

## Review and Evaluation of Clinical Data

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<b>NDA (Serial Number)</b>	<b>21196</b>
<b>Sponsor:</b>	<b>Orphan Medical, Inc.</b>
<b>Drug:</b>	<b>Xyrem</b>
<b>Proposed Indication:</b>	<b>Narcolepsy</b>
<b>Material Submitted:</b>	<b>Major Amendment</b>
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<b>Reviewer:</b>	<b>Ranjit B. Mani, M.D.</b>

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## 1. Background

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

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

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

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

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

The primary purpose of this amendment is to address concerns raised by this Division about the validity of data in the original NDA that were derived from the long-term, open-label, individual investigator Scharf Study. These concerns were raised by an Agency inspection of the study site, conducted in February 2001. Further details of these concerns are in Section 3 below.

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

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

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

Note that this is a preliminary, and not final, review which may be subjected to further editing.

## **2. Organization Of Clinical Trials In Integrated Summary Of Safety**

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

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

### 2.1.1.1 Integrated Clinical Trials

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

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

\*GHB and placebo were each used for 4 weeks

Further details about the above extension studies are below

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

### 2.1.1.2 Lammers Trial

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

### 2.1.1.3 Long-Term Clinical Trial (Scharf)

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

### 2.1.1.4 Integrated Pharmacokinetic Trials

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

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

## 3. Deficiencies In Scharf Study Data Revealed At Site Inspection

### 3.1 Outline Of Scharf Study

This is a long-term open-label study of sodium oxybate (GHB) for patients in narcolepsy conducted under individual investigator IND # 21654 (Martin Scharf, Ph.D., Cincinnati, Ohio).

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

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

### **3.2 Preliminary Results Of Inspection**

At the request of this Division the Division of Scientific Investigations carried out an inspection of the Scharf study. This inspection was requested after the Agency was informed that the Institutional Review Board for Dr Martin Scharf's sponsor-investigator IND # 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 reportedly disorganized state in which the study records were maintained

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

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

In an effort to ensure that major adverse events in this study were captured the Division made a number of recommendations to the sponsor during meetings and teleconferences held in February-March 2001. The recommendations were in part based on review of safety data for this study that were contained in the original NDA

The recommendations were as follows:

- Obtaining as much information as possible about the status of the 80 patients in the Scharf study who did not enter the Orphan-sponsored OMC-SXB-7 (treatment IND) study; if their current status was not known their health at the time of discontinuation

- from the Scharf study (which the majority of the 80 patients did leave) and for 1-2 months afterward needed to be ascertained.
- Obtaining as much information as possible about all patients listed as having convulsions during the study.
  - Obtaining as much information as possible about all patients whose adverse events were listed as “unevaluable”
  - Obtaining as much information as possible about patients with the following adverse events: confusion and other neuropsychiatric symptoms, and urinary and fecal incontinence
  - Tracing drug dispensing records

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

#### 4. Agency Questions About Orphan-Sponsored Clinical Trials

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

##### 4.1 Exposure Table

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

**Table 9.8.14 Cumulative Duration of Exposure, by Last Dosage — Integrated Clinical Trials**

Duration of Exposure*	Total	Sodium Oxybate Last Dosage (g/d)				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	399	94	266	290	116	118
≥ 6 mo (168 d)	233 (58.4%)	5 (5.3%)	43 (16.2%)	58 (30.3%)	37 (31.9%)	60 (50.8%)
≥ 1 y (336 d)	75 (18.8%)	3 (3.2%)	8 (3.0%)	25 (18.6%)	13 (11.2%)	26 (22.0%)
≥ 2 y (672 d)	37 (9.3%)	1 (1.1%)	3 (1.1%)	12 (4.1%)	7 (6.0%)	14 (11.9%)

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

Data Source: Section 16.1, Data Listing 4.

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

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

##### 4.2 Serious Adverse Events

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

Was this patient hospitalized?

**4.3 Laboratory Data**

**4.3.1 Table Of Interest**

The following table is in the Integrated Summary of Safety.

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

Laboratory Parameter (clinically significant range)		Last Sodium Oxybate Dosage (g/d)	Baseline	Post-Baseline	
Patient Number	Trial <sup>a</sup>			Study Day <sup>b</sup>	Result
<b>Hematology (N = 1)</b>					
Hemoglobin (> 3 g/dL decrease and absolute values < 12.0 g/dL)					
0814	OMC-GHB-3	4.5	16.6	391	11.5
<b>Clinical Chemistry (N = 26)</b>					
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	162
0507	OMC-GHB-3	7.5	39	416	109
	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	09

(continued)

**Table 8.3.21 Potentially Clinically Significant Changes in Laboratory Values from Baseline to Post-Baseline by Last Sodium Oxybate Oral Solution Dosage — Integrated Clinical Trials**

Laboratory Parameter (clinically significant range)		Last Sodium Oxybate Dosage (g/d)	Baseline	Post-Baseline	
Patient Number	Trial <sup>1</sup>			Study Day <sup>2</sup>	Result
<b>Clinical Chemistry (N = 25) (continued)</b>					
<b>Glucose (continued)</b>					
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
		4.5	101	716	66
	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
		6.0	42	331	15
0844	OMC-SXB-6	3.0	92	53	58
1565	OMC-GHB-3	6.0	168	278	286
		6.0	168	650	403
	OMC-SXB-7	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
<b>Total bilirubin (≥ 100% increase and absolute values &gt; 1.5 mg/dL)</b>					
0208	OMC-GHB-3	9.0	1.1	213	2.5
0504	OMC-GHB-3	4.5	0.4	136	1.6
1509	OMC-GHB-2	6.0	0.9	15	2.1

<sup>1</sup> Trial during which post-baseline value was obtained.

<sup>2</sup> Day relative to start of treatment (trial duration).

Data Source: Appendix Section 16.1, Patient Data Listings 4, 12, and 13.

#### 4.3.2 Questions About Table

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

#### 4.4 Additional Questions

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

#### **4.5 Additional Request**

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

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

#### **5. Contents Of Submission**

The main sections of this submission cover the following areas

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

The submission also includes the following SAS datasets

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

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

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

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

##### **6.1 Background**

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

Study OMC-SXB-7 began early in 1999.

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

The Division was especially, but not solely, interested in

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

## **6.2 Sponsor's Methods**

The sponsor reports undertaking the following

- A review of source documents, Case Report Forms and data listings for all 80 patients who did not enter the OMC-SXB-7 study under treatment IND # 57271
- Where necessary present day follow-up was sought in some patients to obtain further information such as the reason for withdrawal, the patient's medical history prior to enrollment, and whether adverse events continued after drug withdrawal. Such follow-up information was requested for 19 patients and collected by site personnel for 10 patients.

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

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

Included in this submission are

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

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

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

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

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

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

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

#### 6.4 Discontinuations Due To Adverse Events

The 23 patients listed in the table in Section 6.3 as having discontinued to adverse events consisted of

- 10 deaths
- 13 non-fatal adverse events

Tabular summaries of these patients are below

Also see Section 6.5.4 for further details about deaths and adverse event discontinuations.

##### 6.4.1 Deaths

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

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

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

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

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

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

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

Patient No.	Pt Initials	Sex	Age at Trial Entry (yrs)	Date Started GHB Treatment	Date of Last Dose	Reason for Discontinuation	Comments
01-019		M	41	7/12/1987	7/30/1989	Adverse Event	Attempted suicide by GHB overdose
01-064		F	13	6/16/1987	5/00/89	Adverse Event	Increased Seizure Activity
01-066		F	44	3/25/1985	4/20/1991	Adverse Event	High ANA Titer/Possible Drug-Induced Lupus
01-238		M	45	11/30/1983	10/20/1985	Adverse Event	Decrease in short-term memory (COSTART term "amnesia")
01-244		F	55	6/21/1988	5/3/1989	Adverse Event	High ANA Titer/Possible Drug-Induced Lupus
01-247		F	33	7/25/1989	4/30/1990	Adverse Event	Seizure
01-254		F	61	5/2/1988	6/26/1989	Adverse Event	Possible pulmonary toxicity
01-259		F	41	6/3/1987	7/15/1987	Adverse Event	Depersonalization, emotional lability, hypertonia, and pain chest
01-270		F	24	1/16/1994	4/22/1999	Adverse Event	Patient became Pregnant
01-271		M	46	10/24/1994	4/30/1995	Adverse Event	Swelling of ankles and feet
01-273		F	59	11/6/1994	9/30/1995	Adverse Event	Weight loss
01-005		F	49	11/16/1987	7/12/1992	Adverse Event	Increased difficulty sleeping
01-006		M	14	7/24/1985	12/31/1992	Adverse Event	Stimulant-induced rage

Note that in the original NDA 12 patients were listed as having discontinued treatment on account of non-fatal adverse events. Patient #01-243 was listed in the original NDA as having discontinued treatment on account of weight loss; he is not listed in the above table but is listed in the table in Section 6.4.1 since he died 4 months after study drug discontinuation reportedly from a myocardial infarction. Patients 01-006 and 01-270 were not in the original table.

### 6.5 Review Of Individual Narratives And Case Report Forms

I have reviewed the narratives and individual Case Report Forms for all 80 Scharf study patients who did not enter the treatment IND. I have also reviewed the Case Report Forms for the 63 patients in the Scharf study who subsequently entered the treatment IND.

The information contained in the narratives and Case Report Forms is discussed under the following headings.

#### 6.5.1 Source Of Case Report Forms

The Case Report Forms for the Scharf study were created by Premier Research, a contract organization hired by the sponsor (circa 1998) for that purpose as well as for data management, statistical analysis and report writing. The Case Report Forms were created from the available source documents generated over the preceding 15 years over which the study had been conducted.

