rhinitis	52	36.4
Sinusitis	38	26.6

Pruritus	13	9.1
Rash	13	9.1
"Sweat"?	26	18.2
Amblyopia	13	9.1
Conjunctivitis	19	13.3
Otitis media	10	7.0
Ear pain	14	9.8
Eye pain	13	9.1
Abnormal vision	9	6.3
Urinary incontinence	33	23.1

The most common adverse events in this study, at least some of which were due to intercurrent illnesses, included (in descending order of frequency) viral infection, headache, pain, accidental injury, nausea, flu syndrome, pharyngitis, rhinitis, increased cough, sleep disorder, diarrhea, dizziness, fever, abdominal pain, sinusitis and dyspepsia.

The most common adverse events considered to be drug-related by the investigator, and occurring in the first 6 months (in descending order of frequency) of GHB use were sleep walking, dizziness, nausea, pain, dyspepsia, abdominal pain, viral infection and headache. The most frequent adverse events (whether considered related to GHB or not) during that period were headache, viral infection, pain, nausea and dizziness: tables for all adverse events in this time period have been provided by the sponsor

The most common adverse events occurring after the first 6 months of treatment were viral infection, pain, headache and accidental injury. Tables for all adverse events in this time period have been provided by the sponsor.

8.5.4 Common and Drug-Related Side Effects

I have used 2 sets of studies in defining these

- Controlled clinical trials
- All clinical trials

8.5.4.1 Controlled Clinical Trials

In the controlled clinical trials group I have selected those adverse events that have been listed as occurring in $\geq 5\%$ of Xyrem®-exposed patients and at least twice as frequently as those exposed to placebo. The following adverse events, listed using COSTART terms, fit these criteria:

Infection (5%), pain (8%), nausea (12%), vomiting (4%), confusion (5%), dizziness (16%), sleep disorder (7%) and urinary incontinence (4%)

8.5.4.2 All Clinical Trials

The 3 most common adverse events in GHB-treated patients across the 2 main clinical trial subsets (Integrated Clinical Trials, Integrated Pharmacokinetic Trials and Scharf Study) were:

Headache, nausea and dizziness.

The next table indicates their incidence in each of the clinical trial groupings

Adverse Event	Integrated Clinical Trials (%)	Integrated Pharmacokinetic Trials (%)	Scharf Trial (%)
Headache	26	13	52
Nausea	21	26	41
Dizziness	18	18	27

8.5.5 Additional Analyses and Explorations

Special analyses were performed by the sponsor for the following adverse events

- Urinary incontinence (and its relationship to seizures)
- Elevated anti-nuclear antibodies

Further analyses explored the relationship of adverse events to dose, duration of treatment, concomitant medication use, age, and gender

These items are discussed in greater detail below

8.5.5.1 Urinary Incontinence And Its Relationship To Seizures

8.5.5.1.1 BACKGROUND

Animal studies have shown a relationship between the use of high doses of GHB, and symptomatology as well as EEG changes that resemble those of absence seizures in humans. An experimental animal model for absence seizures has in fact been developed using sodium oxybate. Myoclonic jerks have also been seen in patients (outside the United States) in whom anesthesia has been induced with GHB.

In our original review of Treatment IND # 57271, this Division had noted that several GHB treated patients were noted to have nocturnal urinary incontinence. There was a concern as to whether unrecognized seizures were responsible for the episodes of incontinence in these patients.

Based on the above a more detailed analysis of urinary incontinence in clinical trials of GHB, and its possible relationship to hitherto-unrecognized seizures was requested by this Division

8.5.5.1.2 METHODS

The sponsor conducted an analysis of urinary incontinence using the following methods

- Adverse events suggestive of urinary incontinence were searched for in the databases for both trials
- Adverse events that appeared to be of central nervous system origin were also looked for.
- A questionnaire was distributed to all investigators whose patients had reported urinary incontinence in Studies OMC-GHB-2 and OMC-GHB-3. The questionnaire asked investigators to list any additional nocturnal observations that would suggest the presence of seizures, ascertain the patient's urological

history prior to beginning GHB treatment and to note any new neurological symptoms

- Patients who had both central nervous system adverse events and urinary incontinence were identified as were patients who had urinary incontinence and central nervous system adverse events contemporaneously
- Overnight EEG recordings were made prospectively in 6 patients who had a prior history of incontinence during sodium oxybate treatment at a dose of 9 g/day. Note that only 4/6 patients had recordings done with what was believed to be an adequate number of scalp electrodes to reliably detect electrical seizure activity (the EEG recorded during polysomnography does not typically use enough scalp electrodes to reliably detect seizure patterns). In addition polysomnogram EEG recordings were looked at retrospectively in 2 additional patients who had urinary incontinence
- The data were reviewed by an independent expert in epilepsy, Dr Nathan Crone, who was asked to render an opinion as to whether the episodes of incontinence that have occurred during clinical trials of GHB could have been due to seizures.
- Other experts were also consulted by the sponsor regarding whether GHB could cause seizures.
- The medical literature was also reviewed.

8.5.5.1.3 RESULTS

8.5.5.1.3.1 Incontinence In Studies OMC-GHB-2 And OMC-GHB-3

- In OMC-GHB-2, 15 events of enuresis/urinary incontinence occurred in 8 of the 136 patients participating in that trial. 5 of these patients had at least one episode occurring at night; in the remaining 3 there is insufficient information to indicated that the incontinence occurred at night. The distribution of these events based on the daily dose of GHB taken at the time of incontinence is in the following table (note that patients were randomized equally to the placebo, 3 g/day, 6 g/day and 9 g/day doses in this study)

GHB Dose (g/day)	Number of events of incontinence
6	3
9	11
0*	1

*Not taking study drug or placebo

- In OMC-GHB-3, 51 events of enuresis/urinary incontinence occurred in 13 of the 188 patients who participated in this study. A single patient accounted for 15 events. 20/51 events were considered related to GHB by the investigator. Only a few of these events are specifically documented as having occurred at night. The distribution of these events based on the daily dose of GHB taken at the time of incontinence is in the following table

GHB Dose (g/day)	Number of events of incontinence
2.3	1
3	1
4.5	5
6	27
7.5	1
9	16

- One additional patient in each trial (OMC-GHB-2 and OMC-GHB-3) experienced fecal incontinence. The doses of GHB at the time of incontinence were 9 g/day and 6 g/day, in the OMC-GHB-2 and OMC-GHB-3 trials respectively. The patient participating in the OMC-GHB-2 trial had a single episode of fecal incontinence after which the study drug was stopped. The patient participating in the OMC-GHB-3 trial had multiple episodes of fecal incontinence, a previous history of milk allergy with diarrhea, and a negative sigmoidoscopy.
- The central nervous system adverse events that occurred in patients who had urinary incontinence included the following
 Tremor, disorientation, confusion, impaired concentration, tingling in head, tingling/numbness in face, numbness of left hand, face and leg, abnormal muscle sensations, muscle jerks/spasms, "drunkenness", and poor balance/unstable gait/poor equilibrium/impaired coordination
- 2 patients in OMC-GHB-2 and 2 patients in OMC-GHB-3 had central nervous system adverse events contemporaneously with urinary incontinence. These adverse events were disorientation, confusion and muscle jerks. Narratives have been provided for these 4 patients and do not provide any strong evidence that these patients had seizures of any kind, although one of these adverse events (muscle jerks) could conceivably have represented myoclonic jerks. Unfortunately, descriptions of the events are lacking. These 4 patients are summarized in the following table.

Study	Patient ID #	Age/Gender	GHB Dose At Time Of Incontinence	Contemporaneous Central Nervous System Adverse Event
OMC-GHB-2	0702	59/F	9 g/day	Confusion
OMC-GHB-2	0124	57/M	9 g/day	Confusion
OMC-GHB-3	0219	65/F	9 g/day	Disorientation
OMC-GHB-3	0819	57/M	3 g/day	Muscle jerks*

*This patient had a single episode of incontinence which occurred at the same time as his muscle jerks began. However the muscle jerks persisted long after his episode of incontinence ended

8.5.5.1.3.2 *Incontinence In Other Clinical Trial Groupings*

- In the 5 integrated clinical trials 32 of the 402 patients experienced urinary incontinence; 2 patients had fecal incontinence.
- In the 8 integrated pharmacokinetic trials 2 of 144 subjects experienced urinary incontinence and 1 subject experienced fecal incontinence. None of these individuals was observed to have seizures
- No patients in the Lammers or Scrima studies experienced incontinence.

8.5.5.1.3.3 *EEG Studies*

- In the prospective overnight EEG recordings in 6 patients, only one had urinary incontinence during the recording. No electrical seizure activity was apparent in any of the 6 patients. Note that the patient who had incontinence (Initials:(b)(had what was believed to be an adequate number of scalp electrodes for the recordings.
- No electrical seizure activity was seen on either of the 2 retrospectively reviewed polysomnogram EEG recordings although one recording was stated to be of poor quality.

- The sponsor believes that the EEG data described here represent a reasonable attempt to show that GHB does not cause clinically subtle seizures, and that enuresis associated with GHB is not caused by seizures.

8.5.5.1.3.4 *Animal Data In Literature*

The sponsor has summarized the animal data in the medical literature as follows.

- As noted above GHB is used to induce absence seizures in an experimental animal (monkey) model developed by O. Carter Snead. In that model, following an IV dose of 400mg/kg GHB, the EEG and behavioral effects in the monkey consist of an initial low-voltage slowing of brain rhythms combined with drowsiness from which the animal can be easily aroused. This state then progresses to paroxysmal rhythmic 2.5 to 3 per second high-voltage slowing, punctuated by spikes, during which the animal exhibits staring, occasional rhythmic eye movement, dilated pupils, unresponsiveness to any stimuli, and myoclonic movements. Such paroxysms are frequently precipitated by auditory stimuli. The doses and serum concentrations at which these phenomena occur depend on the age of the animal and the elapsed time between administration of the dose and drawing of the blood sample
- Higher doses can also cause generalized tonic-clonic seizures.
- Epileptiform abnormalities on EEG typically appear at GHB serum levels greater than 300 µg/ml, corresponding to a dosage threshold of 200 mg/kg. Myoclonic seizures occur at levels greater than 500 µg/ml.
- In contrast, a pharmacokinetic study of GHB in six patients with narcolepsy showed that after a typical 3 g oral dose the peak serum level of GHB did not exceed 125 µg/ml.

8.5.5.1.3.5 *Clinical Data In Literature*

These data are summarized below

- There are many anecdotal case reports and case series of intoxication with GHB reported in the medical literature, and related to illicit use of that drug
 - Many of these incidents include reports of tonic-clonic seizures. In most of these it is not clear how much GHB was ingested, and adverse reactions were often associated with concomitant alcohol consumption.
 - In one of the rare instances where the dose of GHB ingested could be estimated a 40-year-old man had a “tonic-clonic major motor seizure without a previous history of epilepsy” about 20 minutes after taking about 115 mg/kg of GHB.
 - GHB has been used in Europe as an anesthetic, and as a sedative in intensive care units, at doses of about 50 mg/kg.
 - This dose of GHB has not been associated with seizures.
 - A German study examined the effect of GHB on the EEG of 31 patients after abdominal surgery. After injection of 50 mg/kg intravenously, no seizure-like electrical activity was observed in the EEG

8.5.5.1.3.6 *Expert Opinions*

- According to Dr Martin Scharf, one of the experts consulted by the sponsor, no bed-partners of patients taking GHB had reported phenomena that might be considered seizure-like. Dr Scharf reportedly stated that there were about 750 patient-years of exposure to GHB (he was presumably referring to

studies in which he was the principal investigator) and that the majority of these patients had bed partners. Since urinary incontinence that results from seizures is most commonly associated with the generalized tonic-clonic variety such seizures might have been expected to awaken a bed partner, at least in some patients.

- Another expert, Dr Mortimer Mamelak, stated that despite a long history of GHB use for a variety of indications there were no reports of seizures occurring in association with use of the drug.
- Dr Nathan Crone's analysis included a review of OMC-GHB-2 and OMC-GHB-3 clinical trial data, data from a recently completed pharmacokinetic trial (OMC-SXB-11), the discussions with Drs Scharf and Mamelak, the prospectively collected EEG data described above, and relevant literature. His conclusions have been summarized by the sponsor as follows:

"After review of the clinical and research literature on the epileptogenic properties of GHB it is Dr. Crone's opinion that GHB does have the potential to cause seizures in humans, but this probably requires higher doses than those planned for the clinical treatment of narcolepsy. The doses used to induce absence and generalized tonic-clonic seizures in animals are probably higher than those used for clinical purposes in humans. There are a handful of reports of seizures due to GHB abuse. Some have occurred with doses that appear to be similar to clinically useful dosages, but the actual amount ingested could not be readily verified. Clinical studies of GHB in patients with narcolepsy have not reported any seizures in association with GHB. EEG recorded during polysomnography may not be sufficient to detect subclinical, electrographic seizure activity. Other than data collected by Dr. Scharf, only one study has been done on the effects of GHB on human EEG. Although this study did not detect any epileptiform changes, future evaluation of the utility of GHB for any clinical purpose should include EEG recordings during administration of GHB, as well as EEG during maneuvers that are known to provoke absence seizures, i.e. hyperventilation and stroboscopic photic stimulation."

8.5.5.1.4 SPONSOR'S CONCLUSIONS

Despite the appearance of absence-like seizure states in primates at intravenous GHB doses "far exceeding the human therapeutic dose", there is no support, in the clinical trials included in this Integrated Summary of Safety or in the literature reporting human experience in therapeutic dosages for a relationship between instances of incontinence reported with GHB and seizures

8.5.5.1.5 CONVULSIONS WITH XYREM® (REVIEWER'S SUMMARY)

"Convulsions" were reported as an adverse event in a number of GHB-treated patients in the NDA safety database. In practically every instance no additional qualitative descriptions of this adverse event are available, even in instances where narratives and Case Report Forms have been provided (i.e., in instances where convulsions have been listed as a serious adverse event or adverse event discontinuation). It is also unclear as to what extent the term "convulsions" truly referred to an epileptic phenomenon (e.g., it is unclear how frequently the term "convulsion" was used to describe an attack of cataplexy or whether tremor or myoclonus was referred to as "convulsion").

There were no patients in the entire safety database who had adverse events listed under any other preferred term that would strongly suggest that they had true convulsions.

I have summarized convulsions as recorded as an adverse effect of Xyrem® in the NDA safety database as follows.

- In the controlled clinical trials 2 (1.4% of) GHB-treated patients are listed as having convulsions whereas no placebo-treated patient had convulsions. In neither of these 2 patients was “convulsion” listed as a serious adverse event or as a reason for treatment discontinuation. Detailed descriptions of this adverse event are unavailable
- In the entire integrated clinical trials grouping 10 (2.5% of) GHB-treated patients are listed as having convulsions. In none of these instances was “convulsion” listed as a serious adverse event or as a reason for treatment discontinuation. Detailed descriptions of this adverse event are unavailable
- In the Scharf study, 9 (6.3% of) GHB-treated patients are listed as having convulsions: the sponsor believes that in 5 of those instances the events coded as “convulsions” more likely represented cataplexy; of the remaining 4 patients one had seizures prior to study entry. These patients are summarized in the table below

Of the patients in the table below: 1 patient (# 064; see description in Section 8.4.2.2) was listed as discontinuing treatment on account of seizures and in another patient (# 257; see Section 8.3.2.4) the convulsion was listed as a serious adverse event.

For all 9 patients detailed descriptions of the events called “convulsions” are lacking. Narratives and Case Report Forms are available for 2 patients (#s 064 and 257) but do not help clarify whether the events were true convulsions, epileptic phenomena of any other kind or neither.

Patient ID	COSTART Term	Verbatim Term	No. of Events	Dose (g) ¹
043	Convulsion	Excessive cataplexy	-	6.0
048 ²	Convulsion	Convulsive-like seizure	1	8.3
049	Convulsion	Fall, sudden cataplexy	-	6.0
051	Convulsion	Fell twice, with cataplexy	-	3.0
064	Convulsion	Seizure	1	7.5
		Seizure	1	6.0
		Seizure	1	6.0
		Seizure-morning	1	6.0
		Seizure-afternoon	1	6.0
		Seizure-morning	1	6.0
		{Total events}	6	
219	Convulsion	Cataplexy, twice	-	7.5
247	Convulsion	Seizures, continuous jerking	1	6.0
255 ³	Convulsion	Grand mal seizure	1	5.3
257	Convulsion	Violent shaking and vibrations	-	5.3
		Jerking during cataplexy	-	9.0
		Severe cataplexy	-	9.0
		Cataplexy	-	12.0
		Fall due to cataplexy. Patient suffered injury, resulting in increased catalepsy.	-	11.3

¹Dose recorded is the dose at the onset of the adverse event.

²This event for patient 048 was judged a serious adverse event that was related to the study medication.

³Patient 255 had a history of seizures of unknown etiology at enrollment.

- Based on the narratives and Case Report Forms that have been supplied for some patients with convulsions (i.e., those in whom this adverse event was listed as serious or led to study drug discontinuation) it is difficult to determine
 - If they in fact had true convulsions or any epileptic phenomenon at all (clinical descriptions of the episodes were lacking)
 - If at least some patients treated with GHB did have true convulsions, it is not clear that GHB caused their convulsions; confounding factors included the use of concomitant medications such as stimulants or tricyclic antidepressants which are themselves reputed to have epileptogenic properties
 - One patient (# 255 in the above table) was documented as having a seizure disorder even prior to receiving GHB
 - Another patient recorded as having convulsions (see Section 8.4.2.2) during a GHB study may have had convulsions even prior to the study: she also had a history of a left frontal lobe lesion and burr hole surgery
- The sponsor has stated that absence-like seizure states occur in primates at intravenous GHB doses “far exceeding the human therapeutic dose”. In fact the safety margin between the highest human dose used in efficacy trials and that used in primate models to induce absence seizures, while it certainly exists, may not extremely wide as the following indicate
 - The highest human dose used in efficacy trials is 9 g/day. In a 60 kg individual this dose is equal to 150 mg/kg/day or 5550 mg/m²/day

- Intravenous doses of 400 mg/kg in monkeys are sufficient to induce clinical absence seizures. Assuming that GHB has an oral bioavailability of 30% in monkeys this would be equivalent to an oral dose of 1333 mg/kg or 26660 mg/m²
- Intravenous doses of 200 mg/kg in monkeys are sufficient to induce epileptiform abnormalities on an EEG. Again, assuming that GHB has an oral bioavailability of 30% in monkeys this would be equivalent to an oral dose of 667 mg/kg or 13340 mg/m²
- Epileptiform abnormalities on EEG typically appear at GHB serum levels greater than 300 µg/ml, corresponding to a dosage threshold of 200 mg/kg. Myoclonic seizures occur at levels greater than 500 µg/ml.
- A pharmacokinetic study of GHB in six patients with narcolepsy showed that after a typical 3 g oral dose the peak serum level of GHB did not exceed 125 µg/ml.
- In an additional pharmacokinetic study in 13 healthy individuals, after 2 nightly doses of GHB of 9 g each the mean C_{max} was 142 µg/mL (coefficient of variation 35%)

8.5.5.1.6 REVIEWER'S COMMENTS

- In controlled clinical trials urinary incontinence was more frequent in those treated with GHB than in those treated with placebo (5% vs 0%) suggesting that, while not very common, urinary incontinence may be caused by that drug. Furthermore, urinary incontinence in GHB-treated patients may be dose-related.
- In controlled clinical trials fecal incontinence was seen in 1 GHB-treated patient (1%) but not in any placebo-treated patient. A number of other instances of fecal incontinence were seen in the entire database, but the overall incidence of this adverse event was much lower than that of urinary incontinence
- Based on the circumstantial evidence supplied above, there is no firm evidence that urinary incontinence in any patients treated with GHB was caused by seizures, whether generalized tonic-clonic or of another kind. However only one patient appears to have had an episode of incontinence while actually undergoing EEG monitoring; in that instance the EEG did not show any evidence of epileptiform activity; this patient did appear to have an adequate number of scalp electrodes and montages.
- In the open-label Scharf study which was not included in the sponsor's formal analysis of incontinence, 33 patients (23.1%) had urinary incontinence. 1 patient (0.7%) had fecal incontinence. There has been no formal attempt by the sponsor to determine if any of these instances could have been secondary to seizures. All that the sponsor has done is to provide a summary table for those with convulsions providing further details for the patients summarized under the previous bullet. This table is above.
- Overall, the evidence that urinary incontinence associated with therapeutic use of GHB is due to unrecognized seizures, or that GHB is epileptogenic at therapeutic doses, is not strong at present. However either possibility cannot be excluded based on the available information which is very limited: studies conducted to address this matter have also been very limited in scope so far and further studies to evaluate this issue may be warranted.