#### 6.5.2 Structure Of Case Report Forms

The Case Report Forms were composed of the following separate entry items

- Demographics
- Date of diagnosis of narcolepsy
- Date of pre-treatment polysomnogram
- Mean latency on Multiple Sleep Latency Test

- Date of commencement of GHB
- Daily dose of GHB at commencement
- Previous narcolepsy medications
- Concomitant medications at study entry
- Medical history
- Physical examination
- Dosing record
- Results of hematology, clinical chemistry, urinalysis and electrocardiogram testing done during study
- Adverse events
- Medications used to treat serious adverse events
- Disposition data: assessment date, whether patient was still enrolled in study, if discontinued→ date of last dose, and reason for discontinuation

### *6.5.3 Deficiencies In Structure Of Case Report Forms And Additional Related Concerns*

After reviewing all Case Report Forms for the Scharf study the following items were identified that rendered the review of the data contained in the forms problematical

- The sheets on which entries are made and even entries on individual sheets (i.e., listings of adverse events) are not arranged in chronological order making review difficult. Neither are the sheets grouped by category.
- A clear distinction is not always made between the screening history and physical examination, e.g., symptoms are sometimes entered instead of abnormalities of physical examination
- There are no entries for any follow-up visits to either the study center in Cincinnati or to any physicians located where patients were living.
- There are no entries in the Case Report Forms that would indicate that the study site regularly contacted participating patients over the telephone to ascertain their status (i.e., status of narcolepsy, adverse events, and concomitant medications). Such determinations appear to have been based largely, if not almost entirely, on patient diaries
- Dosing records appear to have been reconstructed based on patient diaries and not on the study center's records of what patients were instructed to take
- Adverse event entries appear to be based at least partly on patient diaries. It is therefore unclear to what extent adverse events that might have been captured by more active regular surveillance by the study center may have been captured
- For patients who were irregular or lacking in accuracy in making diary entries or returning their diaries, records of dosing and adverse events could be unreliable
- It is unclear how the last date of dosing was determined for patients who discontinued from the study; it appears to have been based on diary entries in a substantial number. In other instances where the last date of dosing was unknown, patients may have taken study drug for several months after the last diary-based entries were made in the Case Report Form.
- The Case Report Forms do not actually document the clinical status of patients at the time of study drug discontinuation. Indirect inferences

- regarding their clinical status can be made from the last dosing change, adverse event, electrocardiogram and laboratory data in the Case Report Forms if these were sufficiently close temporally to when GHB was stopped. Such data can provide some reassurance that these patients were not gravely ill at the time of discontinuation; if they were in fact very seriously it is unlikely for them to have been able to complete their diaries. Admittedly in a number of patients who discontinued from the Scharf study, post-treatment confirmation of health status is available from attempts at follow-up
- For patients who did not enter the treatment IND but did continue in the Scharf study, no follow-up information (i.e., adverse events, laboratory and electrocardiogram data) is available after 1998-early 1999 which is when the Case Report Forms were created. The sponsor states that since these patients continued in the Scharf study no active recent attempts at follow-up were needed.
  - **Many source documents (mainly in the “progress notes” category) supplied with the Case Report Forms are undated and unsigned.**
  - The sponsor’s narratives have in some instances, not included serious adverse events listed in the supplied Case Report Forms. The sponsor appears to have chosen only events that were considered by the investigator to be GHB-related for further description.  
For example, Patient # 01-012 (initials      ), had an episode of “disorientation, stupor, and weakness” that necessitated hospitalization. This incident is not described in the sponsor’s narrative

#### 6.5.4 Deaths And Adverse Event Discontinuations

##### 6.5.4.1 Deaths

None of the deaths listed above were causally attributable to GHB

##### 6.5.4.2 Adverse Event Discontinuations

Narratives have been prepared by me for all individual adverse event discontinuations except Patient 01-271 (Initials      ) and are contained elsewhere in this review, in the main Safety Review or both.

In the case of Patient 01-271, a source document indicates that the patient’s swelling resolved within a month of discontinuing GHB.

#### 6.5.5 Patients Discontinued From Scharf Study For Non-Compliance

##### 6.5.5.1 Background

I have discussed these patients separately since the material that the investigator received from them (e.g., diary entries, laboratory and electrocardiogram data) is especially likely to have been deficient.

As indicated earlier, for the majority of patients in this category material supplied with the Amendment did not contain information obtained actively by the investigator about their health status at the time of discontinuation. As I do not have direct access to the content of their diaries (except in the few instances where excerpts have been provided) and can make only indirect inferences from

Patient # initials	Date Of Completion of Disposition Sheet* In Case Report Form	Recorded Date Of Last GHB Dose**	Date Of Start Of Last Adverse Event Recorded In Case Report Form	Date Of Last Laboratory Test	Date Of Last Electrocardiogram	Date Of Last Change In GHB Dose	Follow-Up After Discontinuation
01-216	1/28/98	2/22/87	2/9/87	2/9/87	2/5/85	2/16/87	(contacted in March 2001) No attempt
01-217	2/18/98	7/19/86	7/15/86	9/4/85	5/6/85	7/9/86	No attempt
01-222	2/24/98	4/21/88	2/3/88	5/27/88	No record	4/18/88	No attempt but see footnote *****
01-223	2/25/98	1/24/87	12/11/86	5/29/87	6/24/86	10/5/86	Study site received letter from patient dated 3/31/87  No subsequent attempt at follow-up
01-240	2/3/98	Unknown but patient was formally withdrawn from study on 7/5/88 in a phone conversation	No adverse events recorded	1/4/88	No record	No record	No attempts at follow-up
01-246	2/11/98	4/22/87	7/14/86	1/12/87	1/12/87	7/16/86	Not attempted
01-248	2/17/98	10/13/86	10/22/86	No record of laboratory tests	6/18/86	10/10/86	Not attempted
01-251	2/27/98	11/21/86	1/31/85	7/29/87	4/11/86	11/21/86	Not attempted
01-256	2/27/98	6/30/88	Not recorded *****	3/29/88	3/29/88	3/13/88	Not attempted
01-258	2/26/98	Unknown	3/27/91	10/7/90	10/7/90	3/21/91	Study coordinator spoke with patient on 11/27/91: he was still taking GHB at that time  Study coordinator spoke with patient on 1/3/92 to request logs. Unclear whether he was still taking medication at that time.  Additional follow-up not attempted
01-263	2/26/98	5/31/91	3/4/91	4/22/91	12/29/89	3/6/91	Letter from patient dated on 12/19/91 stating that GHB was of benefit but that he discontinued that medication because of its bad taste
01-267	4/8/98	7/31/97	1/16/97	12/30/97	11/30/96	5/30/97	Not attempted
01-268	3/4/98	Unknown	8/96	11/3/97	4/30/97	1/25/97	Not attempted
01-288	3/19/99	Unknown *****	10/23/98	7/7/98	7/298	7/2/98	Study coordinator spoke to patient on 2/11/99 to ask for study logs and to inform her that no further medications would be shipped out unless logs were received

\*The date entered in the disposition sheet is designated as an "assessment date." However, there is no evidence that the "assessment" consisted of an evaluation of the patient's status. Data entered on this sheet consisted of the following

- whether the patient was still enrolled in study
- if discontinued: date of last dose, and reason for discontinuation

\*\*The basis on which this date was determined is unclear. In addition there are inconsistencies between the source document and Case Report Form regarding the timing of the last dose

adverse event listings, dosing records, and laboratory/electrocardiogram data I have chosen to rely on whatever additional information has been provided about their status at the time of discontinuation for firm confirmation of their status at the time that treatment with GHB was terminated: such information is available in source documents (when provided), narratives and to a slight degree in the Case Report Forms themselves

**6.5.5.2 Summary Of Patients Who Were Discontinued From The Scharf Study For Non-Compliance**

24 patients were discontinued from the Scharf study on account of non-compliance: in 22 patients non-compliance involved not submitting study diaries sufficiently regularly, and in the remaining 2 patients, failure to follow dosing instructions. The details of these patients are in the next table

Patient # Initials	Date Of Completion of Disposition Sheet* In Case Report Form	Recorded Date Of Last GHB Dose**	Date Of Start Of Last Adverse Event Recorded In Case Report Form	Date Of Last Laboratory Test	Date Of Last Electrocardiogram	Date Of Last Change In GHB Dose	Follow-Up After Discontinuation
01-048	2/3/98	2/28/89	2/7/89	11/23/88	11/23/88	2/13/89	No attempt
01-063	2/28/98	5/31/97***	4/19/91	7/1/97	7/1/97	5/1/97	Unsuccessful attempt (in March 2001)  Last phone contact with patient on 8/19/97: patient had recently seen a liver specialist but outcome of assessment was uncertain
01-201	2/25/98	12/31/83	12/24/83	5/7/84	5/7/84	12/31/83	Adverse events including peripheral edema resolved after study drug was withdrawn (contacted in March 2001)  A source document (progress note) dated 1/18/91 indicated that after leaving the Scharf study the patient received GHB from another physician for "some time"
01-203	2/19/98	5/14/84	5/8/84	4/17/84	4/17/84	4/21/84	Patient clarified history of suicide attempts prior to entering Scharf study (contacted in March 2001)
01-207	1/30/98	3/31/85	3/30/85	8/20/84	8/20/84	9/14/84	No attempt
01-209	2/4/98	10/2/84	7/18/84	6/18/84	6/18/84	9/30/84	No attempt
01-210	2/6/98	5/3/85	4/23/85	10/22/84	10/30/84	3/13/85	No attempt
01-212	5/16/86	11/16/85	8/13/85	7/23/85	7/25/85	11/17/85	No attempt
01-213	2/27/98	12/23/85	12/25/85	5/28/85	5/28/85	12/24/85	No attempt
01-215	1/29/98	10/30/88	10/29/88	1/20/88	11/11/85	9/18/88	Telephone contact with patient in November 1988 indicated that patient had not received letter of discontinuation  Adverse events including dizziness and other symptoms had resolved

\*\*\*The last recorded adverse event was during her initial period of treatment with GHB (see narrative in Section 6.5.10.1). However during her second period of treatment she was reported to have abnormal liver function tests but these were not recorded as an adverse event.

\*\*\*\*A source document (letter to the patient dated 4/16/86) indicates that the last logs were received from this patient 4/16/86

\*\*\*\*\*A source document (progress note) indicated that the last study logs from this patient were received in September of 1985. Also note that for this patient the last recorded GHB dose change is one day AFTER the date of the last recorded dose of GHB

\*\*\*\*\*A source document (progress note) indicates that the last set of study logs were received from the patient on February 22, 1987

\*\*\*\*\*A source document (progress note) indicates that the last set of study logs were received from the patient on February 21, 1986

\*\*\*\*\*A letter from the patient dated 5/25/88 indicates that she submitted study logs from the period 7/2/87 to 4/21/88

\*\*\*\*\*A source document (progress note) indicates that the last set of study logs were received from the patient on July 1987

\*\*\*\*\*See narrative in Section 6.5.10.5

\*\*\*\*\*Last recorded diary entry was on 3/31/97

\*\*\*\*\*Last recorded diary entry was on 10/31/98

#### Note that

- Except where otherwise indicated based source documents and narratives (that cover both the study and follow-up periods), for none of the patients in the above table was any information provided that indicated each patient's health status, based on a telephone conversation or face-to-face assessment, at any time during the study or at study termination. **Only indirect evidence of each patient's health status is available from the adverse event records, dosing records, laboratory tests and electrocardiograms; under the circumstances the best that can be assumed about their status is that if they were able to have these tests done and submitted and to submit daily logs for dosing and adverse events, they were clearly alive and probably not gravely ill.**
- Based on the latter assumption, and also based on follow-up contacts when available, most patients in the above table are unlikely to have been dead or seriously ill at the time of study discontinuation, assuming that the date of study drug discontinuation is derived from patient diaries (the method used to obtain the last date of treatment with GHB is not clearly stated). The exceptions are Patients 01-240 and 01-268, in whom the dates of study drug discontinuation are unknown and on whom no follow-up information is available
- Patient 01-256 had an unresolved adverse event (a paranoid mental state) at the time of discontinuation, the outcome of which is unclear.
- Patient 01-063 had an unresolved abnormality of liver functions

#### 6.5.6 Discontinuations On Account Of Protocol Deviations

These included 2 patients

- Patient 01-276 (Initials ) who failed to meet inclusion criteria: this patient did not have narcolepsy, had a diagnosis of fibromyalgia and myofascial pain syndrome and received GHB for a total of only 3 months without any adverse events other than the flu syndrome. 3 weeks after stopping study medication he wrote to the investigator stating that he continued to have pain and a sleep disturbance.
- Patient 01-211 (Initials ) who was a screening failure and did not receive study drug: this patient failed to meet criteria for narcolepsy

These patients do not need to be further accounted for.