8.5.5.2 *Elevated Antinuclear Antibodies*

This analysis has been confined entirely to the Scharf study

8.5.5.2.1 BACKGROUND

After a patient in the Scharf trial developed elevated antinuclear antibodies in 1991, this phenomenon was further investigated in that study and was also discussed with this Agency

8.5.5.2.2 METHODS

These are described only very briefly in the submission.

After the index case of elevated antinuclear antibodies was noted, the same titers were checked for all "ongoing" patients in the trial; these checks appear to have been initially done on a total of 65 patients over the 2 years after the index case was identified. After discussions with this Agency Dr Scharf continued to check antinuclear antibody titers on all patients participating in this study; data are provided for until 5/31/99, the cut-off date for the Scharf study report. A total of 87 patients had at least one antinuclear antibody titer estimated.

In a proportion of those with positive antinuclear antibodies, antihistone antibody titers were checked.

An attempt was made to correlate the antibody titers with symptoms consistent with systemic lupus erythematosus, medication-induced lupus or any other rheumatic disease using a symptom questionnaire that was supplied to the initial 65 patients who had antibody titers determined.

In each patient in whom antinuclear antibody titers were positive on more than one occasion summaries were made of demographics, antinuclear antibody titers (with specific dates) and adverse events that developed during the course of the study (with specific dates)

The methods of sample collection, storage, analysis and interpretation were not standardized for the antinuclear antibody and antihistone antibody titer estimations: these tests were performed at a variety of laboratories. An antinuclear antibody titer of > 1:40 was considered positive.

The vast majority of patients who had the above antibody titers determined lacked baseline measurements. In the majority of instances (80%) these determinations were made after an extended period of treatment with GHB

8.5.5.2.3 RESULTS

The results of this analysis have been presented as

- Summary text
- Data listings for all patients who had antinuclear antibody and antihistone antibody testing: these listings include patient ID number, date of initial dose of GHB, date of testing, dose of GHB at time of testing and antibody titers
- A table listing all patients who had positive antinuclear antibody tests on at least a single occasion: the table included the patient number, the date treatment was started, the date of

the first antinuclear antibody, the result of the first antinuclear antibody, the total number of antinuclear antibody titer determinations, the number of positive antinuclear antibody determinations and the sequence of antinuclear antibody determinations

- Summaries of demographics, antinuclear antibody titers (with specific dates) and adverse events that developed during the course of the study (with specific dates) for all patients whose antibody titers were positive on more than one occasion

8.5.5.2.3.1 In the population of 65 patients who initially had antinuclear antibody testing done.

- 19/65 (29.2%) of patients had one or more antinuclear antibody elevations ranging from 1:40 to 1:2560
- No correlations were found between positive antinuclear antibody titers and duration of treatment, age or gender
- 15/19 patients who were antinuclear antibody-positive had antihistone antibodies done: these were negative in all but one patient who had a result that was termed “borderline positive” and who did not have symptoms characteristic of lupus
- The symptom questionnaire showed a low overall incidence of symptoms that could have been consistent with lupus with no differences between the subgroup of those with positive antinuclear antibody titers and those in whom these titers were negative

8.5.5.2.3.2 In the total population of 87 patients who had antinuclear antibody testing done

- 26/87 (29.9%) had at least one positive antinuclear antibody test. These patients are summarized in the next table which has been copied from the submission.

PATIENT NO.	DATE RX STARTED	DATE 1 ST ANA	RESULT 1 ST ANA	TOTAL NO. ANA'S	NO. POSITIVE ANA'S	SEQUENCE OF ANA FINDINGS*
3	11/86	7/90	N	10	1	N-N-N-N-N-N-N-N-N-P
4	1/88	12/90	N	15	2	N-N-N-P-P-N-N-N-N-N-N-N-N
15	1/84	5/90	N	10	5	N-P-P-N-N-P-N-N-P-P
17	2/89	1/90	N	12	6	N-P-P-P-P-N-P-P-N-N-N-N
35	6/87	6/90	N	13	7	N-P-P-N-P-N-N-N-P-P-N-N-P-P
39	11/84	12/90	N	12	1	N-N-N-N-N-N-N-N-N-P-N-N-N
41	6/84	1/92	N	17	14	N-P-N-P-P-P-N-P-P-P-P-P-P-P-P-P-P
42	1/87	6/92	N	12	2	N-N-N-N-N-P-P-N-N-N-N-N
45	1/87	2/90	N	14	6	N-N-N-N-N-N-N-P-P-N-P-P-P-P
50	2/84	6/90	N	12	5	N-N-N-N-N-N-P-P-P-P-P-N
51	10/85	12/91	N	10	1	N-N-N-N-N-N-N-N-N-P
54	2/87	6/90	N	9	1	N-N-P-N-N-N-N-N-N
62	6/87	6/90	N	13	2	N-P-N-N-N-N-N-N-N-N-N-P-N
65	11/83	12/90	N	16	1	N-N-N-N-N-N-N-N-N-N-N-N-N-P-N
66	3/85	1/91	P	7	7	P-P-P-P-P-P-P
67	2/86	6/90	P	14	7	P-N-N-P-N-N-P-N-N-P-N-P-P-P
70	5/87	5/90	N	13	1	N-P-N-N-N-N-N-N-N-N-N-N
225	11/84	4/92	N	6	2	N-N-N-N-P-P
227	10/89	2/90	N	15	1	N-N-N-P-N-N-N-N-N-N-N-N-N-N
235	9/84	1/90	N	13	4	N-N-P-N-N-N-P-N-P-N-N-N-P
237	6/90	12/96	P	2	1	P-N
257	5/90	2/92	N	11	5	N-N-N-N-N-N-P-P-P-P-P-P
260	2/84	12/89	N	12	10	N-N-P-P-P-P-P-P-P-P-P-P
267	4/92	8/92	P	13	4	P-N-N-N-N-N-N-N-P-P-P-N
270	1/94	5/95	N	9	5	N-P-N-N-N-P-P-P-P
277	7/96	7/96	N	3	1	N-N-N-P

- In the above table, 9 patients had only a single positive result while the remaining 17 had multiple positive antinuclear antibody determinations
- In the above table 4 patients were positive on their first antinuclear antibody test, whereas the remaining 22 had at least one negative determination prior to a positive one

8.5.5.2.3.3 Among the 17 patients with 2 or more positive antinuclear antibody results

- There were 7 males and 10 females
- Their ages ranged from 15 to 66 years; all were Caucasian
- Daily doses of GHB ranged from 4.5 g to 11 g/day. The most frequent stable dose was 6 g/day
- When the sequence of antinuclear antibody testing was examined several different patterns of positivity/negativity were seen
- Adverse event data obtained from Case Report Forms (which I have examined) indicates the presence of very few rheumatological symptoms
- No patient was diagnosed to have either drug-induced lupus or systemic lupus erythematosus

8.5.5.2.4 SPONSOR'S CONCLUSIONS

- The incidence of positive antinuclear antibody tests in the population in this study appears to be higher than what might be expected in the general population
- Sodium oxybate-treated narcoleptic patients in the Scharf trial who had positive antinuclear antibody titers did not present with, or subsequently develop, symptoms suggestive of systemic lupus erythematosus, drug-induced lupus or any rheumatic disease.
- There is no evidence that chronic treatment with GHB results in an increase in occurrence of any rheumatic or immune-mediated disease.
- In medication-induced lupus, positive antinuclear antibody titers are accompanied in most cases (90%) by antihistone antibodies.
- Use of sodium oxybate may result in elevated antinuclear antibody titers without the corresponding increase in antihistone antibodies seen in patients with drug-induced lupus
- A review of the scientific literature published since 1966 failed to uncover any study that reported the incidence of antinuclear antibodies in narcolepsy. Thus it is impossible to determine if the increased incidence of positive antinuclear antibody tests is related to GHB or narcolepsy, or is unique to this dataset
- Dr Evelyn Hess, an expert in systemic lupus erythematosus and drug-induced lupus, whose opinion was sought by the sponsor, concurred with the sponsor's conclusions. According to her, the most that might be concluded was that sodium oxybate, like many other drugs, may be associated with low level increases in antinuclear antibody titer of no known clinical significance.

8.5.5.2.5 DISCONTINUATIONS DUE TO POSITIVE ANTINUCLEAR ANTIBODIES

2 patients discontinued from the Scharf study on account of positive antinuclear antibody tests. These patients are already described above (Sections 8.4.2.3 and 8.4.2.5)

8.5.5.2.6 REVIEWER'S COMMENTS

- There are clearly a number of readily-evident limitations to the sponsor's analysis. In addition
 - Full details of some analyses have not been supplied (e.g., the actual tables comparing the incidence of symptoms attributable to lupus in the antinuclear antibody-positive and negative groups)
 - Antinuclear antibody titers have been in only a subset of those participating in one study out of a number of studies in this NDA
- At least one patient is stated to have been diagnosed to have "rheumatoid arthritis" close to the time when she was first detected to have a positive antinuclear antibody test (1:640) and after she had received GHB for about 6 years. The test remained positive, sometimes in high titer, while she continued to receive GHB, and for 11 months thereafter. Antihistone antibodies were not checked in this patient. Unfortunately, few details are available regarding this patient's symptoms. However based on the information available for this patient, the following statement by the sponsor is not entirely correct
"Sodium oxybate-treated narcoleptic patients in the Scharf trial who had positive antinuclear antibody titers did not present with or subsequently develop symptoms suggestive of systemic lupus erythematosus, drug-induced lupus or any rheumatic disease."
- There is no firm evidence that any patient treated with GHB developed drug-induced lupus.

8.5.5.3 *Relationship Between Adverse Events And Dose*

8.5.5.3.1 CONTROLLED CLINICAL TRIAL: OMC-GHB-2

This is the only trial in which randomized comparisons between multiple dose groups treated in parallel for the same period of time (1 month) is possible. The table below indicates that while the overall incidence of treatment-emergent adverse events were comparable across treatment groups, certain specific adverse events did show a dose-response and were most common in the 9 g/day dose group. These were: headache, pain, nausea, dizziness, sleep disorder, and incontinence of urine. Note, however, that in this trial patients were not titrated to their assigned doses

Adverse Event (COSTART term)	Treatment Group			
	Placebo (n =34)	GHB 3 g (n = 34)	GHB 6 g (n = 33)	GHB 9 g (n = 35)
Any	24 (70.6)	25 (73.5)	25 (75.8)	26 (74.3)
Headache	7 (20.6)	3 (8.8)	5 (15.2)	11 (31.4)
Infection	1 (2.9)	3 (8.8)	5 (15.2)	0
Infection Viral	1 (2.9)	1 (2.9)	3 (9.1)	0
Pain	2 (5.9)	3 (8.8)	4 (12.1)	7 (20.0)
Pain Back	2 (5.9)	0	2 (6.1)	0
Diarrhea	0	0	2 (6.1)	2 (5.7)
Dyspepsia	2 (5.9)	0	3 (9.1)	2 (5.7)
Nausea	2 (5.9)	2 (5.9)	5 (15.2)	12 (34.3)
Nausea Vomiting	0	0	2 (6.1)	2 (5.7)
Myalgia	0	2 (5.9)	0	0
Myasthenia	0	2 (5.9)	1 (3.0)	0
Amnesia	0	1 (2.9)	0	2 (5.7)
Anxiety	1 (2.9)	1 (2.9)	0	2 (5.7)
Confusion	1 (2.9)	3 (8.8)	1 (3.0)	5 (14.3)
Dizziness	2 (5.9)	8 (23.5)	10 (30.3)	12 (34.3)
Dream Abnormal	0	0	3 (9.1)	1 (2.9)
Hypertension	1 (2.9)	0	2 (6.1)	0
Hypesthesia	0	2 (5.9)	0	0
Sleep Disorder	1 (2.9)	2 (5.9)	4 (12.1)	5 (14.3)
Somnolence	4 (11.8)	5 (14.7)	4 (12.1)	5 (14.3)
Thinking Abnormal	0	1 (2.9)	0	2 (5.7)
Pharyngitis	3 (8.8)	0	3 (9.1)	1 (2.9)
Sweating	0	1 (2.9)	1 (3.0)	4 (11.4)
Amblyopia	1 (2.9)	2 (5.9)	0	0
Tinnitus	0	2 (5.9)	0	0
Dysmenorrhea	1 (2.9)	1 (2.9)	0	2 (5.7)
Incontinence of Urine	0	0	2 (6.1)	5 (14.3)

8.5.5.3.2 OTHER CLINICAL TRIAL GROUPINGS

The sponsor’s analyses indicate the following

- In the Scharf trial no “strong” evidence of a dose-response relationship was seen
- In the Integrated Clinical Trials grouping, based on the dose at the time of onset of the adverse event, a higher incidence of adverse events was seen for the 9 g/day dose as compared with the other dose groups as follows
 - Those with at least one adverse event (74% for the 9 g/day dose group versus 45 to 61% for the other dose groups)
 - Discontinuations due to adverse events (12% for the 9 g/day group versus 3-5% for the other dose groups)
 - In the OMC-GHB-2 trial a dose-response effect was seen for nausea and viral infection that was statistically significant ($p < 0.05$)

Adverse events were not analyzed by dose for the Integrated Pharmacokinetic Trials.

8.5.5.4 Relationship Between Adverse Events And Duration Of Treatment

To determine this relationship the sponsor appears to have performed analyses of the OMC-GHB-3 (2-year) and Scharf trials

In the OMC-GHB-3 trial

- Almost all adverse events appeared within the first 12 months of treatment

- Only 15 additional COSTART terms were reported during the second twelve months: adverse events that occurred during the second 12 months in > 1 patient included gastrointestinal distress (3 patients), bilirubinemia (2 patients), and increased alkaline phosphatase (2 patients)

In the Scharf trial

- The profile of adverse events specifically associated with long-term use of GHB was consistent with the serious illnesses that could be expected in older adults
- The most frequent serious adverse events were related to cardiovascular disease and narcolepsy
- Factors that might contribute to this profile of adverse events included: the increasing age of patients during the trial, underlying cardiovascular abnormalities which were present in 20% of patients at baseline

Note that the only actual analyses that appear to have been performed by the sponsor consisted of separate tables of adverse events for the first 6 months of treatment versus those that appeared after the first 6 months of treatment. I have already discussed these tables in Section 8.5.3.5

8.5.5.5 Relationship Between Adverse Events And Concomitant Medications

No analyses were performed

8.5.5.6 Relationship Between Adverse Events And Age

In the 5 integrated clinical trials subset analyses based on age (< 65 years and ≥ 65 years) were performed for adverse events. The incidence of all adverse events, severe adverse events and discontinuations due to adverse events were similar between the 2 subsets. The incidence of serious adverse events was higher in the older subset, where the sample size was clearly much smaller. The results of these comparisons for GHB-treated patients are illustrated in the following table.

Adverse Events	Age < 65 years N = 356	Age ≥ 65 years N = 43
All adverse events	269 (76%)	29 (67%)
Serious adverse events	12 (3%)	4 (9%)
Severe adverse events	61 (17%)	8 (19%)
Adverse event discontinuations	38 (11%)	5 (12%)

The incidence of the following specific adverse events was also similar between the 2 subsets for GHB-treated patients: nausea, dizziness, headache, vomiting and urinary incontinence.

Adverse Events	Age < 65 years N = 356	Age ≥ 65 years N = 43
Nausea	21%	23%
Headache	26%	21%
Dizziness	17%	21%
Vomiting	7%	7%
Urinary incontinence	6	7%

No similar analyses were performed for the Scharf trial or any other trial grouping.

8.5.5.7 Relationship Between Adverse Events And Gender

In the 5 integrated clinical trials subset analyses were performed based on for adverse events. The analyses for GHB-treated patients showed the following

- The incidence of the total number of adverse events was higher in women (80%) than in men (69%)
- The incidence of serious and severe adverse events, and adverse event discontinuations was similar between the 2 dose groups

These data are illustrated in the following table

Adverse Events	Male N = 171	Female N = 228
All adverse events	116 (68%)	182 (80%)
Serious adverse events	7 (4%)	9 (4%)
Severe adverse events	26 (15%)	43 (19%)
Adverse event discontinuations	15 (9%)	28 (12%)

- The incidence of several specific adverse events in the 2 subsets was as indicated in the table below. As can be seen the incidence of headache, vomiting, nausea and dizziness was higher in women than in men

Adverse event	Women %	Men %
Headache	29	22
Nausea	29	11
Dizziness	24	9
Vomiting	10	3
Urinary incontinence	2	3

8.5.5.8 Relationship Between Adverse Events And Race

No analyses of this relationship were performed

8.6 Laboratory Findings

8.6.1 Extent of Laboratory Testing During Development

The data below refer only to post-treatment laboratory testing.

8.6.1.1 Integrated Clinical Trials

Laboratory parameters analyzed included those listed in the table below

Serum chemistry	Albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, calcium, creatinine, glucose, LDH, phosphorus, potassium, sodium, total bilirubin, and total protein
Hematology	Hematocrit, hemoglobin, total and differential WBC count, RBC count
Urinalysis	pH, specific gravity, glucose, ketones and protein

The frequency at which laboratory parameters were intended to be checked (as per protocol) in these studies is indicated in the following table

Study #	Frequency of safety laboratory testing
OMC-GHB-2	Screening, baseline and weekly during the 4 weeks of study drug administration
OMC-GHB-3	Baseline and every 6 months
OMC-SXB-6	Screening and Month 6
OMC-SXB-7	Baseline and every 6 months thereafter

Scrima	Beginning and end of each 30-day treatment period
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Criteria for determining potentially clinically significant laboratory abnormalities have been specified in the study reports

8.6.1.2 Lammers Trial

There was no provision for checking laboratory parameters during this trial

8.6.1.3 Integrated Pharmacokinetic Trials

No post-treatment laboratory parameters were checked during these trials

8.6.1.4 Scharf Trial

Laboratory parameters analyzed included those listed in the table below

Serum chemistry	Albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, bicarbonate, calcium, creatinine, cholesterol, glucose, LDH, phosphorus, potassium, sodium, total bilirubin, total protein and uric acid
Hematology	Hematocrit, hemoglobin, total and differential WBC count, RBC count, platelet count
Urinalysis	pH and specific gravity

Laboratory parameters were to be checked prior to study entry and semi-annually thereafter. Criteria for determining clinically significant laboratory results have been specified in the study report

8.6.2 Selection of Studies for Overall Drug-Control Comparisons And Other Analyses

3 study groupings have been selected

- Controlled clinical trial: OMC-GHB-2 (this was the only controlled trial in which safety laboratory tests were checked after study drug administration)
- Integrated Clinical Trials
- Scharf trial

8.6.3 Standard Analyses and Explorations of Laboratory Data

8.6.3.1 Controlled Clinical Trial OMC-GHB-2

8.6.3.1.1 CHANGES IN LABORATORY RESULTS OVER TIME

The sponsor has provided 2 shift tables for changes in laboratory data from baseline to Visit 6 (the end of the period of double-blind treatment)

8.6.3.1.1.1 Categorical Change In Laboratory Values From Baseline To Week 6

The sponsor’s table depicts the number of patients in each treatment group who exhibited a change in specific laboratory values from baseline to Visit 6 that fell into one of the following 3 categories: “normal to abnormal”, “abnormal to normal” and “no change” (i.e., no categorical change).