**6.5.7 Discontinuations On Account Of Medication Cost, Medication Cost, Lack Of Efficacy, And Transfer To Another Study**

I have reviewed all the narratives, Case Report Forms and source documents for the 23 patients who discontinued from the Scharf study for the reasons cited in the above heading. In the absence of a specific statement of their health status at the time of discontinuation, I believe it is possible to indirectly infer that none of these patients had an overt grave illness that was not disclosed in these documents. I believe it is possible to make such an inference for the following reasons

- They were well enough to initiate study discontinuation on their own for the reasons cited. If they had additionally discontinued treatment on account of being seriously ill (other than with narcolepsy) it is likely that they would have disclosed the same to the investigator
- The patient who transferred to another study did so because that individual had fibromyalgia and not narcolepsy; it seems unlikely that the investigator would have made the transfer if the patient had a serious treatment-emergent illness.
- Recent follow-up information is available for at least 2 of these patients

**6.5.8 Patients Continuing In Scharf Study**

**6.5.8.1 Description**

8 patients continued in the Scharf trial, i.e., they did not enter OMC-SXB-7 or discontinue from the Scharf trial itself

These patients are summarized in the following table. The data in the table are derived from the Case Report Forms

Patient #/Initials	Date Of Completion of Disposition Sheet* In Case Report Form	Date Of Start Of Last Adverse Event	Date Of Last Laboratory Test	Date Of Last Electrocardiogram	Date Of Last Change In GHB Dose
01-004	10/11/99	6/15/98	12/1/98	12/3/98	5/21/98
01-027	1/23/99	12/26/98	1/23/99	4/18/98	1/1/98
01-054	5/2/98	10/29/98	7/22/98	6/8/98	9/3/88
01-065	9/30/99	1/6/99	1/6/99	1/6/99	1/31/99
01-228	9/30/99	6/10/96	8/27/98	8/27/98	3/22/98
01-262	3/26/98	8/19/98	5/9/96	10/16/97	5/9/96
01-269	6/30/99	1/15/99	1/28/99	4/24/98	1/28/99
01-283	6/1/99	3/26/98	8/13/98	None performed	6/28/98

\*The date entered in the disposition sheet is designated as an "assessment date." However, there is no evidence that the "assessment" consisted of an evaluation of the patient's status. Data entered on this sheet consisted of the following

- whether the patient was still enrolled in study
- if discontinued: date of last dose, and reason for discontinuation

**Note that**

- For none of these patients were source documents provided that indicated each patient's health status, based on a telephone conversation or face-to-face assessment, at any time during the study. Only indirect evidence of each patient's health status is available from the adverse event records, laboratory tests and electrocardiograms.
- Neither was an attempt made by the sponsor to actively determine the current health status of these patients; the sponsor's reason not for doing so was that these patients continued to be in the Scharf study as of 5/31/99.

6.5.8.2 Comments

- There is no direct or indirect information available about the health status of these patients beyond January 1999
- The sponsor should be asked to make an active attempt to determine the current status of these patients

6.5.9 Patients Subjected To Recent Attempts At Follow-Up

6.5.9.1 Criteria For Recent Follow-Up

The narratives for all 80 patients who participated in the Scharf study, who did not enter the treatment IND, and who were not continuing in the Scharf study were reviewed to see if additional follow-up information would be helpful.

Where necessary present day follow-up was sought in some patients to obtain further information such as the reason for withdrawal, the patient's medical history prior to enrollment, and whether adverse events continued after drug withdrawal. Such follow-up information was requested for 19 patients and collected by site personnel for 10 patients.

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

6.5.9.2 Summary Of Patients For Whom Recent Follow-Up Was Attempted

According to the patient narratives in this Amendment follow-up was attempted in March 2001 on the patients listed in the following table

Patient #/Initials	Date of Discontinuation	Reason For Discontinuation	Results Of Recent Follow-Up (March 2001)
01-005/	7/12/92	Adverse event: Increasing difficulty sleeping	Unsuccessful
01-013/	3/26/88	Unable to afford drug; house burned down	Modafinil and imipramine working well
01-019/	7/30/89	Adverse event: Suicide attempt	Still depressed
01-063/	5/31/97	Non-compliance: failure to return diary logs and have laboratory tests done	Unsuccessful
01-064/	5/89 (?)	Adverse event: Increased seizure frequency (frontal lobe cyst)	Seizures continuing
01-200/	9/30/90	Death due to lung cancer	Date of death confirmed with widow
01-201/	12/31/83	Non-compliance: failure to return logs and questionnaires	Adverse events including peripheral edema resolved after study drug was withdrawn
01-203/	5/14/84	Non-compliance: Failure to return diary logs	Patient clarified history of suicide attempts prior to entering Scharf study
01-206/	8/26/84	Patient request on account of sleepwalking with a lighted cigarette	Being treated with dextroamphetamine. Cataplexy not problematical
01-215/	10/30/88	Non-compliance: failure to return logs	Adverse events including dizziness and other symptoms had resolved
01-218/	6/84	Patient request: Did not like adverse effects of GHB	Unsuccessful
01-238/	10/20/85	Adverse event: Impaired memory	Unsuccessful
01-254/	6/26/89	Adverse event: Pulmonary toxicity	Unsuccessful
01-259/	7/15/87	Adverse event: Depersonalization, emotional lability and others	Unsuccessful

Patient #/Initials	Date of Discontinuation	Reason For Discontinuation	Results Of Recent Follow-Up (March 2001)
01-273'	9/30/95	Adverse event: Weight loss	Unsuccessful

### 6.5.9.3 Comments

- Based on patient narratives, follow-up was attempted on only 15 patients, out of the 19 designated for the purpose by the sponsor
- Follow-up was successful in confirming the status of 8/15 patients on whom it was recorded as having been attempted
- Follow-up was unsuccessful in 7/15 patients on whom it was attempted
- No follow-up information is therefore available for 11/19 patients designated by the sponsor as appropriate for follow-up
- A full list of the 19 patients designated by the sponsor for follow-up is not available

### 6.5.10 Unresolved Adverse Events Of Concern

#### 6.5.10.1 Patient # 01-063 (Initials)

This 26-year-old woman with a previous history of narcolepsy and depression was treated with GHB during 2 distinct periods. During the first period lasting 3 years adverse events experienced included sleep walking, enuresis and nausea. At the end of that period she was taken off the study drug after becoming pregnant but was asked to continue to maintain her sleep logs.

6 years later, at the patient's own request, she was resumed on GHB (this was apparently done based on telephone contacts alone). A few months later the investigator discontinued her participation in the study as she had failed to return her diaries or respond to the investigator's request to have liver function tests done.

Some relevant dates are as follows

Start Of Initial Period Of GHB Treatment	5/6/88
End Of Initial Period Of GHB Treatment (GHB treatment stopped on account of pregnancy)	4/19/91
Resumption Of GHB Treatment	4/15/97
Last Dose Of GHB (Unclear how this date was determined)	5/31/97
Last written request for logs (This request stated that if logs were not received by 10/3/97 a further shipment of GHB would not be authorized)	9/29/97
Last recorded phone contact with patient*	8/19/97
Last safety laboratory tests	7/1/97
Last electrocardiogram	7/1/97
Last recorded adverse event	4/19/91 (pregnancy)
Last change in GHB dose	5/1/97

\*The patient indicated that she had not as yet had the requested laboratory tests done (the patient was requested to repeat tests done on 7/1/97 on account of liver function abnormalities). She also indicated that she had seen a liver specialist who was not concerned about her abnormalities of liver function attributing them to her being overweight

Her liver function tests on 7/1/97 were as follows

AST: 26 U/L  
 ALT: 28 U/L  
 Alkaline phosphatase: 158 U/L  
 GGT: 136 U/L

Attempts to contact the patient in March 2001 were unsuccessful.

**Reviewer's Comment: The minor liver function abnormalities are not of serious concern.**

#### 6.5.10.2 01-238 (Initials)

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.

#### 6.5.10.3 01-254 (Initials)

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.

**Reviewer's Comment: This narrative is included here in spite of its apparent resolution; the adverse event was a serious one and warranted study drug discontinuation, very few clinical details are available and recent follow-up was attempted but was unsuccessful.**

#### 6.5.10.4 01-259 (Initials)

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 despite recent efforts by the sponsor to contact the patient; it is unclear therefore if her symptoms eventually resolved.

#### 6.5.10.5 Patient # 01-256 (Initials)

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

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

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

He was withdrawn from the study 2 years after he entered it on account of non-compliance (failure to return his sleep logs)

#### 6.5.10.6 Patient # 01-273 (Initials)

This 59 year old woman with narcolepsy began GHB on 11/6/94 and remained on the drug until 9/30/95 when she discontinued treatment at her own initiative on account of weight loss. Her last dose of GHB was 2.3 g/day.

While in the study she had tumors of the neck and parotid gland removed surgically; further details of these tumors are unavailable.

Attempts to contact the patient by phone on 3/22/96, 6/6/96 and in March 2001 were unsuccessful

### 6.6 Reviewer's Comments

- The extent to which patients participating in this study were systematically monitored for adverse events, either during telephone contacts or at formal visits, remains very uncertain and is certainly not documented in the Case Report Forms or in any source documents that have been provided in this submission.
- Conclusions made above by me that a number of patients who discontinued from the Scharf study were not seriously ill close to the time of their discontinuation are based on indirect inferences. Such conclusions are therefore based on less-than-optimal data
- The following 16 patients who participated in the Scharf Study and did not continue in the treatment IND, must be considered inadequately accounted for

Continued In Scharf Study	Discontinuations For Adverse Events	Discontinuations For Non-Compliance
01-004/ 01-027/ 01-054/ 01-065/ 01-228/ 01-262/ 01-269/ 01-283/	01-238/ 01-254 01-259 01-273.	01-240/ 01-268/ 01-256/ 01-063/

- Recent attempts to follow-up 5 of the patients in the above table have already been made. Attempts at determining current health status need to be made for the following additional 11 patients

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

## 7. Narrative For Patient 01-064 Participating In Scharf Study

A more detailed description of this patient who was recorded as having seizures has been supplied by the sponsor. Both a narrative and Case Report Form have been supplied, as has a consultation letter from Paul G. Moe, MD, a neurologist in Denver, Colorado. Dr Moe's consultation letter was written on 4/26/89 very soon after the patient was instructed to discontinue GHB (see below).

### 7.1 Narrative

This patient (initials \_\_\_\_\_), was 13 years old at the time of study entry. 2 years prior to entering the study she had sustained a fall, was stated to have sustained a concussion and was found on CT scan to have a

left frontal cyst; a burr hole procedure was apparently done at the time she had her head injury. After her fall she began experiencing excessive daytime sleepiness and, later, cataplexy. The narrative states that "polysomnogram testing confirmed the diagnosis of narcolepsy."