The following table which I have derived from the sponsor’s larger table depicts the number of patients who moved from normal to abnormal in each treatment group

Laboratory Parameter	Treatment Group (n = number randomized)			
	Placebo (n =34)	GHB 3 g (n = 34)	GHB 6 g (n = 33)	GHB 9 g (n = 35)
Albumin	1	1	1	1
Alkaline phosphatase	1	1	1	0
SGPT	0	0	1	0
SGOT	0	1	0	0
LDH	0	0	2	0
Phosphorus	2	1	1	0
Total bilirubin	4	3	1	2
Total protein	0	0	0	0
Sodium	1	0	0	0
Potassium	1	0	0	1
Hemoglobin	3	0	0	0
Hematocrit	2	2	0	1
White blood cell count	2	0	0	1
Red blood cell count	2	0	0	0
Neutrophils	2	1	1	2
Lymphocytes	3	2	1	2
Monocytes	1	0	0	1
Eosinophils	0	0	0	0
Basophils	2	3	2	5
Urinary pH	0	0	0	0
Urinary specific gravity	0	0	0	0
Urinary protein	4	2	6	4
Urine glucose	0	0	0	0
Urine ketones	0	1	1	1
Urine occult blood	1	2	2	1
Urine white blood cells	1	0	2	1
Urine red blood cells	2	1	0	0
Urine squamous epithelial cells	1	0	0	0
Urine hyaline casts	1	0	0	0
Urine crystals	0	0	0	0

As the above table indicates

- Very small numbers of patients in each treatment group showed normal to abnormal changes in individual laboratory parameters
- There were no striking differences between the individual GHB groups and the placebo group; neither was there a tendency to a dose response in each treatment group

Note: A maximum of 29 patients in each treatment group had records of individual laboratory parameters for both baseline and Week 6

8.6.3.1.1.2 Mean Change In Laboratory Values From Baseline To Week 6

This sponsor’s table depicts the mean change (and standard deviation) from baseline to Week 6 for each laboratory parameter.

The following table which is extracted from the sponsor’s table shows the mean change only for individual laboratory parameters in each treatment group

Laboratory Parameter	Treatment Group (n = number randomized)			
	Placebo (n =34)	GHB 3 g (n = 34)	GHB 6 g (n = 33)	GHB 9 g (n = 35)
Albumin	-0.10	-0.09	0.14	0.06
Alkaline phosphatase	0.07	-0.21	-4.52	-0.78
SGPT	0.62	-4.62	-4.14	-5.70
SGOT	-1.21	-3.03	-1.86	-1.15
LDH	-1.59	-10.0	4.0	-4.74
Phosphorus	0.25	-0.05	0.07	0.11
Total bilirubin	0.04	-0.07	-0.03	-0.06
Total protein	-0.02	-0.02	0.02	-0.07
Sodium	0.17	-0.07	0.24	-0.19
Potassium	-0.06	-0.09	-0.01	-0.12
Hemoglobin	-0.01	0.21	0.11	-0.15
Hematocrit	-0.42	0.50	0.79	-0.11
White blood cell count	0.20	-0.19	-0.40	-0.53
Red blood cell count	-0.04	0.04	0.05	-0.07
Neutrophils	1.19	-1.10	0.06	-3.55
Lymphocytes	-0.81	1.70	1.23	3.80
Monocytes	-0.08	-0.38	-0.36	-0.15
Eosinophils	-0.11	-0.11	-0.67	-0.11
Basophils	-0.28	-0.10	-0.32	-0.01
Urinary pH	-0.02	0.04	0.52	0.67
Urinary specific gravity	0.00	0.00	0.00	0.00
Urine white blood cells	11.36	-0.33	0.75	-0.04
Urine red blood cells	88.93	0.37	-0.75	-4.27
Urine squamous epithelial cells	0.46	0.41	0.50	0.38
Urine hyaline casts	-0.11	0.00	0.00	0.00

The above table indicates that

- Mean changes in individual treatment groups were minimal and clinically insignificant
- There were no prominent differences between the individual GHB groups and the placebo group; neither was there a tendency to a dose response in the GHB groups

Note: A maximum of 29 patients in each treatment group had records of individual laboratory parameters for both baseline and Week 6

8.6.3.1.2 LABORATORY ADVERSE EVENTS

Laboratory abnormalities that occurred in patients who eventually received study medication, and were determined by the investigator to be abnormal and clinically significant, were considered adverse events and are summarized in the following table. I have used the patient data listings in preparing this table. Note that the study drug was administered only between Visits 4 and 6

Patient ID #	Treatment Group	Laboratory Abnormality	Comments
512	Placebo	Leukocytosis in urine	Abnormality present only at Visit 5; normal at all other visits including Visit 6
1505	Placebo	Elevated alkaline phosphatase, blood glucose and total white blood cell count	Mild elevations present at all visits including screening visit
1509	Placebo	Trace occult blood in urine Mild increase in urine red cells	Trace occult blood present at Visits 2 and 5; increased urine red cells present only at Visit 5
1604	Placebo	Elevated serum potassium	Serum potassium 5.3 meq/L at Visit 5, normal by Visit 6
411	GHB 3 g	Anemia	Mild anemia (hematocrit 35.3 and 36.5 at Visits 3 and 4)
1610	GHB 3 g	Low serum potassium	Serum potassium 3.6, 3.4, 3.3 and 3.4 meq/L at Visits 3, 4, 5 and 6, respectively
506	GHB 6 g	Proteinuria	Mild proteinuria at Visits 1 and 3; normal at other times
1204	GHB 6 g	Elevated ALT and AST	Mild elevations in ALT and AST (< 2 x upper limit of normal) at Visits 2 and 3 only
1502	GHB 6 g	Elevated uric acid and glucose	Mild elevation in blood glucose (123 - 129 mg/dl) at Visits 3 and 5. Mild elevation in uric acid (max 7.7 mg/dl) at Visits 3, 5 and 7
1302	GHB 9 g	Anemia Abnormal urinalysis	Mild anemia at Visit 1 Mild proteinuria and trace occult blood at Visits 2 and 6; hyaline casts at Visit 7

As the table indicates, in not a single instance could a laboratory abnormality in a patient who received GHB be attributed to the drug

8.6.3.2 Integrated Clinical Trials

8.6.3.2.1 CATEGORICAL CHANGES IN LABORATORY TESTS FROM BASELINE TO LAST OBSERVATION

The sponsor's table depicts the number of patients in each treatment group [placebo, and 5 Xyrem® dose groups based on last dose(3 g/day, 4.5 g/day, 6 g/day, 7.5 g/day and 9 g/day)] who exhibited a change in specific laboratory values from baseline to last observation that fell into one of the following 9 categories

Normal to normal	Low to normal	High to normal
Normal to high	Low to low	High to low
Normal to low	Low to high	High to high

For all laboratory parameters, the majority in each dose group ($\geq 67\%$) was in the "normal to normal" category. The percentage with changes in all the other categories in each dose group was in the vast majority of instances very small. No dose-response was readily evident. Moreover, these comparisons are not randomized and vary in the duration of exposure to study drug; they therefore do not carry as much significance as those for a OMC-GHB-2. The significance of these comparisons is therefore small.

The only possibly noteworthy change was in serum calcium; a shift from normal to low was seen in 14/132 (10.6 %) of all patients who had this test done. The distribution of this change across dose groups is illustrated in the following table

Dose Group	Placebo	3 g/day	4.5 g/day	6 g/day	7.5 g/day	9 g/day	Total
Number With Change	0	4	2	3	0	5	14
Total number in dose group	3	16	11	45	14	43	132

None of these patients discontinued treatment on account of the change in serum calcium and there is no evidence that this change was correlated with any symptoms or clinical signs.

8.6.3.2.2 MEAN CHANGES IN LABORATORY VALUES FROM BASELINE TO LAST OBSERVATION

I have reviewed the sponsor's tables which compare the mean changes in hematology, chemistry and urinalysis parameters in Xyrem®-treated patients, based on last dose (5 dose groups: 3 g/day, 4.5 g/day, 6 g/day, 7.5 g/day and 9 g/day) with the corresponding mean changes in those treated with placebo. These changes were very small, clinically insignificant and comparable across treatment groups. No clear dose-response was seen with the comparisons. Since the treatment groups are not randomized and vary in their duration of exposure to study drug; the number in the placebo group represents those treated exclusively with placebo and is exceedingly small (n=3); drug-placebo comparisons are therefore not reasonable. Since the significance of these comparisons is minimal I have not reproduced the sponsor's tables

8.6.3.2.3 POTENTIALLY CLINICALLY SIGNIFICANT LABORATORY RESULTS

These are summarized in the next 2 tables which I have copied from the Integrated Summary of Safety. The following are noteworthy

- An increase in transaminases (SGOT and/or SGPT) in a small number of patients (all increases were < 10 x baseline). In only one of these patients (# 0214; see Section 8.3.1.6) was this increase considered a serious adverse event and/or a reason for GHB discontinuation
- None of the other potentially clinically significant laboratory changes seen below were considered serious adverse events or led to treatment discontinuation.
- There were no laboratory adverse events with a frequency of $\geq 5\%$

Note that there are no further details supplied or explanations offered for the potentially clinically significant laboratory abnormalities noted in the table below: these include several apparent instances of marked hypoglycemia.

Laboratory Parameter (clinically significant range)		Last Sodium Oxybate Dosage (g/d)	Baseline	Post-Baseline	
Patient Number	Trial ^a			Study Day ^b	Result
Hematology (N = 1)					
Hemoglobin (> 3 g/dL decrease and absolute values < 12.0 g/dL)					
0814	OMC-GHB-3	4.5	16.6	391	11.5
Clinical Chemistry (N = 26)					
ALT (SGPT) (≥ 100% increase and absolute values > 75 IU/L)					
0202	OMC-SXB-7	6.0	29	948	262
0214	OMC-SXB-6	9.0	50	877	362
0507	OMC-GHB-3	7.5	39	416	109
		7.5	39	710	86
	OMC-SXB-7	7.5	39	710	86
1610	OMC-GHB-3	9.0	26	398	248
1709	OMC-GHB-3	4.5	23	386	76
AST (SGOT) (≥ 100% increase and absolute values > 75 IU/L)					
0214	OMC-SXB-6	9.0	44	877	189
1610	OMC-GHB-3	9.0	28	398	76
Creatinine (≥ 66% increase and absolute values > 1.5 mg/dL)					
0127	OMC-GHB-3	9.0	0.8	241	1.6
0507	OMC-GHB-3	7.5	1	220	1.7
1501	OMC-GHB-3	3.0	1	720	1.9
	OMC-SXB-7	3.0	1	720	1.9
1505	OMC-GHB-3	6.0	0.6	650	1.7
	OMC-SXB-7	6.0	0.6	650	1.7
Glucose (≥ 33% decrease and absolute values < 70 mg/dL; ≥ 75% increase and absolute values > 200 mg/dL)					
0108	OMC-GHB-3	6.0	229	424	398
0115	OMC-GHB-3	9.0	104	618	217
0410	OMC-GHB-3	7.5	178	201	307
0504	OMC-GHB-3	4.5	86	273	52
05255	OMC-SXB-7	6.0	111	208	65
0550	OMC-SXB-6	6.0	88	210	56
0808	OMC-GHB-3	9.0	76	206	49

Laboratory Parameter (clinically significant range)		Last Sodium Oxybate Dosage (g/d)	Baseline	Post-Baseline	
Patient Number	Trial ^a			Study Day ^b	Result
Clinical Chemistry (N = 26) (continued)					
Glucose (continued)					
0809	OMC-GHB-3	3.0	92	222	54
0810	OMC-GHB-3	4.5	57	219	12
0814	OMC-GHB-3	4.5	101	205	34
	OMC-SXB-7	4.5	101	716	66
		4.5	101	903	65
0815	OMC-GHB-2	3.0	67	33	24
0820	OMC-GHB-2	6.0	42	17	16
	OMC-GHB-3	6.0	42	331	15
0844	OMC-SXB-6	3.0	92	53	58
1505	OMC-GHB-3	6.0	168	278	286
	OMC-SXB-7	6.0	168	650	403
		6.0	168	650	403
1708	OMC-GHB-3	6.0	144	650	49
	OMC-SXB-7	6.0	144	650	49
2134	OMC-SXB-6	6.0	107	176	68
3841	OMC-SXB-6	9.0	124	169	60
Total bilirubin (≥ 100% increase and absolute values > 1.5 mg/dL)					
0208	OMC-GHB-3	9.0	1.1	213	2.5
0504	OMC-GHB-3	4.5	0.4	336	1.6
1509	OMC-GHB-2	6.0	0.9	15	2.1

^a Trial during which post-baseline value was obtained.

^b Day relative to start of treatment (trial duration).

8.6.3.3 Scharf Trial

8.6.3.3.1 MEAN CHANGES IN LABORATORY VALUES FROM BASELINE TO SPECIFIC TIMEPOINTS

The sponsor has provided tables containing descriptive statistics for absolute values and changes in laboratory parameters at specific successive timepoints. These values (absolute and change) are not categorized according to last dose.

On review of these tables it is apparent that across all laboratory parameters, both the mean absolute values and the mean changes are unremarkable.

8.6.3.3.2 PROPORTION OF PATIENTS WITH ABNORMAL TESTS AT SPECIFIC TIMEPOINTS

The sponsor has provided tables specifying the number and percentage of patients with clinically significant abnormalities of laboratory tests for a number of specific timepoints, as well as listings of the patients with abnormalities.

On review of the tables and listings it appears that

- The proportion of patients having clinically significant laboratory abnormalities at each time point is generally small (0 – 16.7% with the vast majority < 5%) except in the case of abnormal serum bicarbonate. The proportion of patients with an abnormal serum bicarbonate at specific timepoints is illustrated in the following table

Time Point	Total Patients at Time Point	Number of Patients With Abnormality (%)
<= 3 months	12	3 (25.0%)
> 3 - <= 6 months	42	2 (4.8%)
> 6 - <= 12 months	42	13 (31.0%)
> 1 - <= 2 years	37	13 (35.1%)
> 2 - <= 5 years	39	17 (43.6%)
> 5 - <=10 years	38	16 (42.1%)
>10 years	22	9 (40.9%)

- The individual patient listings for abnormal laboratory results do not indicate any items of concern.
 - The abnormalities of bicarbonate were all elevations ranging from 31 to 38 mEq/L with only 9 individual readings being > 34 mEq/L; in all 9 instances the values subsequently fell to ≤ 34 mEq/L
 - Abnormalities of random blood glucose consisted of elevations in the vast majority of instances; in many of those instances serial blood glucose estimations were consistently elevated such that these individuals could have had diabetes mellitus. 4 patients had random blood glucose readings that were considered low and ranged from 38 – 48 mg/dL; at least 1 of these patients had elevated blood glucose readings subsequently.
 - There are no clinical details available for these patients and it appears unlikely that these abnormalities were attributable to GHB. Similar elevations in serum bicarbonate were not seen in the Integrated Clinical Trials

8.6.3.3.3 LABORATORY ADVERSE EVENTS

There were no laboratory adverse events that had a frequency ≥ 5%. There were no adverse event discontinuations on account of abnormal standard laboratory tests (positive antinuclear antibody tests which led to treatment discontinuation in 2 patients are discussed in Section)

8.7 Vital Signs

8.7.1 Extent of Vital Sign Testing During Development

The data below refer only to post-treatment vital sign testing

8.7.1.1 Integrated Clinical Trials

Vital signs recorded and analyzed included sitting and standing blood pressure, heart rate, respiration, body temperature and body weight.

The frequency at which vital signs were intended to be checked (as per protocol) in these studies is indicated in the following table

Study #	Frequency of vital sign testing
OMC-GHB-2	Screening, end-of washout period, baseline, weekly during the 4 weeks of study drug administration and 3-5 days after completion of study drug

Study #	Frequency of vital sign testing
OMC-GHB-3	Baseline, 2 weeks and Months 1, 2, 4, 5, 6, 8, 10, 12, 14, 16, 18, 21 and 24
OMC-SXB-6	Screening, Week 2 and Months 2 and 6
OMC-SXB-7	Baseline and Months 6, 12, 18 and 24
Scrima	No provision for checking vital signs

8.7.1.2 *Lammers Trial*

There was no provision for recording vital signs during this trial

8.7.1.3 *Integrated Pharmacokinetic Trials*

Vital signs recorded and analyzed, when specified, included sitting and standing blood pressure, heart rate, respiration, body temperature and body weight.

Vital signs were to be checked in each of the single-dose pharmacokinetic trials as follows.

Study #	Frequency of Vital Sign Checks
OMC-GHB-4	Baseline and 60 hours after dosing
OMC-SXB-8	Baseline and 2, 4 and 8 hours after dosing
OMC-SXB-9	Baseline and 2, 6 and 10 hours after dosing
OMC-SXB-10	Baseline and 1, 3, and 8 hours after dosing
OMC-SXB-11	Baseline and 2, 6 and 10 hours after dosing
OMC-SXB-12	Baseline and 1, 2, 6 and 10 hours after dosing
OMC-SXB-14	Baseline and 2, 6, 10 and 24 hours after dosing
OMC-SXB-17	Baseline and 1, 2, 6 and 10 hours after dosing

8.7.1.4 *Scharf Trial*

There was no provision for checking vital signs in the protocol or Case Report Form.

8.7.2 *Selection of Studies for Overall Drug-Control Comparisons And Other Analyses*

3 study groupings have been selected

- Controlled Clinical trial: OMC-GHB-2 (this was the only controlled clinical trial in which vital signs were checked after administration of study drug)
- Integrated Clinical Trials
- Integrated Pharmacokinetic Trials

8.7.3 *Standard Analyses and Explorations of Vital Sign Data*

8.7.3.1 *Controlled Clinical Trial OMC-GHB-2*

The sponsor has provided a table that displays descriptive statistics for changes in vital signs across dose groups from baseline to Visit 6 (end of period of double-blind treatment). The mean changes seen were not clinically significant. The data suggested a dose-related decrease in weight and sitting diastolic blood pressure. An abbreviated form of the sponsor's main table, including only mean changes is reproduced below

Changes from baseline to Visit 6 in vital signs

Changes in vital signs	Placebo	GHB dose (g)		
		3	6	9
Weight (kg) - mean	0.69	-0.09	-0.34	-0.8
Sitting systolic blood pressure (mm Hg) - mean	1.41	3.56	-1.10	-0.31
Sitting diastolic blood pressure (mm Hg) - mean	2.09	0.53	0.77	-1.83
Standing systolic blood pressure (mm Hg) - mean	4.26	5.47	-1.55	0.00
Standing diastolic blood pressure (mm Hg) - mean	1.74	0.63	-0.55	-2.79
Pulse rate (bpm) - mean	-0.94	1.0	3.16	-1.76
Respiration (breaths per minute) - mean	-0.24	-0.87	-0.2	-0.19

The sponsor's main table also indicates that there were no clinically significant differences between the placebo group and the individual GHB dose groups in minimum and maximum changes for the above adverse events.

8.7.3.2 Integrated Clinical Trials

The sponsor has presented a table containing descriptive statistics for the change from baseline to last observation in vital signs. The tables indicate that mean changes for all parameters were very small and similar across all treatment groups. I have not reproduced these vital signs.

8.7.3.3 Integrated Pharmacokinetic Trials

Individual data listings have been made available for all pharmacokinetic trials except OMC-GHB-4; for the latter trial descriptive statistics have been made available for vital signs.

These data do not reveal any changes that could be considered clinically significant.

8.8 ECG

8.8.1 Extent of Electrocardiogram Testing During Development

The data below refer only to post-treatment electrocardiograms

8.8.1.1 Integrated Clinical Trials

Standard 12-lead resting electrocardiograms were performed.

The frequency at which electrocardiogram testing were intended to be checked (as per protocol) in these studies is indicated in the following table

Study #	Frequency of electrocardiogram testing
OMC-GHB-2	Screening and end of period of study drug administration
OMC-GHB-3	Baseline and Months 6, 12 and 18
OMC-SXB-6	Screening, and Month 6 (if medically indicated)
OMC-SXB-7	No provision for checking electrocardiograms
Scrima	No provision for checking electrocardiograms

8.8.1.2 Lammers Trial

There was no provision for checking electrocardiograms during this trial

8.8.1.3 Integrated Pharmacokinetic Trials

No post-treatment electrocardiograms were checked during these trials

8.8.1.4 Scharf Trial

A standard 12-lead electrocardiogram was to be checked at or prior to study entry, and annually thereafter

8.8.2 Selection of Studies for Overall Drug-Control Comparisons And Other Analyses

3 study groupings have been selected

- Controlled clinical trial: OMC-GHB-2
- Integrated Clinical Trials
- Scharf trial

8.8.3 Standard Analyses and Explorations of Electrocardiogram Data

8.8.3.1 Controlled Clinical Trial: OMC-GHB-2

The number and percentage of patients in each treatment group whose values went from normal to abnormal in each treatment group between the baseline and Week 6 (end of double-blind period) visits is summarized in the following table

Treatment Group	Number	Patient ID #s
Placebo	2 (6 %)	512, 818
GHB 3 g	2 (6 %)	407, 1610
GHB 6 g	1 (3.5 %)	105
GHB 9 g	3 (11.5 %)	206, 217, 1309

Details of all 8 patients are summarized in the following table

Abnormal ECGs at Visit 6

Patient number	Visit 1 Interpretation	Visit 6 Comments on abnormality	Follow-up (for ECGs not labeled NCS at V6)
105	Within normal limits	Sinus bradycardia – not clinically significant	
206	Within normal limits	Consider left atrial enlargement	Not clinically significant as determined by site
217	Within normal limits	Sinus arrhythmia, vertical axis	Not clinically significant as determined by site
407	Within normal limits	Normal sinus rhythm, nonspecific T wave abnormality	Not clinically significant as determined by site No Change from baseline, CRF incorrectly reported
512	Within normal limits	QRS axis range 0 to 14 horizontal axis- not clinically significant	
818	Within normal limits	Sinus tachycardia - not clinically significant	
1309	Within normal limits	OCL unifocal ventricular extra beat (VPC), RR complex V1-V2 indicate primary right bundle branch block with QRS 0.10-0.11 seconds	ECG was repeated on 12/30/97 and read by Dr. Froeb. It was interpreted as Borderline ECG Within normal limits
1610	Within normal limits	Nonspecific T-wave abnormality in anterior-lateral leads when compared with ECG 08/08/97 per Dr Kathawalla - change possibly due to hypokalemia - not clinically significant	

None of the above electrocardiogram abnormalities was felt to be clinically significant.

8.8.3.2 Integrated Clinical Trials

The sponsor has presented shift tables for the categorical change from baseline to last observation in vital signs. The shift categories were:

Abnormal to abnormal	Within normal limits to abnormal
Abnormal to within normal limits	Within normal limits to within normal limits
Abnormal to not done	Within normal limits to not done

The tables indicate that no shifts of > 10% were seen for the entire population or for the “normal to abnormal” category in any single electrocardiogram parameter.

For the within normal limits to abnormal category the distribution was as follows

Dose Group	Placebo	3 g/day	4.5 g/day	6 g/day	7.5 g/day	9 g/day	Total
Number With Change	0	0	2	3	1	3	9
Total number in dose group	3	26	88	141	61	83	402

Note that all patients in each dose group did not have electrocardiograms done both at baseline and subsequently, the last row cannot therefore be used as a denominator to calculate percentages for the second row

8.8.3.3 Scharf Trial

All electrocardiograms in the study were categorized as being normal or abnormal and a shift table generated which demonstrates categorical change by dose group from baseline. This table is reproduced below.

ECG Shift	GHB dose (g) n (%)					
	All Patients	3	4.5	6	7.5	9
Norm to Norm	9 (6.3)	0 (0.0)	3 (6.1)	4 (6.5)	2 (11.1)	0 (0.0)
Norm to Abn ¹	36 (25.2)	1 (20.0)	11 (22.4)	16 (25.8)	4 (22.2)	4 (44.4)
Abn to Norm ²	5 (3.5)	0 (0.0)	3 (6.1)	2 (3.2)	0 (0.0)	0 (0.0)
Abn to Abn	39 (27.3)	0 (0.0)	13 (26.5)	19 (30.6)	5 (27.8)	2 (22.2)

¹Patients included if they had a normal baseline ECG and had an abnormal ECG anytime while receiving GHB.

Source: Section 15-Table 8

²Patients included if they had an abnormal baseline ECG and had a normal ECG anytime while receiving GHB.

Note that of those patients who had baseline electrocardiograms, some had a single repeat recording whether others had multiple recordings done. The interval between recordings was highly variable.

Of the 36 patients who had electrocardiograms that were normal at baseline but abnormal later

- 28 patients had abnormalities that were considered “non-specific, benign and highly unlikely to be clinically significant”
- In the remaining 8 patients the abnormalities were considered to possibly be clinically significant, but probably not related to study medication. The sponsor has provided short descriptions of the conclusions(diagnoses) drawn for the electrocardiograms for these 8 patients. The diagnoses reached in these 8 patients were distributed in the following 4 categories: except for 1 patient each who were considered to have acute pericarditis and ischemic heart disease, the remainder had multiple electrocardiograms. No additional information is available for these patients and there is no evidence that an attempt was made to correlate electrocardiogram abnormalities with symptoms, physical signs or other cardiac tests in these patients.

Left ventricular hypertrophy	1 patient
Ischemic heart disease	3 patient
Conduction system disease	3 patient
Acute pericarditis	1 patient

8.9 Withdrawal Phenomenon and Abuse Potential

An separate review of this subject is being performed by the Controlled Substances Staff of this Agency

8.9.1 Background

As indicated earlier in this review, for many years GHB was distributed in this country as a health food product under a variety of trade names; in 1990 it was removed from the market by this Agency after a number of reports of adverse reactions.

Public Law 106-172 (passed by the United State Congress on February 18, 2000) has allowed for the designation of GHB as a Schedule I agent, with exemption from the security requirements of that schedule for the GHB drug product studied under an FDA-approved IND. Upon marketing approval from the FDA being received, the GHB drug product would become a Schedule III agent with Schedule I penalties for illicit use. All other forms and uses of GHB-containing products would remain under Schedule I, except that use under an FDA-approved IND would be exempted (as noted above).

There have been many reports in the media, over the last few years, of instances of overdose with illegally-manufactured GHB. A number of anecdotal single case reports/case series of a similar nature have also been published in the medical literature. There have also been similar reports linked to the use of related compounds such as gammabutyrolactone (GBL) and 1,4-butanediol (1,4-BD), both of which are converted to GHB in the body.

According to the sponsor, illicit GHB users in this country obtain the drug from the following sources

- Purchase from illegal vendors, including those selling the drug over the Internet
- By home manufacture: both recipes and starting materials are easily available

8.9.2 Purposes For Which GHB Is Misused Or Abused

These are listed by the sponsor as follows:

- As a steroid replacement in the body building community
- As a sleep aid
- As an intoxicant
- As an aphrodisiac
- As a means of enhancing the effects of alcohol and stimulants
- As a "date-rape" drug (related to its sedative and alcohol-enhancing properties)

8.9.3 Clinical Psychological And Physical Dependence In Humans

The sponsor states the following.

- Sodium oxybate does not appear to produce strong psychological or physical dependence

- No formal studies have been conducted to assess dependence with GHB
- A few case reports have suggested that chronic high-dose GHB use outside a clinical setting can, when the drug is withdrawn, lead to an abstinence syndrome comprising insomnia, anxiety, tremors and hallucinations. In the same setting dose-escalation to maintain a clinical effect has also been described. Several case reports also suggest that users outside a clinical setting may sometimes increase their dose to maintain a clinical effect.
- However
 - When GHB was discontinued after 3- and 6-month clinical trials for the treatment of alcohol withdrawal, no abstinence syndrome was seen. However during the 6-month trial an escalation of GHB consumption and craving for that drug was reported in about 10% of patients
 - In a clinical study of GHB in 48 narcoleptic patients, lasting 9 years, no tolerance to the effects of GHB was observed.
- Anecdotal reports and controlled trials suggest a potential cross-tolerance or dependence with alcohol. In alcoholics GHB may not only reduce the symptoms of alcohol withdrawal but may also decrease the consumption of and craving for alcohol
- GHB also relieves the abstinence syndrome that follows spontaneous opiate withdrawal; a similar effect on precipitated opiate withdrawal is blocked by naloxone.

8.9.4 Rebound Symptoms With GHB Withdrawal

In the randomized, double-blind, placebo-controlled, parallel-arm trial OMC-GHB-2, the incidence of adverse events suggestive of REM rebound (sleep disturbance, hallucinations, abnormal dreaming), and the incidence of cataplexy was compared between the following 2 periods

- The period of up to 5 days prior to the completion of double-blind treatment
- A period of up to 5 days between the cessation of double-blind treatment and the post-treatment follow-up visit

The difference in the incidence of adverse events was reported by the sponsor not to be statistically significant. Comparative data are not provided by the sponsor.

The sponsor has however supplied listings of adverse events which might be suggestive of REM rebound during the withdrawal period. 6 patients experienced such adverse events (each patient experienced one adverse event). These are listed in the following table

GHB dose during double-blind phase	Adverse events during withdrawal phase
3 g/day	Abnormal dreaming (1 patient) Sleep disorder (1 patient)
6 g/day	Abnormal dreaming (1 patient) Sleep disorder (1 patient)
9 g/day	Hallucinations (1 patient) Sleep disorder (1 patient)

All adverse events were mild and, except for the instance of “sleep disorder” seen in a patient who received 3 g/day previously (in whom the adverse event

lasted 7 days), lasted 1-2 days only. It is unclear exactly what the term "sleep disorder" refers to.

The sponsor also states that there was no tendency to rebound cataplexy during the short period of withdrawal.

8.9.5 Extent Of GHB Abuse In The United States

According to the sponsor

- Sodium oxybate abuse is mentioned relatively infrequently in Drug Abuse Warning Network reports compared with other sedative/hypnotics that are abused such as benzodiazepines
- Currently sodium oxybate abuse is too rare to be listed in any database
 - In the Drug Enforcement Administration June 1998 Drug/Chemical Review it was stated that 1000 encounters with GHB had been documented over an unspecified period of time
 - Only 32 cases of GHB misuse or abuse had been reported over an 18-month period ending December 1997 in a report presented at a February 1998 American Academy of Pediatric Sciences meeting
 - The Mid-Year 1999 Preliminary Emergency Department Data from the Drug Abuse Warning Network had no mention of GHB
- Only one GHB-related death was reported to the Drug Abuse Warning Network by participating medical examiners between 1992 and 1995; in this instance the death occurred in an individual who had concurrently used alcohol and GHB.

8.9.6 Pre-Clinical Studies Of Drug Abuse Potential

The sponsor has outlined the results of a battery of animal studies that have been done with GHB. These consist of studies of drug discrimination, reinforcing effects, and tolerance and dependence.

A full review of these studies is beyond the competence of this reviewer.

Based on these studies the sponsor has made the following conclusions:

- Drug discrimination studies consistently fail to show cross-substitution with abused depressant drugs such as the benzodiazepines and barbiturates, although there is evidence for some cross-substitution with ethanol over a narrow dose range
- Self-administration studies fail to show evidence for strong reinforcing effects
- Repeated administration of sodium oxybate may result in the development of tolerance.
- Overall, "based on preclinical studies alone, there is no compelling evidence that sodium oxybate represents a significant drug abuse hazard."

8.10 Human Reproduction Data

A single patient is reported to have become pregnant while taking GHB. She is described briefly in Section 8.3.1.5

8.11 Overdose

8.11.1 Background

Descriptions of the clinical effects of GHB overdose are derived almost entirely from anecdotal reports related to illegal use of the drug

Section 8.9.2 describes the circumstances under which GHB is used or abused.

When the above anecdotal reports are reviewed, the identification of the dose of GHB used and determining the causal relationship of the clinical syndrome described to GHB are both problematic for the following reasons.

- The sources of the drug are clandestine and varied, as are the starting materials used to manufacture the drug, and the dose ingested therefore unknown in most instances; in addition an evaluation of illegally manufactured sodium oxybate liquid samples has shown a high level of inconsistency of content.
- In a number anecdotal reports, precursor chemicals, i.e., gammabutyrolactone (GBL) and 1,4-butanediol have been ingested, rather than GHB to which the adverse events have been attributed. Although these precursor chemicals are converted to GHB in the body, their pharmacokinetics are different from GHB: for example, GBL is more lipid soluble and more rapidly absorbed
- Other drugs of abuse are frequently used concurrently including alcohol, methamphetamine, and MDMA. In such instances the adverse event has been attributed to GHB based, in most instances, on the clinical history alone; blood and tissue levels of GHB have been measured only rarely. Thus in those instances it has been difficult to know to what extent GHB contributed to the patient's clinical syndrome.

Of the 5 deaths reported in the medical literature and attributed to GHB consumption, only one was clearly linked to GHB use alone.

8.11.2 Clinical Presentation

According to the sponsor the clinical presentation of GHB overdose is influenced by the dose and frequency of ingestion, and most importantly, concurrent use of other drugs.

Patients presenting in a conscious state may be agitated, combative, anxious and confused, and may exhibit hallucinations. Varying degrees of obtundation may also be seen extending to deep coma that is unresponsive even to pain; deep coma has been associated with doses ranging from 2.5 g to 30 g. With an increased depths of unconsciousness the following may also be observed: bradycardia, hypotension, depressed respiration/Cheyne-Stokes breathing and hypothermia. Obtundation may be potentiated by the concurrent use of alcohol.

Other symptoms and signs may include dizziness, nausea, vomiting, myoclonus, blurred vision, visual field abnormalities, sluggish pupillary reactions, amnesia and hypotonia.

Symptoms may appear as early as 15 minutes after ingestion and may persist for 2 to 96 hours

Note that in the NDA safety database, 2 patients took, or are presumed to have taken overdoses. These patients are further described in Sections 8.3.1.1 and 8.3.2.2.

A further instance of Xyrem® overdose has been reported in the 120-Day Safety Update (see Section 13.10.4)

8.11.3 Treatment

According to the sponsor the treatment of GHB overdose is primarily symptomatic and supportive. The measures to be instituted include

- care of the airway, with intubation and artificial ventilation as needed
- consideration of gastric aspiration and lavage with activated charcoal
- measurement of blood levels of GHB.

While flumazenil and naloxone are ineffective for the treatment of GHB intoxication, intravenous physostigmine has been reported anecdotally to produce rapid reversal of obtundation.

9. Study OMC-SXB-20

This was an open-label study that was intended to evaluate the effects of 4 doses of Xyrem® on sleep architecture. The study report was submitted on 12/16/00, i.e., after the original NDA submission. The sponsor desires that the results of this study be included in labeling.

A brief outline of the study protocol and safety data from this study are presented below.

9.1 Objectives

9.1.1 Primary

The primary objective of this study was to characterize the polysomnographic sleep architecture in narcoleptic patients at 4 GHB doses: 4.5 g, 6.0 g, 7.5 g and 9 g daily

9.1.2 Secondary

The secondary objectives of the study were to

- Assess the effect of Xyrem® on sleep as measured by the Epworth Sleepiness Scale
- Assess the effects of Xyrem® on common symptoms of narcolepsy as measured by the Narcolepsy Symptoms Assessment

- Assess EEG measures of wakefulness under soporific conditions using the Maintenance of Wakefulness Test
- Assess the safety of Xyrem®

9.2 Design/Summary of Investigational Plan

This was an open-label uncontrolled study divided into 2 phases. Stimulant medication was maintained at a constant level during the trial

9.2.1 Phase I

This phase lasted 4 weeks

- In the initial 2 weeks of this phase patients were withdrawn from tricyclic antidepressants, selective serotonin re-uptake inhibitors and hypnotics
- In the last 2 weeks of this phase patients remained free of tricyclics

An overnight polysomnogram was performed at the beginning and end of this phase. The Epworth Sleepiness Scale questionnaire was administered at about the time of each polysomnogram

9.2.2 Phase II

This phase began with the patient receiving 4.5 g of GHB nightly for the initial 4 weeks. At the end of this period the dose was increased to 6.0 g nightly and further to 7.5 g nightly and 9 g nightly at 2 week intervals

Overnight polysomnograms on the night of the first dose of Xyrem® and on the last night of each dose. The Epworth Sleepiness Scale was administered at the end of each dosing period

9.3 Duration

10 weeks

9.4 Sample Size

20-30 planned

9.5 Key Inclusion Criteria

- Informed consent
- Age \geq 18 years
- American Sleep Disorders Association criteria for narcolepsy
- Use of stable doses of tricyclic antidepressants or selective serotonin re-uptake inhibitors for narcolepsy for at least 3 weeks. If taking stimulants must have been on a stable dose for at least 3 weeks
- If female must be
 - Surgically sterile OR
 - 2 years post-menopausal OR
 - If of child-bearing potential must be using effective contraception and must continue this treatment during the study
- Adequate support for duration of trial

9.6 Key Exclusion Criteria

- Unstable diseases in any body system, other than narcolepsy, which would place the patient at risk or compromise the trial objectives
- Use of tricyclic antidepressants or selective serotonin re-uptake inhibitors for depression or for any indication other than narcolepsy
- History of substance abuse, as defined by DSM-IV, currently or within the past year
- History of psychiatric disorders that would preclude study participation
- Serum creatinine > 2 mg/dl; AST or ALT > 2 x upper limit of normal; serum bilirubin > 1.5 x upper limit of normal; pre-trial electrocardiogram results demonstrating a clinically significant arrhythmia or 2nd or 3rd degree A-V block; history of myocardial infarction within the past 6 months
- Any untreated disorder other than narcolepsy that could be considered a primary cause of excessive daytime sleepiness, including sleep apnea syndrome (criteria specified)
- Occupation requiring variable shift or routine night shift work
- Use of sodium oxybate within the preceding 30 days
- Use of any investigational drug within the preceding 30 days
- No clinically significant history of head trauma, seizure disorder or previous intracranial surgery
- Willing to not operate a car or heavy machinery if the clinical investigator feels such a restriction is warranted
- Use of medication for narcolepsy during baseline period, other than a stable dose of stimulant medication ("stable dose" defined as one without any significant change in dose for the 5 - day period just prior to the baseline period)
- Use of hypnotics, tranquilizers, antihistamines (except for the non-sedating variety of such drugs) and clonidine at the start of the baseline period.

9.7 Dosage

See Section 9.2

9.8 Outcome Measures

9.8.1 Primary Efficacy Measures

The following objective overnight polysomnogram parameters

- Wake After Sleep Onset (WASO) in minutes following the first and second dose of Xyrem and the summation
- Total Sleep Time (TST) in minutes following the first and second dose of Xyrem and the summation
- Stage 1 sleep time in minutes following the first and second dose of Xyrem and the summation
- Stage 2 sleep time in minutes following the first and second dose of Xyrem and the summation
- Stage 3 & 4 sleep time in minutes following the first and second dose of Xyrem and the summation

- Rapid Eye Movement (REM) sleep time in minutes following the first and second dose of Xyrem and the summation
- Sleep latency in minutes following the first and second dose of Xyrem
- REM sleep latency in minutes following the first and second dose of Xyrem
- Stage shifts per hour following the first and second dose of Xyrem and an average
- Total awakenings following the first and second dose of Xyrem® and the summation
- Delta power in microvolts²/Hz following the first and second dose of Xyrem and an average

9.8.2 Secondary Efficacy Measures

- Epworth Sleepiness Scale
- Narcolepsy Symptoms Assessment
- Maintenance of Wakefulness Test

9.8.3 Safety Measures

Adverse events, safety laboratory tests, vital signs, electrocardiograms and physical examinations

9.9 Analysis Plan

- Demographic variables at baseline were summarized as follows
 - Gender and race were summarized by the number of patients in each category
 - Age, height and weight were summarized by descriptive statistics
- Efficacy variables were analyzed as follows
 - Inferential statistics were performed for descriptive purposes only as per the sponsor
 - Quantitative polysomnogram variables and the Epworth Sleepiness Scale were analyzed using 2-way ANOVA with patient and dosage as the main effects
 - If a statistically significant difference was found among dose groups using ANOVA, pairwise comparisons using the least significant difference test were performed. If the assumptions for the above ANOVA were not satisfied the rank changes from baseline were analyzed using the ANOVA model. The significance of the mean change from baseline (end of Phase I) in each dose group was determined using a paired t-test or a Wilcoxon signed rank test
 - For the above analysis the level of statistical significance was 0.05 (two-sided)
 - Variables for the narcolepsy symptom questionnaire measured as a change from the beginning of Phase I were presented by number and percentage of patients
- Safety analyses were performed as follows
 - Adverse events were summarized by body system using COSTART term and by relationship to treatment, dose and severity
 - Changes from the beginning of Phase 1 to the end of the study in laboratory parameters were summarized using descriptive statistics
 - Changes from the end of Phase I to the end of the study in vital signs were summarized using descriptive statistics
 - Changes from the beginning of Phase I to the end of the study in electrocardiogram parameters were summarized

9.10 Results

9.10.1 Patient Disposition

- 27 patients were enrolled in the study
- 25 patients were treated with GHB
- 21 patients completed the study

9.10.2 Baseline And Demographic Characteristics

Baseline and demographic characteristics for all 25 treated patients are summarized below

Variable	Mean	Standard Deviation
Age (years)	52.6	8.77
Weight (kg)	84.2	16.36
Height (cm)	166.9	8.32

Gender: Males 28%; Females 72%
 Race: Caucasian 92%; Black 8%

9.10.3 Tricyclic Antidepressants, Selective Serotonin Re-Uptake Inhibitors And Hypnotics At Baseline

These are summarized in the next table, copied from the submission.