Concomitant medications at study entry included slow-release methylphenidate (dose unspecified) and protriptyline 10 mg t.i.d. Her medical history was also remarkable for a scoliosis.

She is believed to have participated in the Scharf study for about 2 years, although the date of her last dose is uncertain. Her dose of GHB during the trial ranged from 3 g/day to 7.5 g/day with the most common dose being 6 g/day.

During the Scharf trial she had 7 "seizures" (investigator term). Descriptions of these episodes are unavailable. Treatment with carbamazepine and divalproex sodium was apparently initiated; both drugs appear to have been used at separate times. After the 7<sup>th</sup> episode she was instructed to stop both divalproex and GHB. An EEG was reported to show "slow discharges" from the "anterotemporal frontal area of the brain (i.e., the region of the brain cyst)" but the narrative does not indicate whether the discharges did in fact originate from the left frontal region.

Headaches and vomiting were among the other adverse events noted during the study. The etiology of these was unclear.

A phone conversation with the patient's mother on 3/21/01, about 12 years after the patient discontinued from the Scharf study, indicated that the patient continued to have seizures of 3 different types, always at night.

Dr Moe's letter indicates that

- Carbamazepine was unhelpful for her seizures and divalproex was used instead
- On one occasion she was found to have a bitten tongue which was presumed to have been due to a seizure
- An EEG on 4/26/99 showed left frontal spike-wave discharges

## **7.2 Reviewer's Comments**

Although a detailed description of this patient's seizures is unavailable, it appears very likely that, assuming she did have seizures, they were related to her left frontal lobe lesion and not to GHB.

## **8. "Reaction Unevaluable" Adverse Events In Scharf Trial**

### **8.1 Background**

The Division had asked the sponsor to obtain as much information as possible about all patients in the Scharf study whose adverse events were listed as "unevaluable".

The sponsor states that

- 75 adverse events were coded as "reaction unevaluable"
- Source records, Case Report Forms and data listings were reviewed
- The following were recorded: verbatim term, number of adverse events, patient record number, adverse event start date and resolution date (if present), relationship to study drug, seriousness, and actions taken.

## **8.2 Categories Of "Unevaluable" Adverse Events**

The sponsor states that the 75 adverse events fell into one of the following categories

- A treatment procedure or medication for
  - A previously described adverse event
  - A condition listed in the patient's medical historyOr a treatment that was transcribed into the Case Report Form in place of the adverse event that precipitated the need for treatment

There were 44 events in these categories

- A diagnostic procedure (n = 16)
- Elective surgery (n = 6)
- Medications taken for unknown conditions (n = 2)
- Other actions that were not adverse events (n = 7). An example of such an action is the prescription of aspirin as prophylaxis against cardiovascular disease

## **8.3 Serious "Unevaluable" Adverse Events**

15/75 of the unevaluable adverse events were considered serious: these are listed below. Each bullet applies to a single unique patient

- Coronary angiography, angioplasty and knee replacement (3 events in a single patient)
- Prolapsed uterus needing hospitalization and surgery
- Aspiration during intubation after an overdose
- Hospitalization for hemorrhoid surgery
- Hospitalization for elective hysterectomy
- Colonoscopy and blood transfusions for treatment of ulcerative colitis
- Bladder suspension surgery
- Elective cosmetic surgery (abdominal plasty)
- Emergency room visit due to GHB overdose (not coded separately as an overdose)
- Toe amputation on account of an infection
- Coronary angioplasty
- Nasal reconstructive surgery as an inpatient for pre-existing apnea/hypopnea and readmission to hospital after surgery with prescription of multiple medications for pain

## **8.4 All "Unevaluable" Adverse Events**

A table has been provided listing all patients who had unevaluable adverse events. The table provides the following information: verbatim term, number of adverse events, patient record number, adverse event start date and resolution date (if present), relationship to study drug, seriousness, actions taken and description of event.

I have read through these listings. In only the following instance are further details warranted

Patient # 01027 (Initials ) was a 58 year old woman who is stated in the tabular summary to have been recorded, first on a standard electrocardiogram, and then on Holter monitoring, to have AV block (first and second degree); further details are not provided. However the patient narrative and Case Report Form indicates that she had AV block even prior to study entry. She also had maturity-onset diabetes mellitus. During the study she also had episodes of chest pain, considered to be due to myocardial ischemia, and leading to hospitalization and cardiac catheterization. She experienced a number of other adverse events during the study including bronchospasm, headache, sleep walking, urinary incontinence, confusion, nausea and vomiting. Her dose of GHB during the study ranged from 2.3 to 6.8 g/day. She remained in the Scharf study.

Patient # 01059 (Initials ), a 49 year old woman had an episode of optic neuritis 3 years prior to study entry. 8 years after her entry into the Scharf study she is described as having multiple sclerosis requiring treatment with methylprednisolone (the event lasted 4 days). She continued in the Scharf Study

### **8.5 Reviewer's Comments**

None of the "adverse events" in the "unevaluable" category appear to be attributable to GHB

## **9. Analysis Of Urinary And Fecal Incontinence In Scharf Trial**

### **9.1 Background**

Urinary and fecal incontinence have been associated with the administration of GHB in clinical trials.

In the original NDA application the sponsor submitted an analysis of urinary and fecal incontinence in the OMC-GHB-2 and OMC-GHB-3 trials. This analysis was especially directed at determining if such episodes could be related to otherwise unrecognized seizures due to GHB. I have described this analysis in the main NDA Safety Review.

The analysis was conducted at the Division's request; during review of Treatment IND 57271 it was noted that a number of patients exposed to GHB had urinary and fecal incontinence.

Prior to submission of this amendment, the Division requested a similar analysis for the Scharf study

### **9.2 Sponsor's Methods**

The data listings for the Scharf study were reviewed for adverse event preferred terms suggestive of

- Fecal/urinary incontinence
- Adverse events related to the central nervous system

The terms "urinary incontinence" and "enuresis" are considered to be synonymous

The number of such adverse events was as follows:

- 1 instance of fecal incontinence (1 patient)
- 140 instances of urinary incontinence in 33 patients
- 704 central nervous system adverse events in 104 patients

A further analysis of the above adverse events was performed to identify those instances of incontinence that occurred in close temporal relationship to a central nervous system adverse event. The results of this analysis are presented below: the final purpose of the analysis was to identify those patients who had incontinence related to central nervous system adverse events that could suggest seizures

### 9.3 Tabular Summary Of Cases Identified By Sponsor

These patients are listed and summarized in the following table

Patient Identifier	Enuresis, Urinary Incontinence or Fecal Incontinence Adverse Events			Central Nervous System Anomalies		
	Verbatim Term	Onset Date	Resolution Date	Verbatim Term	Onset Date	Resolution Date
017	enuresis episode	09/20/92	09/20/92	sleepwalking episode	09/20/92	09/20/92
017	enuresis episode	08/12/93	08/12/93	sleepwalking episode	08/12/93	08/12/93
048	enuresis	09/11/84	09/11/84	confusion	09/11/84	09/11/84
048				numb all over	09/11/84	09/11/84
048	urinary incontinence with seizure	02/07/89	02/08/89	convulsive-like seizure	02/07/89	02/08/89
207	wet the bed	03/22/85	03/22/85	sleepwalking	03/22/85	03/22/85
247	enuresis	04/27/90	04/27/90	seizure (continuous jerking all over)	04/27/90	04/27/90
255	urinary incontinence	02/21/91	02/21/91	brief grand mal seizure (while at Dr. Office)	02/21/91	02/21/91
257	loss of bowel control	01/26/91	01/26/91	intense body shaking	01/26/91	01/26/91
257	loss of bladder control	01/26/91	01/26/91	jerking during cataplexy	01/26/91	01/26/91
262	bedwetting 3 episode	01/24/96	01/31/96	dizzy	01/24/96	01/25/96
262				felt like head rolling around	01/24/96	01/25/96

### 9.4 Narratives For Selected Patients In Above Table

More detailed descriptions are warranted for the following patients. These descriptions are based on a review by me of the sponsor's narratives, Case Report Forms and source documents (when provided)

#### 9.4.1 Patient # 01-048

This patient was a 27 year old woman with a history of febrile seizures at age 2 and of narcolepsy for 8 years. Concomitant medications at study entry included dextroamphetamine, diazepam, flurazepam, methylphenidate (immediate and controlled-release), imipramine and meprobamate.

The day she entered the study, and while taking a dose of 6 g/day she felt dizzy, noted twitching of her face, had palpitations and was laughing continuously. According to the Case Report Form this cluster of adverse events lasted 3 days. This event presumably began after she received the drug as the relationship to the drug is listed in the Case Report Form as being "unknown."

About a week after she entered the study she was reported to be disoriented on a single day; at that time she was also taking GHB in a dose of 6 g/day. Further details of this episode are unavailable. A further week later she was again disoriented/confused on a single day; she was believed to be continuing to take 6 g/day of GHB at that time. Further details of that episode are also unavailable.

About 5 months after study entry she woke sweating, numb, tingling from head to toe, heard a loud roaring, had a dry mouth and felt disoriented, dizzy and was breathing in a "strange" way. She was still taking GHB in a dose of 6 g/day at that time. She called her neurologist who suggested that the episode was an anxiety attack and recommended diazepam (which she did not have available) and re-breathing from a bag that she had expired into

About 11 months after entering the Scharf study and while taking a GHB dose of 7.5 g/day she had an episode of urinary incontinence which occurred on the same date as complaints of "numbness all over", confusion, night sweats, shortness of breath and nausea.

About 1 ½ years after study entry she was reported to be behaving in a bizarre manner at work: she raised the ambient temperature to 95 degrees F using the thermostat, was continually drinking Coca-Cola®, appeared pale and was noted to stagger and to have hiccups. She was taking GHB in a dose of 6 g/day at that time. Both GHB and triazolam, which she was also taking were discontinued; GHB alone was re-started initially in a dose of 3 g/day with the dose being increased later to 6 g/day. During the period of study drug interruption an EEG was done which was reported to be normal.

The narrative supplied states (apparently on the basis of information in the source document) that about 3 years after she first entered the study a concern was raised by her physician that she was misusing triazolam which he then declined to prescribe, leading to her seeing 2 other physicians within the next 3 months. A further 2 years later she was reported to be taking triazolam, clobazam and propoxyphene-acetaminophen without informing the investigator.

About 5 ½ years after entering the Scharf study she reported an episode of urinary incontinence that occurred at the same time (as recorded in a source document) as a "convulsive-like" seizure associated with loss of consciousness; she appears to have been receiving GHB in a dose of 8.3 g/day at that time. Her hospital history and physical examination record indicates that this witnessed episode of loss of consciousness occurred without warning, that she had both stiffening and jerking during the episode (which lasted 5 minutes) and she was flaccid and drowsy afterward, taking 4-5 hours to recover. She was hospitalized and testing revealed a normal EEG and head CT scan without contrast, and negative urine and serum drug screens, except for the detection of propoxyphene in her urine.