Preferred Term	Total
Number of Patients	25 (100%)
Patients Receiving Medications	22 (88%)
Clozapine	3 (12%)
Fluoxetine	5 (20%)
Fluvoxamine	1 (4%)
Paroxetine	2 (8%)
Protriptyline	1 (4%)
Sertraline	4 (16%)
Venlafaxine	6 (24%)

TCA = Tricyclic antidepressant. SSRI = Selective serotonin reuptake inhibitors.

All medications were completed prior to the start of treatment.

9.10.4 Protocol Deviations

These are summarized in the next table copied from the submission. The table applies to all 25 treated patients

Type of Protocol Deviation	No. of Protocol Deviations
Inclusion/exclusion criteria	6
Compliance	7
Concomitant medication	28
Study visit interval	17
Error in dosing medication	23
Efficacy measure	33
Safety measure	
Laboratory procedure	2
Other safety measure	2
Other	7
Total	125

9.10.5 Treatment Compliance

Treatment compliance at each dose level is summarized in the following table copied from the submission. Mean compliance at each dose level was high.

Number of Patients	Dose (g)				
	4.5	6.0	7.5	9.0	Total
	25	22	22	21	25
Compliance (%)					
N	25	22	22	21	25
Mean	95.9	95.5	92.7	93.3	94.9
SD	11.45	9.63	9.06	13.45	7.62
Median	100.0	95.0	95.0	93.0	96.7
Minimum	58.0	70.0	67.0	63.0	70.0
Maximum	107.0	119.0	105.0	129.0	100.5

9.10.6 Extent Of Exposure

The mean duration of treatment was 63.3 nights (standard deviation: 21.29)

9.10.7 Efficacy Results

See summary in NDA Efficacy Review

9.10.8 Safety Results

9.10.8.1 All Adverse Events

18 out of 25 (72% of) patients participating in the study reported at least 1 adverse event.

A summary of adverse events in several broad categories, by dose at onset, is provided in the next table, copied from the submission.

	Xyrem Dosage at Onset (grams)				
	4.5	6.0	7.5	9.0	Total
Number of Patients	25 (100%)	22 (100%)	22 (100%)	21 (100%)	25 (100%)
All Events					
Patients with At Least One Adverse Event	10 (40%)	9 (41%)	6 (27%)	10 (48%)	18 (72%)
Patients with Serious Adverse Events	0	0	0	0	0
Patients with Related Adverse Events	6 (24%)	6 (27%)	5 (23%)	7 (33%)	13 (52%)
Patients with Severe Adverse Events	0	1 (5%)	0	0	1 (4%)
Patients Discontinued Due to Adverse Event	1 (4%)	0	1 (5%)	0	2 (8%)

Note that the patient listed in the table as having a SERIOUS adverse event did not in fact have one, according to the sponsor. 4 days prior to beginning study drug the patient was diagnosed to have a yeast infection and was treated with miconazole nitrate suppositories 5 mg daily. Her white blood cell count was elevated at 11.43 K/microliter at screening. After a single dose of Xyrem® 4.5 g she withdrew her consent to participate in the study and was not available for further visits or telephone contacts. I have reviewed the Case Report Form for this patient

The next 2 tables list treatment-emergent adverse events, by dose at onset, that occurred in ≥ 5% of patients in any dose group

COSTART Preferred Term	Xyrem Dosage at Onset (grams)				
	4.5	6.0	7.5	9.0	Total (a)
Number of Patients	25 (100%)	22 (100%)	22 (100%)	21 (100%)	25 (100%)
Patients With Adverse Events	10 (40%)	9 (41%)	6 (27%)	10 (48%)	18 (72%)
Body as a Whole	3 (12%)	3 (14%)	1 (5%)	2 (10%)	9 (36%)
Accidental injury	0	1 (5%)	0	0	1 (4%)
Back pain	1 (4%)	0	1 (5%)	1 (5%)	3 (12%)
Flu syndrome	0	1 (5%)	0	0	1 (4%)
Infection	0	1 (5%)	0	1 (5%)	2 (8%)
Cardiovascular System	0	0	1 (5%)	0	1 (4%)
Migraine	0	0	1 (5%)	0	1 (4%)
Digestive System	4 (16%)	3 (14%)	0	5 (24%)	8 (32%)
Anorexia	0	0	0	3 (14%)	3 (12%)
Nausea	1 (4%)	2 (9%)	0	2 (10%)	5 (20%)
Vomiting	1 (4%)	1 (5%)	0	1 (5%)	3 (12%)
Metabolic and Nutritional System	1 (4%)	2 (9%)	1 (5%)	0	4 (16%)
Edema	1 (4%)	2 (9%)	0	0	3 (12%)
Generalized edema	0	0	1 (5%)	0	1 (4%)
Musculoskeletal System	1 (4%)	0	0	1 (5%)	2 (8%)
Myasthenia	0	0	0	1 (5%)	1 (4%)
Nervous System	3 (12%)	2 (9%)	2 (9%)	3 (14%)	8 (32%)
Anxiety	0	0	1 (5%)	0	1 (4%)
Dizziness	0	0	0	1 (5%)	1 (4%)
Emotional lability	2 (8%)	0	0	0	2 (8%)
Paresthesia	0	0	0	1 (5%)	1 (4%)
Sleep disorder	0	0	1 (5%)	1 (5%)	2 (8%)
Somnolence	0	2 (9%)	0	0	2 (8%)

COSTART Preferred Term	Xyrem Dosage at Onset (grams)				
	4.5	6.0	7.5	9.0	Total (a)
Number of Patients	25 (100%)	22 (100%)	22 (100%)	21 (100%)	25 (100%)
Respiratory System	1 (4%)	1 (5%)	1 (5%)	0	3 (12%)
Bronchitis	0	1 (5%)	0	0	1 (4%)
Respiratory disorder	0	0	1 (5%)	0	1 (4%)
Sinusitis	0	1 (5%)	0	0	1 (4%)
Skin	1 (4%)	1 (5%)	0	0	2 (8%)
Contact dermatitis	0	1 (5%)	0	0	1 (4%)
Special Senses	1 (4%)	0	1 (5%)	0	2 (8%)
Taste perversion	0	0	1 (5%)	0	1 (4%)
Urogenital System	1 (4%)	0	2 (9%)	0	2 (8%)
Breast abscess	0	0	1 (5%)	0	1 (4%)
Urinary incontinence	1 (4%)	0	1 (5%)	0	2 (8%)

^a Patients are counted only once in each category, and only once in each body system summary.

A dose response did appear to be present for some adverse events such as anorexia, nausea and dizziness

9.10.8.2 Deaths And Serious Adverse Events

There were no deaths or serious adverse events. As noted earlier, the sole serious adverse event listed in the table in Section 9.10.8.1 was not a serious adverse event at all.

9.10.8.3 Adverse Event Discontinuations

2 patients discontinued treatment on account of adverse events. They are described further below:

9.10.8.3.1 PATIENT # 17304

This 67 year old woman had a past history of a tonsillectomy and of lumpectomy and radiation therapy for right-sided breast cancer.

In Study OMC-SXB-20 she received Xyrem® in the following consecutive dosing regimes: 4.5 g/day for 35 days; 6 g/day for 14 days; and 7.5 g/day for 1 day. On Study Day 51, after receiving her first dose of Xyrem® 7.5 g/day she experienced an “increase” in obstructive sleep apnea (it is unclear if she had obstructive sleep apnea earlier, either

preceding or during the trial) at which time Xyrem® was discontinued. Her subsequent course is unknown.

9.10.8.3.2 PATIENT # 42305

This 56 year old woman had a past history of depression with onset > 3 years prior to participating in the study. On Study Day 10 while receiving Xyrem® 4.5 g/day the patient experienced a worsening of depression; this adverse event resulted in her discontinuing Xyrem® on Day 27. Her depression reportedly resolved by Day 35

9.10.8.4 Laboratory Data

Mean changes from baseline and isolated abnormal values that were noted in the hematology and clinical chemistry data did not appear to be clinically significant. I have reviewed the individual patient data listings.

9.10.8.5 Vital Signs

Based on the descriptive statistics and individual listings provided, changes in vital signs were minimal and not clearly dose-related. I have reviewed the individual patient data listings.

9.10.8.6 Electrocardiograms

Only 1 patient had an electrocardiogram that was considered normal at baseline and abnormal at the end of the study. This abnormality was eventually determined to represent an old inferior wall myocardial infarction.

5 patients had electrocardiograms that were abnormal both at baseline and at study end. Details of the abnormalities noted are not provided.

9.11 Reviewer's Comments

The spectrum of adverse events seen in this study are broadly similar to those seen in other clinical studies of Xyrem® and do not raise any special concerns.

10. Safety Data From Study OMC-SXB-21

This study was intended to assess the long-term efficacy of Xyrem® based on a randomized withdrawal paradigm. The study is of relevance to the safety of Xyrem® in that it evaluates the potential adverse consequences of the abrupt withdrawal of therapeutic doses of the drug, including the incidence of rebound cataplexy.

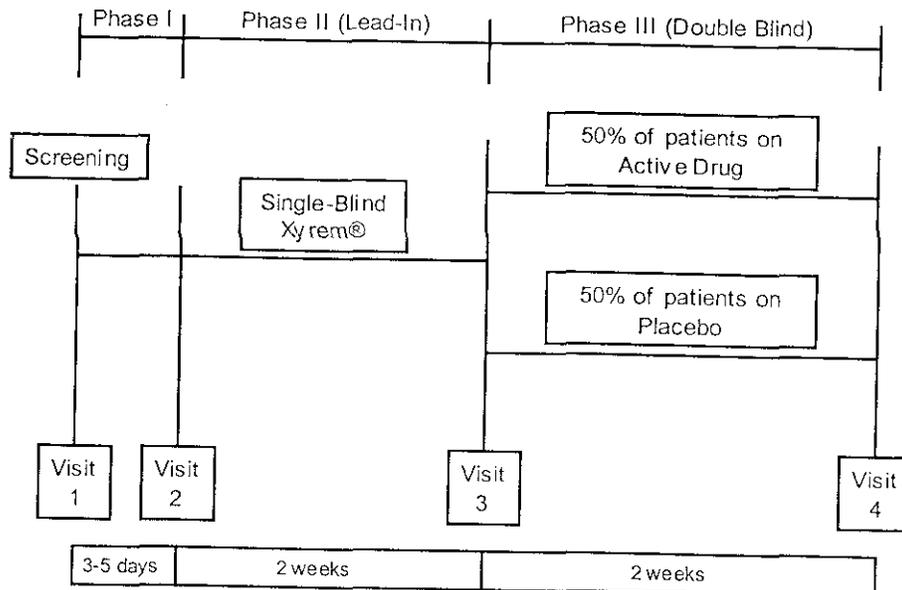
10.1 Brief Summary Of Study Protocol

10.1.1 Objective

To provide evidence for the long-term efficacy of Xyrem® based upon the return of cataplexy symptoms upon cessation of a minimum of 6 months of open-label treatment with active drug

10.1.2 Design

The design of the study is schematically summarized below



10.1.3 Duration

4 weeks (2 weeks of a double-blind withdrawal phase)

10.1.4 Sample Size

60 patients, with 30 in each treatment group in Phase 3, of the study will be included in the trial

10.1.5 Key Inclusion Criteria

- Informed consent
- Age ≥ 16 years
- Willing and able to complete the entire trial
- At least 5 cataplexy attacks per week prior to receiving any treatment (tricyclic antidepressants, selective serotonin uptake inhibitors, or Xyrem®) for cataplexy
- If female must be
 - Surgically sterile OR
 - 2 years post-menopausal OR
 - If of child bearing potential must be using a medically accepted means of birth control and must agree to continue such treatment for the duration of the study
- Treated continuously for the symptoms of narcolepsy with Xyrem® for at least 6 months, and not more than 3.5 years
- Willing to not operate a car or heavy machinery if the clinical investigator feels such a restriction is warranted
- Adequate support for the duration of the trial

10.1.6 Key Exclusion Criteria

- Unstable diseases in any body system, other than narcolepsy, which would place the patient at risk or compromise the trial objectives
- Psychiatric disorders that would preclude participation in, or completion of, the trial
- History of substance abuse, as defined by DSM-IV, currently or within the past year
- Serum creatinine > 2 mg/dl; AST or ALT > 2 x upper limit of normal; serum bilirubin > 1.5 x upper limit of normal; pre-trial electrocardiogram results demonstrating a clinically significant arrhythmia or 2nd or 3rd degree A-V block; history of myocardial infarction within the past 6 months
- Any untreated disorder other than narcolepsy that could be considered a primary cause of excessive daytime sleepiness, including sleep apnea syndrome (criteria specified)
- Occupation requiring variable shift or routine night shift work
- Use of tricyclic antidepressants, selective serotonin uptake inhibitors or medications for cataplexy other than Xyrem® in the 30 days prior to Visit 1 of the study
- Clinically significant history of head trauma; previous invasive cranial surgery; seizure disorder; use of anticonvulsant medication

10.1.7 Concomitant Medications

- The following medications were prohibited during the trial: selective serotonin uptake inhibitors and tricyclic antidepressants.
- Patients were to be cautioned regarding the use of opioid analgesics and skeletal muscle relaxants
- Alcohol was prohibited during the trial
- Over-the-counter medications needed careful review by the clinical investigator prior to use; non-sedating alternatives were to be used wherever possible
- Stable doses of stimulant medication could be used to treat excessive daytime sleepiness as clinically indicated

10.1.8 Dosage

Previously established dose of Xyrem® ranging from 3 to 9 grams daily

10.1.9 Schedule

- The visit schedule was as in the schematic above.
- The following were to be checked at Visit 1 alone: informed consent; selection criteria, medical history, cataplexy history prior to use of any medications, and “support systems”.
- Physical examinations, including neurological examinations were to be performed at Visits 1 and 4
- Daily diaries were to be provided and/or checked at visits 2, 3, and 4. Diaries were to record cataplexy and adverse events.

- Concurrent medications, vital signs and adverse events were to be checked at every visit
- A pregnancy test were to be checked if applicable at Visit 1
- Routine hematology and chemistry were to be checked at Visits 1 and 4

10.1.10 Outcome Measures

10.1.10.1 Efficacy Measure

Frequency of cataplexy attacks

10.1.10.2 Safety

Adverse events, laboratory data

10.1.11 Analysis Plan

10.1.11.1 Demographic And Baseline Variables

- The 2 double-blind period treatment groups were to be compared in regard to demographic and baseline variables
- Quantitative variables were to be analyzed using either a t-test or a Wilcoxon rank sum test as appropriate
- Qualitative variables were to be analyzed using Fisher's exact test

10.1.11.2 Primary Efficacy Parameter

- The primary efficacy parameter was the change in the number of cataplexy attacks per week in the 2-week period following Visit 3 (endpoint), compared with the 2-week period prior to Visit 3 (baseline). If a subject withdrew prior to Visit 4 the weekly average would be calculated based upon the data that were available
- The efficacy population was to consist of all those randomized at Visit 2 who had some post-baseline efficacy data
- The above change in the weekly number of cataplexy attacks was to be analyzed using a non-parametric ANCOVA as follows
 - The baseline number of cataplexy attacks and the change in the weekly number of cataplexy attacks were to be replaced by their corresponding ranks (mean ranks will be used when ties occur).
 - The ANCOVA would be constructed from the residuals derived from the ordinary least squares prediction of the change in the weekly number of cataplexy attacks based on a simple linear model
 - The treatment groups would then be compared with respect to these residuals using the Wilcoxon rank sum test.
 - Prior to completion of the analysis a test would be performed to compare the slopes for the 2 treatment groups.
- The significance of the mean change from baseline for each treatment group would be determined using the Wilcoxon signed rank test

10.1.11.3 Safety Parameters

- The safety population would consist of all those randomized to receive drug at Visit 3 who had some post-baseline safety data

- Adverse events would be summarized by treatment group and organized by preferred term and body system. Treatment groups would be compared to the incidence of each adverse event using Fisher's exact test
- Laboratory data would be summarized in tabular form as well as with the use of shift tables. Treatment groups would be compared in regard to the mean change from baseline using ANOVA. Within each treatment group the significance of the mean change from baseline was to be analyzed using a paired t-test

10.1.11.4 Sample Size Rationale

- The sample size calculation was based on the change in weekly cataplexy attacks comparing the 2 weeks prior to randomization and the 2 weeks after randomization
- The assumptions for the sample size calculation were as follows
 - Power of 80 %
 - 2-sided α of 0.05
 - A 50 % increase in the total number of cataplexy attacks in the placebo group, and a 10 % increase in a Xyrem® group
 - A standard deviation, based on a log transformation, of about 0.30 for the change in total number of cataplexy attacks (based on a previous study)
- Based on the above, a sample size of 22 patients would be required per treatment group to detect a treatment difference.
- To allow for a minor departure from the above assumptions a total of 30 patients would be randomized to each treatment group

10.2 Protocol Amendments

These have been incorporated into the above protocol outline.

10.3 Actual Analyses Performed

The analyses were performed according to the protocol

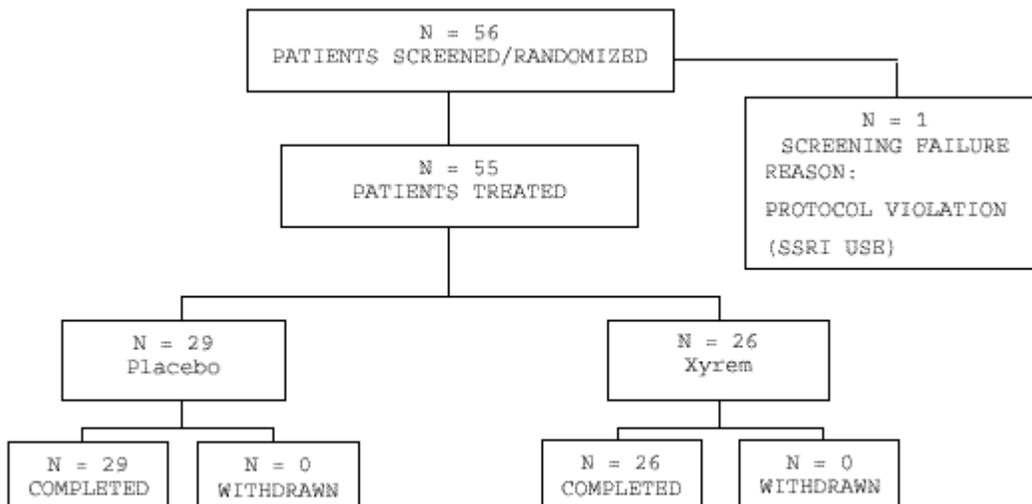
10.4 Efficacy Results

The full efficacy data are presented in this review as rebound cataplexy, which was seen in this study, is a manifestation of the abrupt withdrawal of GHB which is further described as part of this review.

The study was conducted at 14 centers. Each center enrolled between 1 and 7 patients

10.4.1 Patient Disposition

Patient disposition is summarized in the following schematic copied from the submission



Note that 1 randomized patient failed screening because of concomitant use of a selective serotonin re-uptake inhibitor (paroxetine). The blind was broken on 1 patient shortly after completion of the trial on account of a serious adverse event.