The patient's participation in the Scharf study was terminated by the investigator 2 days after the above "convulsive-like" seizure occurred. A week after termination of her participation in the study she informed site personnel that she was taking GHB without permission

#### **9.4.2 Patient # 01-247**

This patient was a 33 year old woman with a preceding history of urinary incontinence and of psychiatric illness with multiple hospitalizations; her psychiatric illnesses apparently included major depression and a suicide attempt. Medications at study entry included L-tyrosine, methylphenidate, temazepam, dextroamphetamine, imipramine, protryptiline, fluoxetine and alprazolam. The Case Report Form indicates that in addition to a diagnosis of narcolepsy, the possibility that she could have had obstructive sleep apnea could not be excluded.

At least 11 episodes of incontinence are documented in the Case Report Form, prior to the episode described in the next paragraph. Details of those episodes are unavailable; no concomitant symptoms are recorded.

About 9 months after study entry and while ostensibly taking a GHB dose of 6 g/day she reported having a "seizure" ("continuous jerking all over"). Although the sponsor's narrative states that this episode occurred in conjunction with an episode of incontinence that is not clearly documented in the Case Report Form.

A source document indicates that although the frequency of her attacks of cataplexy improved with GHB she had increasing difficulty sleeping after her second dose of GHB; her physician felt that she was depressed and treated her with triazolam 0.25 mg daily beginning 2 months before her seizure and after discontinuing temazepam which she was taking earlier. 3 days after withdrawing from triazolam she had a seizure.

She then withdrew from the Scharf trial but over a year later requested that she be enrolled again because of poor control of cataplexy (she was apparently not re-enrolled). At that time she attributed her "seizure" to excessive use of GHB and concomitant alcohol use in the setting of depression and accompanying a failing marriage.

About 2 months after beginning study drug she was reported to have an episode of sleep-walking.

#### 9.4.3 Patient # 01-255

This patient was a 46 year old man who reportedly had 2 seizures, 7 months and 4 months prior to entry into the Scharf study: details of these seizures are unavailable. He was also paranoid and was reported to have difficulty controlling his temper. Medications at study entry included imipramine, phenytoin, dextroamphetamine, and pemoline. He was recorded as having obstructive sleep apnea in addition to narcolepsy, and impaired vision caused by macular degeneration.

About 10 months after study entry and while taking GHB in a dose of 5.3 g/day he had urinary incontinence in a doctor's office at the same time that he had what was described as a "brief grand mal seizure". Surprisingly the Case Report Form has no record of this episode; neither have any source documents been supplied to substantiate this possibility.

GHB was apparently continued with the patient participating in the study for at least 7 years.

While participating in the study he apparently had multiple episodes of sleep walking. Early in the study he reported nausea, dizziness and periods of depression, as well as a feeling of frustration and panic early one morning. About 7 years into the study he was recorded as having an episode of bedwetting.

#### 9.4.4 Patient # 01-257

This patient was a 32 year old man. In the year prior to his entry into the Scharf study he was involved in an automobile accident that reportedly resulted in a whiplash injury and a concussion, as well as residual tingling in his hands, and weakness in his upper body. In addition to having narcolepsy he had also been diagnosed to have obstructive sleep apnea. Concomitant medications at study entry included protriptyline, methylphenidate, buspirone and methamphetamine.

About 1 month after study entry he was recorded as having the following symptoms: excessive sweating, chills, blurred vision, memory loss and violent shaking and vibrations. At that time he was taking GHB in a dose of 5.3 g/day. Although the sponsor maintains that this episode was related to a bout of tonsillitis I am not able to substantiate that from the Case Report Form

About 8 months after he began taking GHB, and while he was receiving a dose of 9 g/day, he was described as being incontinent of urine and stool during events that were described as consisting of "intense body shaking" and "jerking during cataplexy". The patient had however continued to receive GHB since that time at least until 8 years after study entry without any recurrence of the same events. However about 6 years after he began taking the study drug he had episodes of bedwetting and sleep walking at a time when he was taking GHB in a dose of 12 g/day.

About 5 years after study entry he fell on a butcher's knife which penetrated his abdomen and exited from his back injuring his colon. The mechanism of this incident has not been described, but other falls due to attacks of cataplexy have been noted in the Case Report Form.

Among the more common adverse events reported during the study were nausea, headache, feelings of weakness and jitteriness.

His Case Report Form also records an episode, 8 years after he began taking GHB, of "periods of apnea and hypoxemia" leading to an emergency hospitalization and intubation. This adverse event apparently resolved in a day, but further details are unavailable.

As noted above, this patient did not discontinue from the Scharf study

### **9.5 Patients With Sleepwalking And Incontinence**

- The sponsor has provided narratives for both patients (#s 01-017, 01-207) listed in the above table as having enuresis and sleep walking. The narratives state both patients had enuresis that were associated with episodes of sleepwalking
- The following are noteworthy in regard to Patient # 01-017, who was 63 years old at the time of entry into the study
  - 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 overdosed on GHB twice, reportedly during periods of sleepwalking; on one occasion he was comatose and needed intubation and artificial ventilation but recovered.
  - 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.
- The following were noted for Patient # 01-207, a 32 year old woman
  - This patient had multiple episodes of sleepwalking.
  - She wet her bed on the same date as one of her episodes of. It is uncertain that the episodes of sleepwalking and bed wetting actually coincided.
  - She was ultimately withdrawn from GHB on account of non-compliance
- A description of the actual behavior of both patients during periods of sleepwalking is unavailable.

### **9.6 Sponsor's Conclusions**

- In only 10 instances were episodes of fecal or urinary incontinence associated temporally with adverse events that could be related to the central nervous system
- In 6/10 instances the episodes, while attributable causally to GHB, were associated with sleepwalking, confusion and dizziness, all events that were not believed to represent epileptic phenomena

- In the remaining 4/10 instances the central nervous system adverse events that occurred in close temporal relationship to the episodes of urinary/fecal incontinence could have represented seizures. However
  - Patient # 01-255 who had a witnessed convulsion associated with an episode of incontinence, had seizures prior to study entry.
  - Patient # 01-257 had incontinence during a cataplexy attack and not a seizure (the sponsor has supplied a publication that describes how narcolepsy/cataplexy alone can result in fecal incontinence)
  - For Patients 01-247 and 01-048 one cannot rule out the possibility that incontinence was caused by seizures and that the seizures were due to GHB.

### **9.7 Reviewer's Comments**

- 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.
- Further discussions of convulsions in GHB-treated patients are in Sections 12 and 15
- I agree that the witnessed convulsion with incontinence in Patient # 01-255 is unlikely to have been due to GHB but a description of the episodes that occurred prior to beginning the drug would have been helpful (i.e., were they true seizures?)
- It appears to be widely recognized in the medical community that muscle twitching can accompany attacks of cataplexy.
- It also seems unlikely that the episode of fecal and urinary incontinence in Patient # 01-257 occurred coincidentally with a convulsion; it appears more likely that the episode was coincident with an attack of cataplexy. Whether his subsequent episodes of bedwetting and sleep walking could have been related to epileptic phenomena is entirely a matter of speculation.
- For Patient 01-247 I agree it is possible that incontinence was caused by seizures; in Patient 01-048 it appears quite clear that the episode of incontinence accompanied a convulsion. In both instances it is possible that the episodes were causally related to GHB use. However
  - In Patient 01-247 the reported seizure could have also been related to alcohol or triazolam withdrawal
  - In Patient 01-048, given her reported history of benzodiazepine overuse, it is not inconceivable that her convulsion was related to benzodiazepine withdrawal, but that has not been confirmed
- In the absence of an adequate description of the episodes of "sleepwalking" seen in patients who may or may not have had incontinence on the same day it is not possible to state whether or not any of these were epileptic phenomena. It is not impossible that some of these episodes represented partial complex seizures but such seizures (as opposed to generalized tonic-clonic seizures) are generally not believed to be caused by chemical agents/drugs. Partial complex seizures may rarely be associated with incontinence
- It is also possible that the episodes of sleepwalking represented non-epileptic confusional states induced by GHB (see Section 10).

- Periods of automatic behavior are common in patients with narcolepsy, but are reported to occur during the day. It is unclear whether any of the episodes of sleepwalking reported in the Scharf study can be attributed to narcoleptic automatic behavior
- **There is no evidence that the episodes of sleepwalking represented true somnambulism (a non-REM sleep disorder)**
- The episodes of sleepwalking are however disturbing in themselves especially since overdoses of GHB are reported to have been taken during these episodes, with serious consequences in at least one instance.

## 10. Adverse Events Coded As “Confusion” In Scharf Study

### 10.1 Background and Methods

At the Division's request, adverse events coded using the preferred term “confusion” in the Scharf study were characterized further. This analysis pertained to all 143 patients who were enrolled in the study

The dosage at onset of each adverse event was determined (using the algorithm in Section 10.2) and the start and stop dates for the adverse events recorded.

A tabular summary of all patients who had such an adverse event was prepared. Narrative summaries were prepared for all patients

### 10.2 Overall Summary

10/143 (7.0%) GHB-treated patients had at least one adverse event coded under the preferred term “confusion.” Their distribution by dose and severity is displayed in the following table which I have copied from the submission.

Confusion: All Events	Total <sup>a</sup>	Xyrem Oral Solution Dosage (g/d) at Onset <sup>b</sup>				
		3.0	4.5	6.0	7.5	9.0
Patients with at Least 1 AE	10 <sup>c</sup>	0	4	3	3	0
Patients with SAEs	1	0	0	0	1	0
Patients with Related AEs	5	0	1	2	2	0
Patients with Severe AEs	1	0	1 <sup>c</sup>	0	0	0
Patient Discontinuation due to an AE	0	0	0	0	0	0
Patient Deaths	0	0	0	0	0	0

<sup>a</sup> Patients are counted only once in each category.

<sup>b</sup> Dosage at onset.

<sup>c</sup> Patient 027 experienced 3 events of “disoriented” which were considered severe.

As the table above indicates

- In 1 patient, “confusion” was considered to be a serious adverse event
- “Confusion” did not lead to treatment discontinuation in any patient
- This adverse event did show a clear dose response
- In 5 patients the investigator felt that this adverse event was drug-related.

Note that dose assignment in the above table was based on the following algorithm

Dose At Onset (g/day)	Dose Assignment (g/day)
≤ 3.0	3.0

> 3.0 to ≤ 4.5	4.5
> 4.5 to ≤ 6.0	6.0
> 6.0 to ≤ 7.5	7.5
> 7.5	9.0

Note that a proportion of patients experienced adverse events coded under the term "confusion" on more than one occasion. Thus the 10 patients experienced a total of 15 adverse events categorized as "confusion."

### 10.3 Verbatim Investigator Terms

The actual investigator terms were in the following categories

Investigator Term	Number of Patients
Disoriented	5
Disoriented (when awakening from sleep)	1
Confusion	1
Mental confusion	1
Confused	1
Confused sometimes (not a lot)	1
A little confused at 2.25 AM	1

Note that individual patients may have had several episodes occurring under the same investigator term or category of investigator term

### 10.4 Tabular Summary

The sponsor has provided a table for all patients who had an adverse event coded using the preferred term "confusion". The table provides the following data: patient ID #, initials, sex, age, dosage at onset of confusion, start and stop date for adverse event, investigator term, whether serious or not, frequency, relationship to study drug, severity and relevant medical history. I have not reproduced the table in this review. The following table outlines noteworthy items in the sponsor's table.

Start and stop dates for confusion specified	11 events (in 6 patients)
Duration of confusion for events where start and stop dates were specified	1 day: 10 events 14 days: 1 event
Preceding medical illnesses that may have contributed to confusion	Head injury (2 patients)
Number of patients with confusion > 50 years old	6

### 10.5 Narrative For Patient With Confusion As A Serious Adverse Event

I have read the sponsor's narrative and supplemented it with a Case Report Form

#### 10.5.1 Patient 01-012 (Initials)

This man was 74 years old at the time of study entry. He had a past history of cardiomyopathy, left bundle branch block, a possible left hilar mass and sleep apnea, as well as narcolepsy. Concomitant medications included diltiazem, pemoline, protriptyline, digoxin and indomethacin.

He initially took GHB in a dose of 4.5 g/day. About 2 years after beginning GHB his dose was increased to 7.5 g daily. 10 days after that dose increase, and after his first nightly dose he had an episode of

"disorientation, stupor and weakness" that necessitated hospitalization overnight and a reduction in dose of GHB to 6 g daily for one day. The episode resolved and did not recur despite the patient taking GHB for the next 8 years, except for a 17-month interruption; however medication records do not provide any evidence that he took a dose of  $\geq 6$  g/day subsequently. Study medication was eventually discontinued on account of knee replacement surgery, and surgery for a ruptured abdominal aortic aneurysm, at the patient's request.

During the study he was also described as having periods of central apnea which required temporary discontinuation of GHB at least once.

### **10.6 Narratives For Additional Patients With Confusion**

The sponsor has provided narratives for all remaining 9 patients who had the adverse event of confusion. The following narratives are noteworthy. Case Report Forms were available for Patients 016, 215, 248 and 251.

#### **10.6.1 Patient 01-016 (Initials)**

This 29 year old man with narcolepsy had a single episode when he was "disoriented" and had an "unsteady gait", 1 year after beginning GHB and while taking a dose of 5.3 g/day; the episode is stated to have ended the day it began. Following the episode his dose of GHB was reduced. He continued GHB for a further 2 years but all subsequent doses were  $\leq 3.8$  g/day. He eventually discontinued taking the drug for financial reasons.

During the study he was also listed as having 2 episodes of "sleepwalking" and was also noted to have heavy snoring and periods of apnea.

#### **10.6.2 Patient 01-027 (Initials)**

This 55 year old woman with narcolepsy received GHB for a total of 14 years at a dose of 4.5 g/day. About 8 years after beginning treatment she had an episode of disorientation, nausea, vomiting, retching and sweating. 4 months later she had 2 episodes, at an interval of 2 weeks, of disorientation with a loss of muscle tone. Each episode resolved in less than a day. The patient eventually transferred to the OMC-SXB-7 study.

#### **10.6.3 Patient 01-048 (Initials)**

A narrative for this patient has been provided in Section 9.4.1

#### **10.6.4 Patient 01-215 (Initials)**

This 46 year old woman with narcolepsy who sustained a skull fracture 5 years prior to study entry took GHB in a variable dose of 4.5 to 10.5 g/day in 2 or 3 divided doses despite being prescribed 7.5 g/day (this is not consistent with what has been entered in the medication logs in the Case Report Form. About 4 months after entering the study she reported symptoms of nausea, a tipsy feeling, blurred vision, and a swollen face and hands. These symptoms persisted for 14 days, no action was taken and her doses subsequently were variable and as high as 10.5 g/day. She continued in the study for a further 4 years when she was discontinued on account of non-compliance which involved not submitting daily sleep log diaries and modifying dosing schedules without prior consultation with Dr Scharf.

A number of unexplained fits of laughter (termed "hysterical" in one instance, and "uncontrollable" at other times), and episodes of "sleepwalking" (during one of which she tried to drink nail polish remover). Episodes of headache, nausea, dizziness, blurred vision, enuresis, "fogginess", "stumbling around-unsure of self on feet after gamma", "drugged effect, vision blurred, unsteady on feet", "drunken stupor; rage", other similar events, and sleeplessness, were also noted during the study.

A telephone contact with the patient 12 ½ years after she discontinued from the study indicated that her neurological adverse events, with the exception of blurred vision, had resolved once GHB was discontinued.

### **10.6.5 Patient 01-235 (Initials)**

This 49 year old patient with narcolepsy began taking GHB in a dose of 6 g/day. Shortly after beginning the drug he reported "disorientation" which he attributed to taking too much GHB. It is unclear how long this symptom lasted. He continued GHB for 15 years. For a period of 3 years beginning 6 months after he started taking the drug treatment was interrupted on account of non-compliance (failure to submit daily sleep log diaries)

### **10.6.6 Patient 01-248 (Initials)**

This 73 year old man with a history of narcolepsy, sleep apnea and sleepwalking described mental confusion after taking GHB (prescribed dose: 4.5 g/day) for 5 days. Further details of this symptom are unavailable. He was reported by the investigator to take medication irregularly and without following the investigator's instructions. He was dropped from the trial after 3 months on account of non-compliance: he offered his medication to others not participating in the clinical trial and took his own medication irregularly.

### **10.6.7 Patient 01-251 (Initials)**

This 65 year old man with narcolepsy and sleep apnea was taking a nightly dose of 7.5 g when 2 months after study entry he reported feeling "drunk", confused and unsteady. The subsequent duration of this adverse event is unknown. He participated in the study for 2 ½ years but then discontinued after he was noted to be non-compliant (he did not return his daily diary logs).

Other adverse events noted during the study included "sleep walking", feelings of shakiness, an upset stomach, "felt like he was on a drug binge", "interrupted breathing" and "dry heaves."

## **10.7 Reviewer's Comments**

- As contemporaneous formal mental status examinations were not carried out in patients with "confusion" it is unclear if any patients coded as having this adverse event were really confused, as the term is conventionally understood. This adverse event appears to have been recorded based largely, if not entirely on patients symptoms
- Nevertheless "confusion" as it pertains to these patients and the other associated symptoms (e.g., unsteadiness) are not unexpected with a drug that has sedative properties

## **11. Neuropsychiatric Adverse Events In Scharf Study**

### **11.1 Background**

At the Division's request neuropsychiatric adverse events in the Scharf study were characterized further by the sponsor.

The sponsor's methods were as follows:

- Adverse events COSTART-coded under the following preferred terms were selected from the all adverse events that occurred in the Scharf study: overdose, suicide attempt, depersonalization, depression, emotional lability, hallucinations, hostility, neurosis, paranoid reaction, stupor, and thinking abnormal.
- Source documents, Case Report Forms and data listings were reviewed for patients with the above adverse events
- Tabular and narrative summaries of events were then constructed.
- A review of the literature relevant to the incidence of neuropsychiatric adverse events in narcolepsy was completed

- The dosage at onset of each adverse event was determined and the start and stop dates for the adverse events recorded. Dosage at onset was assigned using the following algorithm

Dose At Onset (g/day)	Dose Assignment (g/day)
≤ 3.0	3.0
> 3.0 to ≤ 4.5	4.5
> 4.5 to ≤ 6.0	6.0
> 6.0 to ≤ 7.5	7.5
> 7.5	9.0

### 11.2 Overall Summary

The adverse events selected were those that occurred before the cut-off date of May 31, 1999.

41/143 (28.7%) GHB-treated patients had at least one adverse event coded under one or more of the neuropsychiatric adverse event terms outlined in Section 11.1. Their distribution by dose and severity is displayed in the following table which I have copied from the submission.

Neuropsychiatric: All Events	Total <sup>a</sup>	Xyrem Oral Solution Dosage (g/d) at Onset <sup>b</sup>				
		3.0	4.5	6.0	7.5	9.0
<b>Number of Neuropsychiatric AE's</b>	<b>84</b>	<b>3</b>	<b>14</b>	<b>23</b>	<b>25</b>	<b>19</b>
Patients with at Least 1 AE	41 <sup>c</sup>	1	9	12	11	8
Patients with SAEs	4 <sup>d</sup>	0	1	0	1	2
Patients with Related AEs	12 <sup>e</sup>	0	1	4	3	4
Patients with Severe AEs	7 <sup>f</sup>	2	2	0	2	1
Patient Discontinuation due to an AE	2	0	0	1	0	1
Patient Deaths	0	0	0	0	0	0

<sup>a</sup> Patients are counted only once in each category patients are classified by the highest dose at which a neuropsychiatric AE occurred.

<sup>b</sup> Total number of patients in each dosage group represents the dosage at onset

<sup>c</sup> Patients are classified here by highest dose at which any neuropsychiatric AE occurred

<sup>d</sup> 2 patients experienced more than one Neuropsychiatric AE designated as serious, patients are classified here by the highest dose at which any neuropsychiatric AE occurred

<sup>e</sup> 6 patients experienced more than one Neuropsychiatric AE designated as related to study medication, patients are classified here by the highest dose at which any neuropsychiatric AE occurred

<sup>f</sup> 1 patient experienced more than one Severe AE designated as neuropsychiatric.

As the table above indicates

- No patients died as a result of such adverse events
- 4 patients had serious neuropsychiatric adverse events
- 2 patients discontinued GHB on account of neuropsychiatric adverse events
- Such adverse events did not appear to be increased in frequency with increased dosage
- The 41 patients with neuropsychiatric adverse events had a total of 84 such events

### 11.3 Distribution Of Individual Neuropsychiatric Adverse Events

The distribution of individual COSTART-coded neuropsychiatric adverse events is as illustrated in the following table

Note that patients may have had adverse events in more than one category

COSTART Term	Number Of Patients
Total	41
Depression	22
Stupor	6
Suicide Attempt	1
Overdose	2
Paranoid Reaction	1

COSTART Term	Number Of Patients
Emotional Lability	10
Thinking Abnormal	9
Neurosis	2
Depersonalization	7
Hostility	6
Hallucinations	1

#### **11.4 Specific Neuropsychiatric Adverse Events**

##### **11.4.1 Depression**

The sponsor has provided a table summarizing all patients coded to have the COSTART preferred term "depression."

The table provides the following data: patient ID #, trial #, sex, age, dosage at onset of confusion, start and stop date for adverse event, investigator term, whether serious or not, frequency, relationship to study drug, severity and relevant medical history. I have not reproduced the table in this review.

In regard to the table the following are noteworthy

- Verbatim investigator terms included "depression", "feels quite depressed", "very down", "not happy", and "possible depression". The sponsor points out that the COSTART term "depression" as used in this particular context is not equivalent to a psychiatric diagnosis of Major Depressive Disorder using DSM-IV criteria.
- 22/143 (15.4%) patients experienced a total of 28 adverse events coded as depression
- 2 patients had a recorded previous history of depression and 2 of other psychiatric symptoms (visual and auditory hallucinations; paranoia and difficulty controlling temper)
- In only 1 patient was depression considered a serious adverse event (and warranted hospitalization). This patient also attempted to commit suicide and discontinued taking GHB
- No other patients had to discontinue treatment on account of depression
- "Stop" dates for depression are not available for 17/23 patients

##### **11.4.2 Emotional Lability**

The sponsor has provided a table summarizing all patients coded to have the COSTART preferred term "emotional lability."