10.4.2 Protocol Deviations

- One patient was allowed into the trial despite having been treated with GHB for 3.7 years (the inclusion criteria specified that the duration of treatment should be from 0.5 to 3.5 years)
- One patient was allowed to continue in the trial despite receiving bupropion as a medication for cataplexy
- 3 patients overmedicated
- For “efficiency” 2 patients who were taking 3 g/day at study entry and continued to take that dose during the study were listed as taking 4.5 g/day
- For a number of patients Visits 1 and 2 were combined.

10.4.3 Medication Compliance

As the following table indicates medication compliance was comparable for the 2 Phase III treatment groups

Trial Medication Administration	Xyrem (N=26)			Placebo (N=29)		
	Phase II	Phase III	Total	Phase II ^a	Phase III	Total
Days Treated						
11	0	2		0	3	
12	1	1		0	0	
13	1	5		4	5	
14	14	13		20	13	
15	4	3		0	6	
16	1	0		0	0	
17	4	1		4	1	
18	1	1		1	1	
Duration of Treatment (Nights)						
Mean	14.7 ± 1.43	13.9 ± 1.48	28.6 ± 2.50	14.4 ± 1.35	14.0 ± 1.50	28.4 ± 1.95
Range	12-18	11-18	24-36	13-18	11-18	24-36
Compliance (%)						
Mean ± SD	105.9 ± 17.24	106.1 ± 18.80	106.0 ± 17.44	99.7 ± 6.07	102.4 ± 15.12	101.1 ± 9.28
Range	95-171	85-185	90-178	85-119	72-167	82-139

^a Placebo group patients received Xyrem during Phase II.
 SD = Standard deviation.

10.4.4 Baseline And Other Demographic Characteristics

These characteristics are summarized in the next 2 tables copied from this submission. Although gender, and baseline frequency of cataplexy attacks were not entirely balanced between the treatment groups the sponsor describes the differences as not being statistically significant. Note that the daily dose of Xyrem® did appear balanced between the Phase III treatment groups.

Characteristics	Total	Treatment Group		p-Value
	(N=55)	Xyrem (N=26)	Placebo (N=29)	
Age (years)				
Mean ± SD	47.7 ± 16.66	47.9 ± 17.06	47.6 ± 16.60	0.955
Range	16.3 - 82.6	19.1 - 82.6	16.3 - 70.0	
Sex (n, %)				
Male	23 (42%)	8 (31%)	15 (52%)	0.172
Female	32 (58%)	18 (69%)	14 (48%)	
Weight (kg)				
Mean ± SD	80.5 ± 20.09	83.8 ± 24.31	77.6 ± 15.22	0.250
Range	54.0 - 142.0	54.0 - 142.0	55.0 - 127.0	
Height (cm)				
Mean ± SD	170.1 ± 10.25	169.6 ± 10.42	170.6 ± 10.24	0.710
Range	152.0 - 188.0	152.0 - 188.0	155.0 - 188.0	
Race (n, %)				
Caucasian	52 (95%)	23 (88%)	29 (100%)	0.099
African-American	2 (4%)	2 (8%)	0	
Asian	0	0	0	
Hispanic	1 (2%)	1 (4%)	0	
Other	0	0	0	
Time on Xyrem (months)				
Mean ± SD	21.22 ± 12.28	23.27 ± 12.36	19.38 ± 12.13	ND
Range	7 - 44	8 - 38	7 - 44	

(continued)

Characteristics	Total	Treatment Group		p-Value
	(N=55)	Xyrem (N=26)	Placebo (N=29)	
Cataplexy attacks (2-week baseline)				
N	55	26	29	0.436
Mean	12.6	9.0	15.7	
SD	31.75	19.25	39.88	
Median	3.0	1.9	4.0	
Minimum	0.0	0.0	0.0	
Maximum	197.0	86.8	197.0	
Daily Dosage of Xyrem at Screening (n, %)				
3.0 g/d	2 (4%)	1 (4%)	1 (3%)	ND
4.5 g/d	9 (16%)	4 (15%)	5 (17%)	
6.0 g/d	15 (27%)	7 (27%)	8 (28%)	
7.5 g/d	15 (27%)	7 (27%)	8 (28%)	
9.0 g/d	14 (25%)	7 (27%)	7 (24%)	

ND = Not determined. SD = Standard deviation.

10.4.5 Primary Efficacy Analysis

An intent-to-treat analysis was performed as specified in the protocol comprising all patients who received one or more doses of trial medication during the double blind withdrawal period and had recorded baseline and post-baseline efficacy measures

The results of the primary efficacy analysis are outlined in the table and figure below. For those receiving Xyrem® during the double-blind withdrawal phase there was no median change from baseline in the number of cataplexy attacks

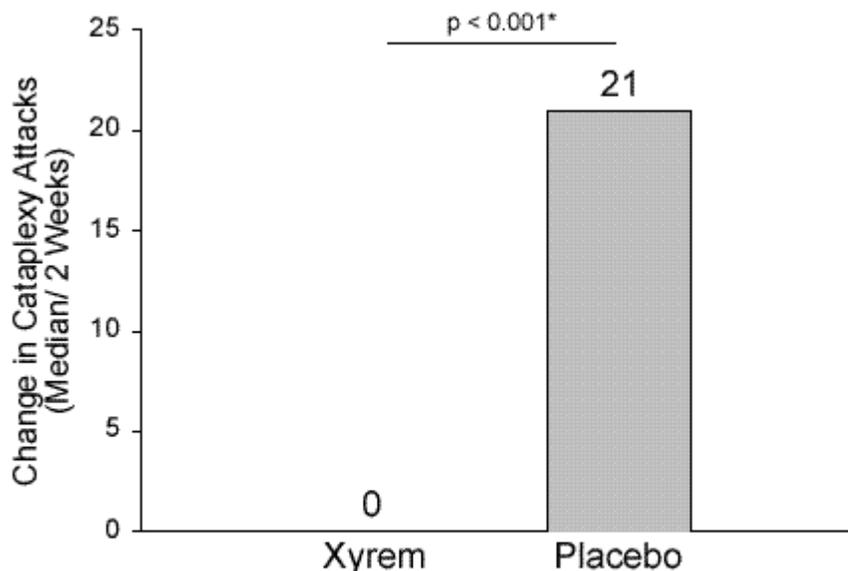
over the 2 week period of withdrawal. For those receiving placebo during the withdrawal phase the median change in the number of cataplexy attacks during as compared with baseline showed an increase. The difference was statistically significant ($p < 0.001$). Note that the table and figure below depict median change

	Xyrem (N=26)			Placebo (N=29)		
	Phase II	Phase III	Change	Phase II*	Phase III	Change
Number of cataplexy attacks (per 2 weeks)						
Mean ± SD	9.0 ± 19.25	12.6 ± 30.34	3.6 ± 20.73	15.7 ± 39.88	50.4 ± 81.09	34.6 ± 55.72
Median	1.9	1.1	0.0	4.0	21.0	21.0
Minimum	0.0	0.0	-24.3	0.0	0.0	-15.0
Maximum	86.8	138.3	87.2	197.0	269.2	206.2
Rank change						
Mean ± SD			18.1 ± 12.65			36.9 ± 13.31*
Median			16.5			39.0
Minimum			1.0			3.0
Maximum			52.0			55.0

SD = standard deviation.

* Placebo group patients received Xyrem during Phase II.

* $p < 0.001$, from ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction.

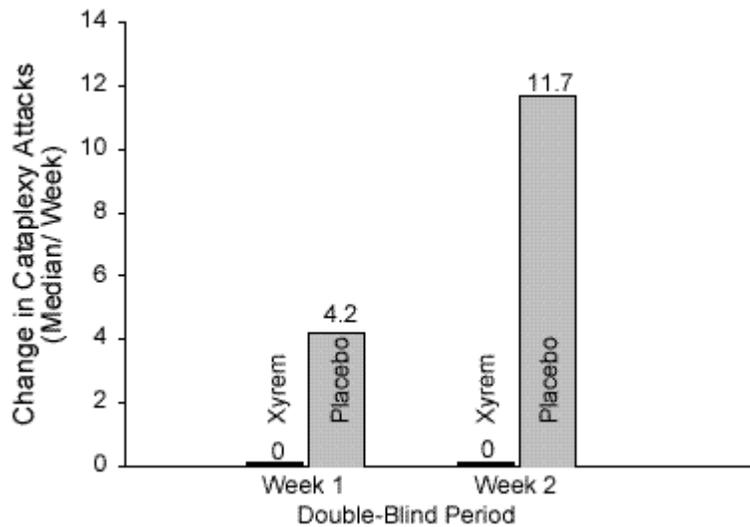


* $p < 0.001$, from ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction.

As the next table and figure indicate the median change from baseline by week in the number of cataplexy attacks mirrors that for the primary efficacy analysis above

Number of Cataplexy Attacks	Xyrem			Placebo		
	Phase II ^a	Phase III	Change	Phase II ^a	Phase III	Change
Week 1						
Number of Patients	26	26	26	29	29	29
Mean ± SD	4.5 ± 9.62	5.3 ± 11.84	0.8 ± 7.48	7.9 ± 19.94	21.1 ± 35.13	13.2 ± 22.02
Median	0.9	1.0	0.0	2.0	7.0	4.2
Minimum	0.0	0.0	-15.4	0.0	0.0	-7.5
Maximum	43.4	50.8	25.2	98.5	126.0	87.5
Week 2						
Number of Patients	26	26	26	29	29	29
Mean ± SD	4.5 ± 9.62	7.2 ± 18.66	2.7 ± 13.74	7.9 ± 19.94	29.7 ± 47.30	21.8 ± 35.16
Median	0.9	0.5	0.0	2.0	13.0	11.7
Minimum	0.0	0.0	-10.7	0.0	0.0	-7.5
Maximum	43.4	87.5	62.0	98.5	168.0	143.5

^a Baseline (Phase II) was determined by normalizing the total number of cataplexy attacks during the 2-week Phase II period to 7 days.



No formal analyses were carried out to evaluate differential effects at study sites, or to evaluate drug-drug or drug-disease interactions.

10.4.6 Analysis Of Secondary Efficacy Measures

This study had no secondary efficacy measures

10.5 Safety Results

10.5.1 Exposure

All 55 patients who received study medication were included in the safety analysis.

Information on the extent of medication compliance is described in the table in Section 10.4.3

Information on medication dose at study entry is further described in the table in Section 10.4.4.

26/55 (47%) of patients received their Xyrem® dose at study entry during the baseline and randomized withdrawal phases

29/55 (53%) of patients received their Xyrem® dose at study entry during the baseline phase of this study but received placebo during the randomized withdrawal phase

10.5.2 Deaths, Serious Adverse Events And Adverse Event Discontinuations

No deaths, serious adverse events or adverse event discontinuations are listed as having occurred during the study.

However a single patient (# 0232; Initials (b)(6) developed an acute paranoid psychosis 3 days after participation in OMC-SXB-21 ended and after resuming GHB in OMC-SXB-7. A more detailed narrative for this patient is as follows:

This 44 year old woman with no previous history of psychiatric illness began taking Xyrem® on 4/1/99; from January 2000 onwards she took a stable dose of 9 g/day.

She entered OMC-SXB-21 from OMC-SXB-7. Concomitant medications at that time included modafinil, verapamil, ranitidine, aspirin and ibuprofen. She completed OMC-SXB-21 on 7/28/00 and re-entered OMC-SXB-7 taking 9 g/day again. After the blind for OMC-SXB-21 was broken it was confirmed that she had taken Xyrem® 9 g/day throughout that study as well.

On 8/1/00 she was hospitalized in an acutely paranoid state. She discharged herself from the hospital but was readmitted on 8/3/00. During her hospitalization she was treated with haloperidol, temazepam and clomipramine (clomipramine had been discontinued on 5/9/00). No GHB was administered after 7/30/00 and on 8/14/00 she told the investigator that she well. Clomipramine was apparently stopped and then resumed on 9/28/00 with a return of paranoia for a limited duration; this drug was however continued as apparently was modafinil. By 10/12/00 she had apparently returned to normal.

10.5.3 Other Adverse Events

The following tables copied from the submission display all adverse events that occurred during each phase of the study. The incidence of all adverse events during Phase III (the randomized withdrawal phase) are of particular interest; as the table indicates, the incidence of all adverse events in each treatment group was very low during this period. Of minor note is the presence of anxiety, dizziness, insomnia, "sleep disorder" and somnolence, each in 1-2 patients who received placebo during that phase, whereas none occurred in those receiving Xyrem®, which might suggest the infrequent presence of a mild withdrawal syndrome; however the total sample enrolled in this study and the number of those with these specific adverse events is too small to be conclusive.

Body System COSTART Term	Total* (N=55) n (%)	Treatment Group	
		Xyrem (N=26) n (%)	Placebo (N=29) n (%)
Phase I			
Patients with Adverse Events	4 (7%)	1 (4%)	3 (10%)
Body as a Whole	1 (2%)	0	1 (3%)
Accidental injury	1 (2%)	0	1 (3%)
Metabolic & Nutritional System	2 (4%)	1 (4%)	1 (3%)
Alkaline phosphatase increased	1 (2%)	1 (4%)	0
BUN increased	1 (2%)	0	1 (3%)
Creatinine increased	1 (2%)	0	1 (3%)
Hyperglycemia	1 (2%)	0	1 (3%)
Hyperuricemia	1 (2%)	0	1 (3%)
Nervous System	1 (2%)	0	1 (3%)
Peripheral neuritis	1 (2%)	0	1 (3%)
Respiratory System	1 (2%)	0	1 (3%)
Pharyngitis	1 (2%)	0	1 (3%)
Phase II			
Patients with Adverse Events	9 (16%)	4 (15%)	5 (17%)
Body as a Whole	3 (5%)	1 (4%)	2 (7%)
Asthenia	1 (2%)	1 (4%)	0
Headache	3 (5%)	1 (4%)	2 (7%)
Digestive System	2 (4%)	2 (8%)	0
Diarrhea	1 (2%)	1 (4%)	0
Nausea	1 (2%)	1 (4%)	0
Metabolic & Nutritional System	1 (2%)	0	1 (3%)
Hyperglycemia	1 (2%)	0	1 (3%)
Respiratory System	1 (2%)	0	1 (3%)
Rhinitis	1 (2%)	0	1 (3%)

Body System COSTART Term	Total* (N=55) n (%)	Treatment Group	
		Xyrem (N=26) n (%)	Placebo (N=29) n (%)
Phase II (continued)			
Skin	1 (2%)	0	1 (3%)
Fungal dermatitis	1 (2%)	0	1 (3%)
Pruritus	1 (2%)	0	1 (3%)
Skin benign neoplasm	1 (2%)	0	1 (3%)
Skin nodule	1 (2%)	0	1 (3%)
Urogenital System	1 (2%)	1 (4%)	0
Vaginitis	1 (2%)	1 (4%)	0
Phase III			
Patients with Adverse Events	12 (22%)	3 (12%)	9 (31%)
Body as a Whole	4 (7%)	1 (4%)	3 (10%)
Accidental injury	1 (2%)	0	1 (3%)
Chest pain	1 (2%)	1 (4%)	0
Headache	2 (4%)	0	2 (7%)
Cardiovascular System	1 (2%)	0	1 (3%)
Migraine	1 (2%)	0	1 (3%)
Hemic-lymphatic System	1 (2%)	0	1 (3%)
Lymphadenopathy	1 (2%)	0	1 (3%)
Metabolic & Nutritional System	1 (2%)	0	1 (3%)
SGOT increased	1 (2%)	0	1 (3%)
SGPT increased	1 (2%)	0	1 (3%)
Nervous System	5 (9%)	0	5 (17%)
Anxiety	2 (4%)	0	2 (7%)
Dizziness	1 (2%)	0	1 (3%)
Insomnia	1 (2%)	0	1 (3%)
Sleep disorder	1 (2%)	0	1 (3%)
Somnolence	1 (2%)	0	1 (3%)
Respiratory System	2 (4%)	1 (4%)	1 (3%)
Dyspnea	1 (2%)	1 (4%)	0
Pharyngitis	1 (2%)	0	1 (3%)
Skin	2 (4%)	1 (4%)	1 (3%)
Contact dermatitis	1 (2%)	1 (4%)	0
Rash	2 (4%)	1 (4%)	1 (3%)
Urogenital System	1 (2%)	1 (4%)	0
Urinary incontinence	1 (2%)	1 (4%)	0

* Patients are counted only once in each category.

10.5.4 Laboratory Data

The changes in hematology and clinical chemistry parameters may be summarized as follows

10.5.4.1 Mean Changes From Baseline To Last Observation

- Statistically significant changes from baseline were seen for
 - Monocytes (increase) and potassium (decrease) in the Xyrem® group
 - Total protein and albumin (decrease) and ALT (increase) in the placebo group
- Statistically significant differences between treatment groups for changes in baseline were seen for lymphocyte count and sodium
- Mean changes in each of the above categories were minor and inconsequential

10.5.4.2 Categorical Shifts From Baseline To Last Observation

All changes occurred in < 10% of patients in each treatment group and appeared to be of no consequence

10.5.4.3 Changes From Baseline In Individual Patients

No changes of clinical consequence were seen

10.5.5 Vital Signs

Descriptive statistics for changes in vital signs from baseline to last observation are summarized in the next table copied from the submission. As the table indicates these changes were inconsequential.

Parameter	Xyrem	Placebo
Number of Patients	26	29
Pulse (bpm)		
Mean	3.9	-0.3
SD	12.57	11.64
Median	5.5	0.0
Minimum	-31.0	-24.0
Maximum	32.0	22.0
Respiration (breaths/min)		
Mean	0.1	1.7
SD	2.80	2.32
Median	0.0	1.0
Minimum	-5.0	-2.0
Maximum	8.0	8.0
Diastolic Blood Pressure (mm Hg)		
Mean	1.8	0.2
SD	9.40	8.92
Median	0.0	0.0
Minimum	-20.0	-18.0
Maximum	19.0	20.0
Systolic Blood Pressure (mm Hg)		
Mean	3.1	-3.2
SD	11.65	13.15
Median	5.0	0.0
Minimum	-20.0	-32.0
Maximum	24.0	18.0
Body Temperature (°C)		
Mean	-0.0	-0.1
SD	0.59	0.70
Median	0.0	0.0
Minimum	-1.7	-1.9
Maximum	0.9	0.9
Body Weight (kg)		
Mean	-0.5	1.0
SD	2.00	2.78
Median	0.0	0.0
Minimum	-6.0	-2.0
Maximum	4.0	13.0

10.6 Sponsor's Conclusions Regarding Safety

These may be summarized as follows

- The incidence and severity of adverse events was low during this trial
- Withdrawal symptoms such as anxiety occur infrequently on abrupt withdrawal of chronic therapeutic doses of GHB

10.7 Reviewer's Comments

I concur with the sponsor's conclusions

11. Key Information From Integrated Summary Of Safety And OMC-SXB-21 Safety Data

11.1 All Adverse Events

The most common adverse events that appeared to be related to GHB use (based on a higher incidence in Xyrem® treated individuals in placebo-controlled trials), and were more frequent with higher doses of that drug, included headache, “pain” (unspecified), nausea, dizziness, and urinary incontinence. These appeared to be both reversible and infrequent.

In the Integrated Clinical Trials grouping the incidence of all the above adverse events, with the exception of headache, nausea and dizziness, was relatively low. In the Scharf trial the incidence of all the above common adverse events was considerably higher, presumably reflecting the duration of the trial, at least in part.

The issue of whether urinary incontinence in patients treated with GHB could be caused by unrecognized seizures has been explored further by the sponsor to a limited degree (see Section 8.5.5.1). Currently there is no strong evidence that GHB in the doses proposed for clinical use is epileptogenic or that urinary incontinence in patients treated with GHB is caused by unrecognized seizures. However the data provided so far that attempts to address these issues is very limited and either possibility cannot be ruled out.

11.2 Deaths

None of the deaths in the Xyrem® safety database could be causally linked to the drug; all 11 deaths occurred in the long-term, open-label, Scharf study and appeared to be due to intercurrent illnesses or accidents unrelated to Xyrem®.

Death occurred in 7.7% of patients participating in the Scharf study

11.3 Serious Adverse Events

Serious adverse events that could be causally linked to GHB use, at doses in the therapeutic range, included various combinations of the following: nausea, vomiting, dizziness, confusion, restlessness, agitation, somnolence and generalized weakness. There has been no comment by the investigator as to whether the reported “generalized weakness” represented true muscle weakness or not.