The table provides the following data: patient ID #, trial #, sex, age, dosage at onset of confusion, start and stop date for adverse event, investigator term, whether serious or not, frequency, relationship to study drug, severity and

relevant medical history. I have reproduced the table below.

Patient No./Initials	Sex/Age <sup>a</sup>	Dosage at Onset (g/d)	AE Start Date	Trial Day		Verbatim Term	Serious	Relationship/Severity	Relevant Medical History
				Start	Stop				
001/	M/49.0	9.0	10/30/86	1078		Emotional lability	No	Not Related/Not Indicated	Narcolepsy with Cataplexy, Impotence
015/	F/54.6	6.0	01/20/84	9		(Moodiness) Finding fault with everything	No	Not Related/Not Indicated	Narcolepsy
024/	F/51.8	6.0	12/15/83	1		Crying	No	Unknown/Not Indicated	Narcolepsy, Migraines
048/	F/27.7	7.5	10/26/83	0	3	Laughing continuously	No	Unknown/Not Indicated	Narcolepsy, Febrile Convulsion (Age 2)
063/	F/27.0	4.5	09/13/88	130		"Heart Aches"	No	Not Related/Not Indicated	Narcolepsy, Memory Problems, Depression with Recurrent Melancholia, Dizzy Episodes when Walking and Laying Down

Patient No./Initials	Sex/Age <sup>a</sup>	Dosage at Onset (g/d)	AE Start Date	Trial Day		Verbatim Term	Serious	Relationship/Severity	Relevant Medical History
				Start	Stop				
215/	F/46.2	8.3	12/25/83	60	60	Hysterical laughing	No	Not Related/Not Indicated	Narcolepsy, Skull Fractures (1978)
	F/46.3	7.5	02/01/84	98	98	Fit of laughing	No	Not Related/Not Indicated	
	F/46.3	7.5	02/02/84	99	99	Laughing uncontrollably	No	Not Related/Not Indicated	
	F/46.4	10.5	03/06/84	132	132	Uncontrollable laughter	No	Possibly Related/Not Indicated	
	F/46.4	7.5	03/14/84	140	140	Fits of hysterical laughter	No	Not Related/Not Indicated	
238/	M/45.2 <sup>b</sup>	22.5 <sup>c, d</sup>				Emotional interplay (Reported by Physician on 07/02/85)	No	Possibly Related/Not Indicated	No history available
257/i	M/33.0 <sup>b</sup>	12.0 <sup>c</sup>				Tearful	No	Not Related/Not Indicated	Narcolepsy, Whiplash/Concussion, Difficulty left Binocular Focusing Hard Moving All Positions

Patient No./Initials	Sex/Age <sup>a</sup>	Dosage at Onset (g/d)	AE Start Date	Trial Day		Verbatim Term	Serious	Relationship/Severity	Relevant Medical History
				Start	Stop				
258/	M/54.1	3.0	11/23/90	9	11	Emotional	No	Not Related/Moderate	Narcolepsy
259/	F/41.1	5.3	06/06/87	3		Crying a lot	No	Probably Related/not Indicated	Narcolepsy

<sup>a</sup> Age at AE start date.  
<sup>b</sup> Age at trial start date.  
<sup>c</sup> Highest dose of sodium oxybate taken during the trial.  
<sup>d</sup> Patient took a dose of 22.5g on one day. His most common dose during the trial was 9g.

The following are noteworthy in regard to the above table

- No serious adverse events included emotional lability

- One patient discontinued treatment on account of emotional lability
- Bouts of laughter in 2 patients
- It is unclear what the term "heartaches", coded as emotional lability, refers to. It could mean periods of depressed mood rather than emotional lability (she had a previous history of depression and melancholia). The Case Report Form for this patient does not list this adverse event at all.
- None of the "emotional lability" events were considered serious.
- One patient (#01-259) discontinued treatment on account of emotional lability

### 11.4.3 Thinking Abnormal

The sponsor has provided a table summarizing all patients who had an adverse event coded using the preferred term "thinking abnormal."

This table is below

Patient No./ Initials	Sex/ Age <sup>a</sup>	Dosage at Onset (g/d)	AE Start Date	Trial Day		Verbatim Term	Serious	Relationship/ Severity	Relevant Medical History
				Start	Stop				
031/	M/51.5	6.0	12/14/85	381	381	Can't seem to get my thoughts together	No	Unknown/Not Indicated	Narcolepsy, Head Injury 1972 with 1 week amnesia
064/	F/14.2	5.3	11/06/87 <sup>b</sup>	152		Mixes things up- transposes numbers i.e. thinks 280 but writes 208	No	Unknown/Not Indicated	Narcolepsy, Concussion 4/85; Frontal lobe lesion
207/	F/32.1	6.0	02/01/84	0	0	Incoherence	No	Probably Related/Not Indicated	Narcolepsy
018/	F/46.0	7.5	11/01/83	6		Very talkative- after gamma dose	No	Possibly Related/Not Indicated	Skull Fractures, 1978
	F/46.1	7.5	12/08/83	43		Fogginess	No	Unknown/Not Indicated	
	F/46.3	7.5	02/03/84	100	100	Fogginess lasted couple of hours	No	Possibly Related/Not Indicated	
218/	F/40.3 <sup>b</sup>	7.5 <sup>d</sup>				Being in a fog	No	Possibly Related/Not Indicated	Narcolepsy

Patient No./ Initials	Sex/ Age <sup>a</sup>	Dosage at Onset (g/d)	AE Start Date	Trial Day		Verbatim Term	Serious	Relationship/ Severity	Relevant Medical History
				Start	Stop				
238/	M/45.7	9.0	06/25/84	208	209	Can't seem to concentrate	No	Possibly Related/Not Indicated	No History Available
218/ (Cont)	M/45.9	7.5	09/04/84	279	280	Negative thinking	No	Possibly Related/Not Indicated	No History Available
257/	M/31.0 <sup>b</sup>	12.0 <sup>d</sup>				Problem concentrating	No	Not Related/Not Indicated	Narcolepsy, Whiplash / Concussion, Obstructive Sleep Apnea
267/	F/61.4	4.5	05/00/92 <sup>c</sup>	16		Foggy and Lightheaded feeling	No	Not Related/Not Indicated	Narcolepsy, Sleep apnea
279/	F/37.0	5.4	02/26/98	531		Foggy Minded	No	Not Related/ Moderate	
	F/37.2	2.3	05/15/98	609	617	Inability to Concentrate	No	Not Related/ Severe	

<sup>a</sup> Age at AE start date.  
<sup>b</sup> No start date indicated for this AE so age at study start is used for age at onset of AE.  
<sup>c</sup> Exact onset date calculated from the midpoint of the known period (i.e. the 15<sup>th</sup> of the month).  
<sup>d</sup> Highest dose of sodium oxybate taken during the trial.

Note that

- The verbatim terms indicate that patients coded as having the "thinking abnormal" adverse event complained of difficulty thinking clearly with one exception.

- The exception is Patient 01-215 who is described further in Section 10.6.4
- This adverse event was not considered serious in any patient and did not lead to medication discontinuation

#### 11.4.4 Depersonalization

The sponsor has provided a table summarizing all patients who had an adverse event coded using the preferred term "depersonalization". The table is below

Patient No./ Initials	Sex/ Age*	Dosage at Onset (g/d)	AE Start Date	Trial Day		Verbatim Term	Serious	Relationship/ Severity	Relevant Medical History
				Start	Stop				
048/	F/29.1	6.0	03/22/85	513	530	Bizarre behavior at work, turning up thermostat to 95 Degrees, continually drinking Coke, pale, staggering, hiccups	No	Probably Related/ Not Indicated	Narcolepsy, Febrile Convulsion (Age 2)
049/	F/46.5	6.0	03/17/87	120	121	Whole body felt weird	No	Not Related/Not Indicated	Narcolepsy, Apnea, Trigeminal Neuralgia
239/	F/61.3	6.8	07/22/85	234	234	Felt crazy	No	Probably Related/Not Indicated	Narcolepsy
251/	M/65.1	6.8	05/04/84	16		Felt like he was on a drug binge (unsure of himself)	No	Unknown/Not Indicated	Narcolepsy, Depression

Patient No./ Initials	Sex/ Age*	Dosage at Onset (g/d)	AE Start Date	Trial Day		Verbatim Term	Serious	Relationship/ Severity	Relevant Medical History
				Start	Stop				
259/	F/41.1	5.3	06/06/87	3		"Zombie like" State	No	Probably Related/Not Indicated	Narcolepsy
268/	M/22.9	4.5 <sup>b</sup>	12/00/93 <sup>c</sup>	157		Feelings of helplessness after one dose	No	Unknown/Not Indicated	Narcolepsy
274/	M/17.1	4.5	01/22/95	27		Later felt funny, vibrating internally - intermittently	No	Not Related/Not Indicated	Narcolepsy, Depression

\* Age at AE start date.  
<sup>b</sup> Dose at onset determined from the highest dose of the known period.  
<sup>c</sup> Event onset date calculated from the midpoint of the known period (i.e. 12/15/93).

As the verbatim terms in the above table indicate, this adverse event encompassed a variety of symptoms. None were considered serious and only one patient (#01-259; see Section 11.5.2) discontinued treatment on account of this adverse event.

#### 11.4.5 Hostility

The sponsor has provided a table summarizing all patients coded to have the COSTART preferred term "hostility."

These patients are summarized in the following table which I have copied from the submission

Patient No./Initials	Sex / Age <sup>a</sup>	Dosage at Onset (g/d)	AE Start Date	Trial Day		Verbatim Term	Serious	Relationship/Severity	Relevant Medical History
				Start	Stop				
001/	M/49.0	9.0	10/30/86	1078		Volatile Temper	No	Not Related/Not Indicated	Narcolepsy with cataplexy
070/	F/51.7	5.3 <sup>b</sup>	06/00/87	34 <sup>c</sup>		Temper Tantrums (Intermittently throughout)	No	Unknown/Not Indicated	Narcolepsy, Headache and seizure activity; Depression; Memory Impairment X20 years stopped 1984
	F/51.7	5.3 <sup>b</sup>	06/00/87	34 <sup>c</sup>		Short tempered	No	Unknown/Not Indicated	
215/	F/46.4	7.5	03/08/84	134	134	Rage	No	Possibly Related/Not Indicated	Narcolepsy, Skull Fractures 1978
238/	M/45.5	9.0	04/02/84	124		Feisty	No	Possibly Related/Not Indicated	No history available
	M/45.8	9.0	07/23/84	236		Angry	No	Possibly Related/Not Indicated	

Patient No./Initials	Sex / Age <sup>a</sup>	Dosage at Onset (g/d)	AE Start Date	Trial Day		Verbatim Term	Serious	Relationship/Severity	Relevant Medical History
				Start	Stop				
255/	M/46.4	4.5	05/07/90	20	20	Frustration	No	Not Related/Not Indicated	Paranoid-Difficult controlling temper; visual impairment; sleep apnea; narcolepsy; seizures 9/89 and 12/89
286/	M/36.4	5.3	12/27/91	499		Angry	No	Not Related/Not Indicated	Severe Headaches; Depression and Irritability caused by Ritalin at high doses

<sup>a</sup> Age at AE start date.