In 2 patients who may have or did take a drug overdose manifestations included coma, respiratory depression, incontinence and a flaccid tone.

Note that serious adverse events were seen in 4.5% of patients who participated in the Integrated Clinical Trials and 37.8% of those who participated in the Scharf trial; the much higher incidence in the Scharf trial is probably due to the duration of that study.

11.4 Adverse Event Discontinuations

Adverse event discontinuations that could be causally linked to GHB use, at doses in the therapeutic range, included varying combinations of the following: headache, nausea, vomiting, fatigue, reduced initiative and libido, dizziness, impaired memory, confusion, restlessness, agitation, paranoia, hallucinations, urinary and fecal incontinence, somnolence and generalized weakness (including difficulty maintaining an upright posture). Adverse events in that constellation of symptoms were seen in 5/102 patients receiving GHB in the randomized controlled trial OMC-GHB-2 but were not seen in any of 34 patients who received placebo. Such adverse events do appear more common at higher doses of GHB.

Particularly noteworthy was a single healthy 39 year-old subject participating in a pharmacokinetic trial who developed dizziness, nausea, vomiting, respiratory depression and fecal incontinence after a single (and initial) oral dose of 4.5 g of GHB, administered after an overnight fast.

One patient who may have taken a drug overdose manifest with coma, respiratory depression, incontinence and a flaccid tone (this patient is also listed as having a serious adverse event).

The proportion of patients discontinuing treatment on account of adverse events in the Integrated Clinical Trials, Scharf trial and Integrated Pharmacokinetic Trials were 10.9%, 8.4%, and 1.4%, respectively.

11.5 Laboratory Data

- No clinically relevant or clinically-correlated changes in routine safety laboratory tests-hematology, clinical chemistry and urinalysis-were seen
- As described in detail earlier (see Section 8.5.5.2), elevated antinuclear antibody titers were seen in a proportion of patients participating in the Scharf study. Further details are as follows
 - This test was not protocol-specified and was performed at a variable frequency only after the detection of the index case, a patient reported to have rheumatoid arthritis. Testing was performed in a variety of laboratories
 - Antinuclear antibody testing was not performed in patients participating in any other clinical trials of GHB
 - 87 patients participating in this study had antinuclear antibody titers tested on one or more occasions. 26 of these patients (29.9%) had one or more positive titers
 - 2 patients discontinued from the Scharf study on account of positive antinuclear antibody titers.
 - The *sine qua non* of drug-induced lupus is stated to be the presence of appropriate symptoms associated with the presence of antihistone antibodies. 15 patients with positive antinuclear antibody titers had antihistone antibodies tested for: one of these patients was borderline positive, the others were negative.
 - Only one patient who had positive antinuclear antibody titers is reported to have had symptoms suggestive of a systemic rheumatic disease (the index patient who was diagnosed to have rheumatoid arthritis; see Section 8.4.2.3). This patient did not have antihistone antibody testing done

11.6 Electrocardiograms

No clinically pertinent changes in electrocardiograms were seen that could be attributed to Xyrem®.

11.7 Vital Signs

A mild dose-related reduction in weight and sitting diastolic blood pressure was seen in GHB-treated patients in the randomized, controlled trial OMC-GHB-2.

No other clinically significant changes in vital signs were seen.

11.8 Withdrawal Phenomena

- The randomized withdrawal study OMC-SXB-21 was primarily intended to assess the long-term efficacy of Xyrem®. Spontaneous and elicited adverse event indicated the presence of anxiety, dizziness, insomnia, "sleep disorder" and somnolence, each in 3-7% of patients who received placebo during that phase, whereas none occurred in those receiving Xyrem®. These data might suggest the infrequent presence of a mild withdrawal syndrome; however the total sample enrolled in this study and the number of those with these specific adverse events is too small to be anywhere near conclusive.
- In OMC-SXB-21 the frequency of cataplexy attacks was increased to a statistically significant level in those who received placebo during the withdrawal phase relative to those who received GHB during that period.
- In the randomized, controlled, parallel-arm efficacy trial OMC-GHB-2, adverse events that were noted during a 5-day period following drug withdrawal included abnormal dreaming, hallucinations and an unspecified sleep disorder (a total of 3/102 patients who received GHB during this study had these adverse events and only 1 patient, who had previously received a Xyrem® dose of 9 g/day, had hallucinations). The sponsor reports that the frequency of cataplexy was not increased during the 5-day observation period following drug withdrawal.
- Thus, in the small number of patients formally studied there is very limited evidence that narcoleptic patients receiving therapeutic doses of GHB experience more than infrequent and mild withdrawal symptoms, other than an increased frequency of cataplexy

12. Literature Review

In this NDA the sponsor has provided full publications as well as synopses for clinical studies of GHB that have been reported in the medical literature, but are not otherwise included in this application. These studies fall into 2 categories

- Studies conducted in healthy individuals
- Studies conducted for a variety of medical indications

These studies are summarized in tabular form below

12.1 Published Studies Conducted In Healthy Individuals

These are summarized in the following table

Author	Purpose Of Study	Dose Of GHB	Number Of Subjects Exposed To GHB	Age Range	Adverse Events
Yamada	Effect of GHB on EEG	10-30 mg/kg Intravenous Single dose	12	20-33	None reported
Lee	Evaluation of metabolism of GBL	1 g Oral Single dose	4	Not available	None reported
Palatini	Pharmacokinetics of GHB	12.5 to 50 mg/kg Oral Single dose	8	22-26	Nausea, dizziness, drowsiness

The extent to which adverse events were systematically monitored for in these studies is unclear from the published reports ; the reports by Yamada and Lee do not specifically state that no adverse events occurred.

12.2 Published Studies Conducted For Specific Medical Indications

There are also 17 additional published reports supplied by the sponsor that describe studies done for several specific medical indications:

- These indications include alcohol withdrawal, alcohol dependence, opiate withdrawal, insomnia, sleep apnea, nocturnal myoclonus, neonatal startle disease, and as an anesthetic agent.
- Only 6 of these studies were controlled
- These studies have exposed a total of 152 subjects/patients to mainly single, oral or intravenous doses of GHB.
- The maximum individual doses used were as follows
 Oral: 50 mg/kg or 4.5 g
 Intravenous:150 mg/kg
- In a single open-label study for opiate withdrawal in 2 patients the dose used was 30 or 50 mg/kg every 4 hours for 7-8 days
- Adverse events that were reported across these studies include dizziness, vertigo, nausea, headache, gastric ulceration, drowsiness, pneumonia, semi-liquid stools and muscle pain. However in a number of publications the authors did not either list adverse events or specifically state that no adverse events occurred.

These studies are summarized in the next table

Author	Indication	Dose Of GHB	Number Of Subjects Exposed To GHB	Age Range (years)	Adverse Events
Gallimberti	Alcohol withdrawal syndrome	50 mg/kg Oral Single dose	11	28-63	Dizziness
Gallimberti	Reduction of alcohol consumption and alcohol craving	50mg/kg/day Oral 1 year	43	13-38	Vertigo, dizziness, nausea, headache and gastric ulceration
Gallimberti	Opiate withdrawal	25 mg/kg Oral Single dose	27	22-33	Dizziness
Oyama	Effects on fat and carbohydrate metabolism when used as an anesthetic	100-150 mg/kg Intravenous Single dose	10	14-48	None reported
Mamelak	Sleep induction in insomniacs	1-3 g/day Oral 3 nights	5	35-60	None reported
Mamelak	Insomnia	1-4.5 g/day Oral 3 nights	8	34-60	None reported
Van den	Anesthesia for	26.7 to 50 mg/kg	14	Not available	None reported

Author	Indication	Dose Of GHB	Number Of Subjects Exposed To GHB	Age Range (years)	Adverse Events
Bogaert	Cesarean section	Intravenous Single dose			
Mamelak	Narcolepsy and sleep apnea	60 mg/kg/day in 2 divided doses Oral 11 weeks	1	53	None reported
Strong	Reducing intracranial pressure in severe head injury	4 g Intravenous Multiple boluses	6	Not available	None reported
Hasenbos	Anesthesia for respiratory surgery	50 mg/kg Intravenous Single dose	1	64	Pneumonia
Scrima	Obstructive sleep apnea	50 mg/kg in 2 divided doses Oral 1 night	1	64	None reported
Scrima	Nocturnal myoclonus	50 mg/kg in 2 divided doses Oral 1 night	4	37-48	None reported
Bedard	Periodic leg movements in sleep in narcoleptic patients	2.25 g/day Oral 1 month	12	34-55	None reported
Ferrara	Pharmacokinetics in alcohol-dependent subjects	25 mg/kg b.i.d Oral Minimum of 7 days 50 mg/kg Oral Single-dose Day 10	10	34-56	Transient drowsiness
Series	Effects on slow-wave sleep in obstructive sleep apnea	60 mg/kg in 2 divided doses Oral 1 night	8	45 ± 2	None reported
Berthier	Neonatal startle disease	100 mg/kg (max) Intravenous Escalating doses (daily?) for 17 days	1	Newborn	None reported
Gallimberti	Opiate withdrawal syndrome	30-50 mg/kg every 4 hours for 7-8 days	2	24-30	Muscle pain; semi-liquid feces

The extent to which adverse events were systematically monitored for in these studies is unclear from the published reports ; except for the reports by Gallimberti (all), Hasenbos and Ferrara, the others do not specifically state that no adverse events occurred.

13. 120-Day Safety Update

13.1 Contents

This 120-Day Safety Update was submitted 2/1/01. It contains data from Study OMC-SXB-7 only. This was an open-label safety study conducted as part of Treatment IND # 57271, in patients previously exposed to GHB.

The data presented in this safety update consists of adverse events reported from study initiation (3/3/99) to data cut-off (9/30/00).

An earlier interim report for this study dated 8/9/00 was submitted with the main NDA application. That report contained safety data through a cut-off date of 12/31/99.

Adverse event data from 3/3/99 through 12/31/99 are therefore contained in both the interim report of 8/9/00 (submitted with the original NDA) and in the 120-Day Safety Update.

Data from 2 additional studies, OMC-SXB-20 and OMC-SXB-21, were not in the original NDA, but were submitted on 12/16/00. OMC-SXB-20 was a small open-label study of the effects of 4 doses of Xyrem® on sleep architecture. OMC-SXB-21 was a study of the long-term efficacy of Xyrem® using the randomized withdrawal paradigm. By agreement with this Division data from these studies are not included in the 120-Day Safety Update since they have already been submitted. Safety data from both these studies have been described elsewhere in this review.

13.2 Outline Of Protocol For OMC-SXB-7

The following protocol outline was submitted with the treatment IND

13.2.1 Objectives

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

13.2.2 Design

Open-label, uncontrolled study

13.2.3 Inclusion Criteria

- Informed consent
- Age \geq 12 years
- Previous use of GHB for narcolepsy under an approved IND application: the trials that will feed into this study include OMC-GHB-3, OMC-SXB-6 and the Scharf trial under IND # 21654, all of which are open-label studies: those in OMC-GHB-3 need to have completed at least 12 months of treatment; those in OMC-SXB-6 need to have completed at least 6 months of treatment; those in the Scharf trial could have received treatment for any length of time
- Willing and able to complete the entire trial
- Age \geq 12 years
- If female must be
 - Surgically sterile OR
 - 2 years post-menopausal OR
 - If of child-bearing potential, not currently pregnant and using a medically accepted means of birth control

13.2.4 Exclusion Criteria

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

13.2.5 Sample Size

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

13.2.6 Duration

24 months or until marketing approval, whichever is sooner

13.2.7 Dosage

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

13.2.8 Concomitant Medication

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

13.2.9 Schedule

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

13.2.10 Statistical Considerations

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

13.2.11 Safety Monitoring

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

13.3 Protocol Amendments

These have been incorporated into the above protocol description.

13.4 Patient Disposition

236 patients received treatment as part of this trial; they were at 26 study sites. Their disposition by last Xyrem® dose is illustrated in the following table, copied from the submission.

Patient Disposition	Total	Last Xyrem Oral Solution Dosage (g/d)				
		3.0	4.5	6.0	7.5	9.0
Treated	236 (100%)	5 (2%)	39 (17%)	76 (32%)	59 (25%)	57 (24%)
Discontinued	25 (11%)	0	3	7	5	10
Patient request	9 (4%)	0	1 (3%)	3 (4%)	2 (3%)	3 (5%)
Adverse event	10 (4%)	0	1 (3%)	2 (3%)	1 (2%)	6 (11%)
Protocol deviation	1 (<1%)	0	0	0	0	1 (2%)
Lost to follow-up	2 (<1%)	0	0	1 (1%)	1 (2%)	0
Other	2 (<1%)	0	0	1 (1%)	1 (2%)	0
Lack of efficacy	1 (<1%)	0	1 (3%)	0	0	0

13.5 Demographics

Demographics at study entry are as follows

Mean Age 48.3 years
 Mean Weight 84.4 kg

Gender Males 45% Female 55%

13.6 Dosage

Patient distribution by dose during, and at the end of the trial is summarized in the next table which I have copied from the submission

Dosage	Total	Xyrem Oral Solution Dosage (g/d)				
		3.0	4.5	6.0	7.5	9.0
Last Dosage	236	5 (2%)	39 (17%)	76 (32%)	59 (25%)	57 (24%)
Patient Dosage ^a	236	7 (3%)	48 (20%)	106 (45%)	73 (31%)	59 (25%)

^a Patient Dosage: the number of patients who took the specified dosage at any time during the trial. Patients may be counted multiple times, so the sum of patients exposed to specific dosages (293) exceeds the total number of patients treated in the trial (236).

13.7 Patient Exposure

As noted in the inclusion criteria, patients were enrolled in this study from 3 other sources

Study	Maximum Duration Of Exposure To GHB
OMC-GHB-3	24 months
OMC-SXB-6	6 months
Scharf	16 years

The next table summarizes duration of exposure by dose received during OMC-SXB-7 only.

Drug Administration	Total	Xyrem Oral Solution Dosage (g/d)				
		3.0	4.5	6.0	7.5	9.0
Exposure by Visit						
Visit 1	236 (100%)	4 (2%)	42 (18%)	98 (42%)	47 (20%)	45 (19%)
3 months (Visit 2)	223 (100%)	6 (3%)	37 (17%)	82 (37%)	56 (25%)	42 (19%)
6 months (Visit 3)	207 (100%)	6 (3%)	33 (16%)	68 (33%)	56 (27%)	44 (21%)
9 months (Visit 4)	133 (100%)	4 (3%)	18 (14%)	40 (30%)	39 (29%)	32 (24%)
12 months (Visit 5)	97 (100%)	2 (2%)	8 (8%)	29 (30%)	29 (30%)	29 (30%)
15 months (Visit 6)	48 (100%)	1 (2%)	4 (8%)	12 (25%)	16 (33%)	15 (31%)
18 months (Visit 7)	4 (100%)	0	0	1 (25%)	2 (50%)	1 (25%)
Last visit/end-of-trial	2 (100%)	0	0	2 (100%)	0	0
Duration of Treatment (days)						
N	236	7	48	106	73	59
Mean	284.0	246.9	198.7	230.0	239.2	235.8
SD	130.85	166.44	121.92	135.51	143.52	154.27
Median	272.5	292.0	187.5	187.0	188.0	207.0
Minimum	1.0	1.0	1.0	1.0	1.0	1.0
Maximum	568.0	454.0	464.0	541.0	555.0	568.0

Some patients were exposed to more than 1 dosage in the trial, so the sum of patients exposed to specific dosages (N= 293) exceeds the total number of patients in the trial (N= 236).

The mean duration of treatment in this updated study report was 284 days (0.78 years). Given that there were 236 patients enrolled in the study, the mean exposure to GHB for this study, based on this updated study report, was 184 patient-years.

In the earlier interim report for this study submitted with the original NDA, 145 patients had been exposed to the study drug for a mean duration of 104.4 days (0.29 years). The patient-exposure to GHB at that time was calculated as being 42.1 patient-years.

The additional exposure to GHB included in this safety update is therefore estimated at 141.5 patient-years

The 55 patients participating in the randomized withdrawal efficacy study, OMC-SXB-21, were drawn entirely from those participating in OMC-SXB-7. Patient exposure to GHB in OMC-SXB-21 is included in the above table, which takes into consideration those patients who were on placebo for 2 weeks during OMC-SXB-21.

13.8 Safety Results

13.8.1 All Adverse Events

The broad categories of adverse events and their distribution by dose are indicated in the following table, copied from the submission

As the table indicates serious adverse events, adverse event discontinuations and severe adverse events were all most common at the 9 g/day dose

	Total	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
	236(100%)	7(100%)	48(100%)	106(100%)	73(100%)	59(100%)
Patients with at least 1 adverse event	146(62%)	4(57%)	26(54%)	56(53%)	37(51%)	33(56%)
Patients with serious adverse events	16(7%)	0	3(6%)	3(3%)	3(4%)	7(12%)
Patients with severe adverse events	24(10%)	0	5(10%)	8(8%)	2(3%)	10(17%)
Patients discontinued due to an adverse event	9(4%)	0	1(2%)	1(<1%)	1(1%)	6(10%)
Patient deaths	1(<1%)	0	0	1(<1%)	0	0

13.8.2 Adverse Event Tables

The following tables outline adverse events that occurred in ≥ 5 % of patients in any treatment group. The tables are copied from the submission

Body System COSTART Preferred Term	Total ^a	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	236 (100%)^b	7 (100%)	48 (100%)	106 (100%)	73 (100%)	59 (100%)
Body as a Whole	72 (31%)	3 (43%)	11 (23%)	24 (23%)	23 (32%)	17 (31%)
Accidental injury	12 (5%)	0	1 (2%)	3 (3%)	3 (4%)	6 (10%)
Allergic reaction ^c	4 (2%)	1 (14%)	0	2 (2%)	1 (1%)	0
Asthenia ^c	5 (2%)	1 (14%)	1 (2%)	1 (<1%)	1 (1%)	1 (2%)
Flu syndrome	11 (5%)	2 (29%)	0	2 (2%)	5 (7%)	2 (3%)
Headache	16 (7%)	2 (29%)	3 (6%)	5 (5%)	2 (3%)	4 (7%)
Infection	17 (7%)	0	1 (2%)	8 (8%)	5 (7%)	3 (5%)
Pain	14 (6%)	1 (14%)	1 (2%)	3 (3%)	4 (5%)	5 (8%)
Viral infection	6 (3%)	0	2 (4%)	1 (<1%)	0	3 (5%)
Cardiovascular System	10 (4%)	0	3 (6%)	4 (4%)	3 (4%)	1 (2%)
Digestive System	37 (16%)	1 (14%)	10 (21%)	12 (11%)	4 (5%)	10 (17%)
Diarrhea	12 (5%)	1 (14%)	3 (6%)	3 (3%)	2 (3%)	3 (5%)
Nausea	15 (6%)	0	2 (4%)	4 (4%)	2 (3%)	7 (12%)
Vomiting	10 (4%)	0	3 (6%)	3 (3%)	1 (1%)	3 (5%)
Hemic-Lymphatic System	8 (3%)	0	0	7 (7%)	1 (1%)	0
Metabolic and Nutritional System	20 (8%)	2 (29%)	1 (2%)	5 (5%)	6 (8%)	6 (10%)
Creatinine increased ^c	2 (<1%)	1 (14%)	0	1 (<1%)	0	0
Hypercholesteremia ^c	3 (1%)	1 (14%)	0	2 (2%)	0	0

Body System COSTART Preferred Term	Total ^a	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	236 (100%)^b	7 (100%)	48 (100%)	106 (100%)	73 (100%)	59 (100%)
Musculoskeletal System	20 (8%)	0	4 (8%)	5 (5%)	5 (7%)	6 (10%)
Nervous System	52 (22%)	1 (14%)	11 (23%)	15 (14%)	10 (14%)	16 (27%)
Depression ^c	2 (<1%)	1 (14%)	0	0	1 (1%)	0
Insomnia	8 (3%)	0	2 (4%)	2 (2%)	1 (1%)	3 (5%)
Sleep disorder ^d	9 (4%)	0	2 (4%)	1 (<1%)	2 (3%)	4 (7%)
Respiratory System	37 (16%)	1 (14%)	8 (17%)	13 (12%)	10 (14%)	5 (8%)
Rhinitis	8 (3%)	0	2 (4%)	1 (<1%)	2 (3%)	3 (5%)
Sinusitis	13 (6%)	1 (14%)	3 (6%)	6 (6%)	2 (3%)	1 (2%)
Skin	14 (6%)	0	1 (2%)	6 (6%)	2 (3%)	6 (10%)
Special Senses	6 (3%)	0	1 (2%)	1 (<1%)	1 (1%)	3 (5%)
Urogenital System	29 (12%)	3 (43%)	4 (8%)	11 (10%)	4 (5%)	7 (12%)
Albuminuria ^c	3 (1%)	1 (14%)	0	1 (1%)	0	1 (2%)
Pyelonephritis ^c	2 (<1%)	1 (14%)	0	0	0	1 (2%)
Urine abnormality ^c	3 (1%)	1 (14%)	0	1 (<1%)	1 (1%)	0

Some patients were exposed to more than 1 dosage in the trial, so the sum of patients exposed to specific dosages (N= 293) exceeds the total number of patients in the trial (N= 236).

The spectrum of adverse events seen is not greatly different from those in the Integrated Summary of Safety in the original NDA. The most common adverse events overall in descending order of frequency were infection, headache, nausea, pain, sinusitis, accidental injury, diarrhea and flu syndrome.

The percentages of adverse events that were classified as mild, moderate or severe, were 36%, 48% and 16%, respectively.

13.9 Deaths

A single patient died during the study. The cause of death was suicide. A narrative for this patient is below:

Patient # 0531 was a 47 year old woman who had earlier participated in the OMC-SXB-6 trial and had been taking Xyrem® 6 g/day since 6/3/99. Her past medical history that the investigator was aware of at screening was remarkable for a bipolar disorder, a previous head injury with coma and a morphine allergy. Concomitant medications included thyroxine, zolpidem, an albuterol inhaler, loratadine, risperidone and temazepam. Subsequently the investigator realized that she had previously made a suicide attempt

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

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

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

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

13.10 Serious Adverse Events

16 patients, including the patient who died, are stated to have had serious adverse events. All are summarized in the tables below

Patient No.	Xyrem Dosage at Onset (g/d)	COSTART Preferred Term	Relationship to Trial Drug	Led to Discontinuation
0214	9.0	Liver function tests abnormal	Unknown	Yes
0232	9.0	Paranoid reaction	Probably related	Yes
05020	9.0	Knee replacement with postoperative paralytic ileus ^a	Not related	No
0508	6.0	Chest tightness/diaphoresis ^b	Not related	No
05257	12.0	Gastroenteritis/dehydration	Not related	No
	12.0	Urinary tract infection	Not related	No
0531	6.0	Death (Suicide)	Not related	Yes
0545	7.5	Chest pain	Not related	No
0931	4.5	Manic depressive reaction (bipolar affective disorder)	Not related	Yes
1131	9.0	Intentional overdose	Definitely related	Yes
14043	7.5	Suicide attempt ^c	Possibly related	Yes
1433	4.5	Breast carcinoma (suspected)	Not related	No
1509	6.0	Gastroenteritis	Not related	No
	6.0	Back pain	Not related	Yes
1630	7.5	Chest pain	Unknown	No
2030	9.0	Psychosis	Possibly related	Yes

Patient No.	Xyrem Dosage at Onset (g/d)	COSTART Preferred Term	Relationship to Trial Drug	Led to Discontinuation
23230 ^d	4.5	Cardiospasm	Not related	No
	4.5	Chills and fever	Not related	No
2536	9.0	Fractured ankle ^e	Possibly related	Yes

Further descriptions have been provided for the following patients, based on a review of all patient narratives. Events in the other patient were felt by me not to be related to the study drug.

13.10.1 Patient # 0214

This patient has already been described in Section 8.3.1.6. His liver function abnormalities were attributed to Hepatitis C infection.

13.10.2 Patient # 0232

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

13.10.3 Patient # 0931

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

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

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

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

13.10.4 Patient # 1131

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

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

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

13.10.5 Patient # 14043

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

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

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

13.10.6 Patient # 2030

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

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

13.11 Adverse Event Discontinuations

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

Patient No. ^a	Xyrem Dosage at Onset (g/d)	COSTART Preferred Term	Relationship to Trial Drug	SAE (Y/N)
0214	9.0	Liver function tests abnormal ^b	Unknown	Y
0232	9.0	Paranoid reaction	Probably related	Y
0531	6.0	Death (Suicide)	Not related	Y
0931	4.5	Manic depressive reaction (bipolar affective disorder)	Not related	Y
1131	9.0	Intentional overdose	Definitely related	Y
1305	9.0	Movement disorder ^c	Unknown	N
14043	7.5	Suicide attempt ^d	Possibly related	Y
1509	6.0	Back pain	Not related	Y
2030	9.0	Psychosis	Possibly related	Y
2536	9.0	Fractured Ankle ^e	Possibly related	Y

13.11.1 Patient 1305

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

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

“movement disorder” was considered to be the same as the periodic leg movements). She discontinued the study medication but her subsequent course is unclear.

13.12 Reviewer’s Comments

- The spectrum of adverse events seen in this Safety Update is broadly similar to that in the Integrated Summary of Safety
- A causal relationship between GHB use and depression/suicide cannot be established from the deaths, serious adverse events and adverse event dropout reports reviewed above; the patients listed had a preceding history of depression or a psychiatric disorder.

14. Risk Management Program

14.1 Structure

In response to a concern that medically prescribed Xyrem® may be diverted for illegal use, or may be consumed accidentally (e.g., by small children), the sponsor has proposed a risk management program. The components of this program are as follows:

14.1.1 Closed-Loop Distribution System

14.1.1.1 Manufacture

The bulk drug will be manufactured at a single site:(b)(4)-----
(b)

The drug product will be manufactured by(b)(4)-----
(b)(4)----- A secondary manufacturer will be (b)(4)-----
(b)(4)----- Both these companies as -----
(b)(4)----- will perform drug substance release
-----ported to be FDA- and DEA-compliant,
“fill-finish” facilities

Following manufacture the drug product will be stored at a facility compliant with Schedule III regulations, where a consignment inventory will be maintained. The inventory will be owned by Orphan Medical, Inc., and the facility will be managed by(b)(4)----- (see below) which will maintain the consignment inventory.

14.1.1.2 Distribution

The primary and exclusive distributor of Xyrem® to patients will be(b)(4)-----
(b)(4)----- A back-up distributor, currently used for the sponsor’s treatment IND # 57271, is(b)(4)----- Xyrem® will NOT be placed in retail pharmacy outlets.

The functions of(b)(4)-----will be to

- Distribute Xyr-----
- Maintain inventory and distribution records
- Maintain a patient registry

(b)(4)-----will purchase its inventory at wholesale pricing from (b)(4)-----
(b)(4)-----that inventory will be maintained at a pre-set level.
Pharmacy purchases from the manufacturer will be “recognized” by Orphan
Medical.

(b)(4)-----will operate in the following manner

- -----hysician to(b)(4)-----
- Upon receipt of a prescription this company will contact the prescribing physician and
 - Identify his/her name, license and DEA registration
 - Verify the prescription
 - (Obtain patient insurance information
- N(b)(4)-----will then verify that the physician is eligible to prescribe Xyrem® ----- the National Practitioner Databank which contains current information about the authority of individual physicians to prescribe controlled substances. This stage of verification will include confirming that the physician has an active DEA number and will check on whether any actions are pending against the physician
- If the physician is a first-time prescriber of Xyrem® that pharmacy will then ship comprehensive printed and video materials to that physician: these materials (see Xyrem® Physician Success Program below) also contain information regarding the proper handling of the drug with an outline of precautions to be taken against diversion
- N(b)(4)-----will then contact the patient’s insurance company to obtain -----is will include obtaining a certificate of medical necessity from the physician and assignment of benefits from the insurance company. Subsequent reimbursement for prescription costs will be taken care of by a (b)(4)-----reimbursement specialist
- N-----will notify the patient of his/her approval status
- Once approval has been established, (b)(4)-----will verify the patient’s home address and availability for ship-----ange shipment through (b)(4)-----or a similar carrier. The shipment will be accompanied by 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
- Receipt of the drug by the patient will be ensured through the following
 - The courier service’s own tracking system for shipments
 - 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
- If the patient is unavailable to accept a shipment of Xyrem® and execute the required receipt, the package will be returned to the pharmacy.
- If a shipment is lost, an investigation will be launched to find it.
- All patient assignment of benefit forms and registry information will need to be signed and sent back to the pharmacy before the next scheduled refill can occur

- Every patient and prescribing physician will be registered with (b)(4)-----n a secure database. The database will contain the physician's name, address, telephone and facsimile numbers, DEA and state license numbers and prescribing frequency. The database will be made available for review by the DEA as well as other federal and state agencies upon request. From this database it will be possible to obtain the following information
 - Prescriptions by physician specialty
 - Prescriptions by patient name
 - Prescriptions by volume (frequency)
 - Prescriptions by dose
- If required by the patient's insurance company the product may be shipped by (b)(4)-----to another pharmacy for patient pick-up. The sponsor anticipates -----be an unusual occurrence, and has a mechanism for verifying the second pharmacy's ability to protect against diversion of GHB before shipping the drug there.
- Prescription refills will be permitted in the number specified in the original prescription. In addition
 - If a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned by the pharmacist
 - A lost, stolen, destroyed, or spilled prescription/supply will be documented and the prescription replaced to the extent necessary to honor the original prescription (e.g., a destroyed or spilled bottle will reduce the prescription refill amount). The pharmacist has the discretion to grant or not grant refill requests under those circumstances and at a minimum will contact the prescribing physician to determine if the physician has any special concerns in regard to that refill request. New supplies of Xyrem® will be sent to the patient only if the pharmacist and physician are in agreement.
 - Repeat instances of lost, stolen, destroyed, or spilled prescriptions/supplies will be flagged for monitoring and future instances thoroughly questioned
- The quantity of medication to provided with each refill will be guided by the following
 - With the first prescription it is planned to provide the patient with only one month's supply of Xyrem®.
 - Following further contact between the pharmacy and patient, and verification that the patient understands the material in the Xyrem® Patient Success Program, supplies of Xyrem® that are intended to last longer than a month may be shipped
 - The quantity of drug shipped to the patient with each refill may also be regulated based on the requirements of the patient's health insurance plan and the terms of the prescription itself
 - It is anticipated that the majority of patients will receive only one month's shipment at a time and never more than 3 months' supply per shipment.

14.1.2 Drug Product Kit

The drug product kit will consist of

- The drug product, a clear solution, in a 240 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 patient information sheet*

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

*The patient information sheet includes the following information

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

14.1.3 Xyrem® Physician Success Program

This program consists of a videotape and printed material.

14.1.3.1 Distribution

This program will be distributed as follows

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

14.1.3.2 Videotape

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

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

14.1.3.3 Printed Materials

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

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

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

14.1.4 Xyrem® Patient Success Program

14.1.4.1 Videotape

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

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

14.1.4.2 Printed Materials

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

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

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

14.2 OPDRA Comments

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

The final recommendations of that Office were as follows:

- The verification process conducted by (b)(4)-----on receiving a formal prescription should include confirmatio-----nt's diagnosis
- Confirmation that physicians have read and grasped the educational material provided by the sponsor could be obtained by requiring each physician to complete a questionnaire prior to dispensing of the drug to the patient

- The proposed consent form should be mandatory rather than optional so as to ensure that each patient fully understands the educational material provided
- The patient registry information and benefit forms should be received by Nova Factor prior to the initial dispensing of the drug.
- Since preparation of each dose is complex, and to avoid overdosage, dispensing in the form of unit dose packages should be considered
- In addition to the standard post-marketing adverse event reporting, post-marketing safety assessments should also focus on drug abuse and dependence, diversion and accidental overdosage (e.g., by small children)

14.3 Comments Of Controlled Substances Staff

Final comments from this Agency group are still pending but the risk management program has been extensively discussed with them at internal meetings and meetings with the sponsor. At these meetings the views of this group have been conveyed to us in several presentations.

14.4 Additional Risk Management Recommendations

At an internal meeting chaired by Dr R. Temple, Office Director, that was held on 4/26/01 it was decided to ask the sponsor to consider including the following additional elements in the risk management program.

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

15. Labeling Review

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

16. Overall Comments

16.1 Clinical Safety

- When GHB is used to treat narcolepsy in doses of 3-9 g/day the most common, and seemingly drug and dose-related adverse events have included the following: headache, unspecified pain, nausea and dizziness. Urinary incontinence is slightly less common, but apparently dose and drug-related as well. More serious, but much less common, adverse events seen at the same dose range, and that could be attributed to Xyrem®, have included vomiting,

confusion, restlessness, agitation, paranoia, hallucinations, somnolence and generalized weakness. No deaths that could be attributed to study drug have been reported at therapeutic doses of GHB

- One healthy 39 year old woman participating in a pharmacokinetic trial developed dizziness, nausea, vomiting, respiratory depression and fecal incontinence, after a single (and initial) oral dose of 4.5 g of GHB, administered after an overnight fast.
- A single older narcoleptic patient who had been taking GHB for approximately 1 ½ years was hospitalized after an overdose of GHB 18 g. At the time of hospitalization, he was comatose and unresponsive. He needed intubation and artificial ventilation, and awoke 6 hours later. This incident suggests that the safety margin between therapeutic and toxic doses, even in narcoleptic patients maintained chronically on GHB, may not be very wide
- At therapeutic doses of GHB all adverse events appear to be reversible
- While currently there is no strong evidence that GHB in therapeutic doses is epileptogenic or that episodes of urinary and fecal incontinence due to GHB are due to seizures, there is insufficient data at present to rule out either possibility.
- “Recreational” use of GHB generally at doses presumed or known to be higher than the therapeutic has been associated with adverse events that included fatalities attributable to the depressant effects of this drug on the nervous system. However concurrent use of alcohol and of other drugs with effects on the central nervous system has been reported in many of these instances
- There is no evidence that GHB is toxic to any major organ other than the nervous system.

16.2 Clinical Efficacy

This may be summarized as follows (please see the NDA Efficacy Review for full details)

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

16.3 Withdrawal Phenomena And Abuse Potential

- There is no evidence from a small formal study with a randomized withdrawal paradigm (OMC-SXB-21) that the abrupt discontinuation of therapeutic doses of GHB used for 6 months to 3 ½ years leads to more than mild and

infrequent withdrawal symptoms, except for a significantly increased frequency of cataplexy.

- There are however a number of anecdotal reports of an actual withdrawal syndrome and, possibly, addiction in illicit “recreational” users of GHB, GBL or 1-4 BD. In all these individuals high doses of GHB or related drugs were believed to have been used at frequent intervals around-the-clock.

16.4 Risk Management Program

The proposed risk management program may be adequate once the additional measures to be proposed by the Agency are incorporated (see Section 14.4)

16.5 Additional Comments

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

17. Study Site Inspections

At the request of this Division the Division of Scientific Investigations carried out an inspection of the Scharf long-term safety study. This inspection was requested after the Agency was informed that the Institutional Review Board for Dr Martin Scharf’s sponsor-investigator IND # 21654 had withdrawn approval for that IND; the approval was stated to have been withdrawn based on protocol violations in a study conducted under that IND in patients with fibromyalgia.

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

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

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

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

A further inspection of the study site is planned, which is to intended to be mainly focussed on data submitted with the Major Amendment of 3/23/01

18. Financial Disclosure Certification

Financial disclosure certification has been submitted with this application.

18.1 Components Of Certification

This certification has 2 components

18.1.1 Certification Pertinent To Dr Lawrence Scrima

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

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

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

18.1.2 Certification Pertinent To Other Investigators

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

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

- Certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)

18.2 Reviewer's Comment

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

19. Major Amendment

On March 23, 2001, the sponsor submitted a major amendment to this NDA

The purpose of the amendment was to address the following

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

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

This major amendment is reviewed in a separate document. Please refer to that review for full details

20. Additional Comments Based On Review Of Major Amendment

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

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

01-004/(b)
01-027/(6)
01-054/-----
01-065/-----
01-228/----
01-240/-----
01-262/-----
01-269/-----

01-283(b)(
01-2686)---
01-256-----

- None of the “adverse events” in the “unevaluable” category that occurred in the Scharf study appear to be attributable to GHB
- Urinary and fecal incontinence both appear to be unusually common adverse events in patients taking GHB and the key issues are whether such episodes are accompaniments of unrecognized convulsions, and whether GHB is capable of causing convulsions at therapeutic doses. Currently the evidence that the vast majority of episodes of incontinence in the entire NDA are related to unrecognized convulsions is weak. There does appear to be at least 1 patient in the Scharf study in whom incontinence clearly accompanied a true convulsion.
- While there are clearly a few patients (n = 2) in the entire NDA safety database who experienced, or may have experienced, convulsions while taking GHB, the presence of confounding factors (e.g., possible benzodiazepine withdrawal) makes it difficult to link the convulsions causally to GHB. Whether GHB is capable of causing other types of seizures, e.g., absence or partial complex, is even less clear
- In this NDA, and especially in the Scharf Study, the term “sleepwalking” has been used as a verbatim (investigator) term for a common adverse event. Detailed clinical descriptions of such episodes are not available for the majority of patients and their mechanism has not been delineated. A separate analysis of these episodes has not been performed by the sponsor and it is not clear how common they are in the Integrated Clinical Trials grouping, but such episodes have been associated with serious consequences (e.g., overdose, pyrogenesis, consuming toxic chemicals) in patients enrolled in the Scharf study
- The information available in this NDA does suggest that GHB is capable, at therapeutic doses, of causing a confusional state (which may be accompanied by psychotic symptoms). The incidence and seriousness of such adverse events may be slightly more pronounced at higher doses, and especially if higher doses are administered without titration. However a confusional state also appears to be capable of occurring at lower and even sub-therapeutic doses of GHB, and after maintenance treatment for several months. The presence of true confusion in patients taking GHB could lead to their taking GHB in a manner other than as prescribed. The symptoms that have been subsumed under the COSTART term “confusion” are not unusual for a sedative-hypnotic drug.
- In the majority of patients who developed “neuropsychiatric” adverse events (e.g., paranoia, hallucinations, anxiety, stupor, etc) while taking GHB in Integrated Clinical Trials it is not possible to attribute causality for the adverse event to GHB. Pre-existing psychiatric illness, and concomitant medications such as stimulants, as well as other factors, could be contributory. Even in patients in whom there was no recorded premorbid history of psychiatric illness the extent to which they were screened for such illness is not clear.

However the occurrence of neuropsychiatric adverse events in patients taking GHB, even if not directly caused by the drug, could place them at risk of intentional or accidental overdose, as is suggested by the narratives in this review

- There is no firm evidence that any patients participating in the Integrated Clinical Trials had drug-induced lupus. However antinuclear antibody and antihistone antibody testing was not performed for patients participating in this study
- There is no evidence suggesting a causal link to GHB for the small number of hypoglycemic an hyperglycemic blood test readings in the NDA; several of the apparently hypoglycemic readings could in fact have represented laboratory errors. Neither is there firm evidence in AERS or in the medical literature that GHB is capable of causing hypoglycemia.
- GHB is unlikely to have been the cause of transaminase elevations seen in a few patients in the Integrated Clinical Trials.
- The total number of patients exposed to GHB in the NDA Safety Database minus the Scharf study appears sufficient to meet ICH guidelines at the 6-month and 1-year levels but not in regard to the total number of patients exposed; however allowance can be given for GHB being designated as an orphan drug and the total number exposed may therefore be acceptable.

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

Further if one concludes (from the efficacy studies) that the 9 g/day dose is the only effective dose and is that to be recommended for general use the number of those exposed to Xyrem® for ≥ 12 months does not meet ICH guidelines

Note that ICH guideline E1A (July 1997) states the following: "100 patients exposed for a minimum of 1 year is considered to be acceptable to include as part of the safety database. The data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use."

21. Conclusions

Deferred

22. Recommendations

Deferred

Ranjit B. Mani, M.D.
Medical Reviewer

J. Feeney, M.D. _____

rbm 5/3/01
cc:
HFD-120
NDA 21196
Homonnay