<sup>b</sup> Dose at onset determined from the highest dose of the known period.

<sup>c</sup> Event onset date calculated from the midpoint of the known period (i.e. 6/15/87).

As is evident from the above table

- The term "hostility" appears to have been used to describe a state of irritability in all 6 patients
- 2/6 patients had a history of excessive irritability prior to recent GHB
- 1/6 had a history of depression earlier
- None of these adverse events was considered serious or led to study drug discontinuation
- 5/6 patients were concurrently receiving methylphenidate with or without other amphetamines

#### 11.4.6 Stupor

The patients who were coded as having this adverse event are summarized in the following table which I have copied from the submission

Patient No./Initials	Sex/ Age <sup>a</sup>	Dosage at Onset (g/d)	AE Start Date	Trial Day		Verbatim Term	Serious	Relationship/Severity	Relevant Medical History
				Start	Stop				
012/	M/76.8	7.5	8/15/86	725	726	Stupor	Yes	Unknown/Not Indicated	Sleep apnea syndrome
017/	M/63.8	7.5	8/2/90	541	541	Unresponsive	Yes	Probably Related/Severe	Apnea and Hypopnea Index = 7.0 post removal of left lung carcinoma
307/	F/32.1	6.0	2/2/84	1	1	Intoxication	No	Probably Related/Not Indicated	
215/	F/46.4	7.5	3/4/84	130	144	Tipsy Feeling	No	Possibly Related/Not Indicated	Skull Fractures 1978
	F/46.4	7.5	3/8/84	134	134	Drunken Stupor	No	Possibly Related/Not Indicated	
251/	M/65.2	7.5	6/19/84	62		Felt Drunk	No	Unknown/Not Indicated	Sleep Apnea; Depression 1977 and 1979

Patient No./Initials	Sex/ Age <sup>a</sup>	Dosage at Onset (g/d)	AE Start Date	Trial Day		Verbatim Term	Serious	Relationship/Severity	Relevant Medical History
				Start	Stop				
257/	M/33.0 <sup>b</sup>	12.0 <sup>c</sup>				Wife reports patient not speaking-acting "Like he's retarded"	No	Unknown/Not Indicated	Whiplash/Concussion; Diff. L-Binocular focusing hard moving all positions; numbness and tingling hands; Obstructive sleep apnea

<sup>a</sup> Age at AE start date.

<sup>b</sup> No start date indicated for this AE so age at study start is used for age at onset of AE

<sup>c</sup> Highest dose of sodium oxybate taken during the trial.

The following additional observations can be made

- The adverse events seen were considered serious in 2 instances
- None led to medication discontinuation
- In the 4 instances where stop dates for the adverse event are available, the event was short-lived
- Investigator terms suggest that the patients' symptoms are not unusual for a sedative-hypnotic drug.

#### 11.4.7 Neurosis

The patients for whom the COSTART term "neurosis" was used are summarized in the following table which is copied from the submission

Patient No./Initials	Sex / Age <sup>a</sup>	Dosage at Onset (g/d)	AE Start Date	Trial Day		Verbatim Term	Serious	Relationship/Severity	Relevant Medical History
				Start	Stop				
070/	F/60.7	5.3	6/21/96	3328		"Having trouble keeping my arms down. I put them on my head they cut off circulation some (Go to sleep) and I wake up and can't find my hands and they are painful"	No	Not Related/Not Indicated	Narcolepsy, Headache and seizure activity; Depression; Memory Impairment X20 years stopped 1984
215/	M/58.0	6.0	9/00/93	3283 <sup>b</sup>	3405	Claustrophobia	No	Possibly Related/Not Indicated	Narcolepsy, Depression

<sup>a</sup> Age at AE start date.

<sup>b</sup> Start day calculated as 9/15/93, stop date recorded as 1/00/94 and calculated as 1/15/94.

The following observations can be made about the above table

- The verbatim term for Patient #01-070 does not suggest a neurosis and the coding term used seems inaccurate
- Further details are currently unavailable for Patient # 01-235 but it seems improbable that his claustrophobia is attributable to GHB.

#### 11.4.8 Overdose

The sponsor has included the following patients in this listing.

- Patient 01-017 (see Section 11.5.4)
- Patient 01-267 (see Section 11.5.5)

Both patients appeared to have taken overdoses accidentally; in the case of Patient 01-017 the overdose has been attributed to “sleepwalking”; and Patient 01-267 had multiple episodes of sleepwalking recorded although not on the night when she took her overdose

The sponsor has not included Patient 01-019 (see Section 11.5.1) in this section. This patient also took a drug overdose but was coded as making a suicide attempt.

#### 11.4.9 Suicide Attempt

A single patient (#01-019) was coded as making a suicide attempt during this study. This patient is further described in Section 11.5.1. As noted in the narrative he had a history of multiple psychiatric conditions including schizophrenia and depression prior to entry into the Scharf trial

#### 11.4.10 Hallucinations

The only patient who was coded as having “hallucinations” during the Scharf study is listed in the following table which I have copied from the submission.

Patient No. / Initials	Sex / Age*	Dosage at Onset (g/d)	AE Start Date	Trial Day		Verbatim Term	Serious	Relationship/ Severity	Relevant Medical History
				Start	Stop				
231/	M/55.0	9.0	10/01/94	1918		Hypnagogic Hallucination - Dove out of bed - Jammed head against wall	No	Probably Related/ Moderate	Narcolepsy, Sleepwalking, Head Injury, Lightheadedness, Periodic Dizziness, Depression

\* Age at AE start date.

As the table indicates the patient had a hypnagogic hallucination which is a manifestation of narcolepsy

#### 11.4.11 Paranoid Reaction

The single patient who had a paranoid reaction while participating in the Scharf study is listed in the next table copied from the submission.

Patient No. / Initials	Sex / Age*	Dosage at Onset (g/d)	AE Start Date	Trial Day		Verbatim Term	Serious	Relationship/ Severity	Relevant Medical History
				Start	Stop				
256/	M/16.4 <sup>b</sup>	4.5 <sup>c</sup>				Acting very paranoid - carries bat w/him while at home and feels someone is watching him	No	Not Related/Not Indicated	Narcolepsy, Occasional blurred vision injury to left orbit years before

\* Age at AE start date.

<sup>b</sup> No start date indicated for this AE so age at study start is used for age at onset of AE

<sup>c</sup> highest dose of sodium oxybate taken during the trial.

A narrative for this patient is below

**11.4.11.1 Patient # 01-256 (Initials)**

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

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

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

He was withdrawn from the study 2 years after he entered it on account of non-compliance (failure to return his sleep logs)

**11.5 Narratives For Serious Neuropsychiatric Adverse Events, and Discontinuations Due To Neuropsychiatric Adverse Events**

These narratives are below

**11.5.1 Patient 01- 019 (Initials)**

This 41 year old man with known narcolepsy, previous "sleep walking" and sleep apnea, and a past history of depression, "anxiety neurosis", a "characterological" disturbance, schizophrenia (as per the source document) 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.

During the study he also had multiple episodes of bedwetting as well as periods of eye pain, double vision, feelings of being off balance.

**11.5.2 Patient 01-259 (Initials)**

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 despite recent efforts by the sponsor to contact the patient; it is unclear therefore if her symptoms eventually resolved.

**11.5.3 Patient 01-Q12 (Initials)**

See Section 10.5.1

**11.5.4 Patient 01-017 (Initials)**

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.

#### **11.5.5 Patient 01-267 (Initials)**

This 65 year old woman had a history of obesity, sleep apnea on treatment, and narcolepsy. She began taking GHB in a dose of 4.5 g daily.

About 4 ½ years after study entry she was reported to have taken an overdose of GHB, consuming a third nightly dose instead of merely two doses. The patient's daughter reported that the patient was shortly afterward incontinent of urine, awoke and (for unclear reasons) was covered with spaghetti sauce. She also appeared dazed and confused. Her diaries are unavailable for that period and it is therefore unclear what her regular dose of GHB was at the time. She was taken to an emergency room but had recovered by that time. She was reported to have continued GHB after that episode but ceased returning any daily diaries at all beginning about 5 ¼ years after study entry and was therefore recorded as having left the study on account of non-compliance. Repeated letters to the patient from the study center were reportedly unanswered. Further information about this patient is unavailable.

During her participation in the study she was also recorded to have multiple episodes of sleepwalking and multiple additional episodes of urinary incontinence, not apparently occurring contemporaneously. She was also seen at an emergency room for an episode of somnolence which was felt to be related to her sleep apnea. She reported swollen ankles and wrists, and pain, numbness and tingling in her feet.

#### **11.6 Additional Narrative**

This narrative is for a patient who discontinued GHB on account of a neuropsychiatric adverse event but was not included in the sponsor's analysis of such events

##### **11.6.1 Patient 01-006 (Initials)**

This 15 year old boy with a history of narcolepsy and cataplexy and reflux esophagitis was taking methylphenidate, protriptyline and ranitidine at the time of study entry. He was begun on GHB in an initial dose of 5.3 g/day.

7 years after enrolment in the study, he was discontinued from GHB apparently (as per a note from Dr Scharf dated March 15, 2001) on account of inconsistent compliance with all his medications. Dr Scharf's

note also indicated that his parents had reported "bizarre behavior", that the patient had an increasing level of conflict with his roommate and that he had difficulty controlling his temper. These difficulties were attributed to concurrent use of dextroamphetamine to treat daytime sleepiness.

He also experienced a number of episodes of sleepwalking while participating in the study. Heartburn, abdominal bloating and other gastrointestinal symptoms were also noted as was a rash attributed to contact dermatitis. Barrett's esophagus was diagnosed by endoscopy.

Based on a follow-up conversation with the patient, documented in a note dated 3/22/01, the patient confirmed that at the time when he discontinued GHB 8 years earlier he had been in conflict with his roommate, a difficulty that he had attributed to GHB. Subsequently he was very depressed but did not improve when GHB was stopped. His depression did however resolve 18 months after it began.

### **11.7 Psychopathology In Narcolepsy**

The sponsor has reviewed medical publications that describe the association between narcolepsy and neuropsychiatric symptoms. The contents of this review have been summarized below in Section 14.7.

### **11.8 Reviewer's Comments**

- I agree that in the majority of patients who developed neuropsychiatric adverse events while taking GHB in the Scharf trial it is not possible to attribute the cause of 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 an 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 above.
- These comments are identical to those in Section 14.8

## **12. Adverse Events Coded As "Convulsions" In Scharf Study**

### **12.1 Background And Methods**

At the request of the Division the sponsor further characterized all patients in the Scharf study who had adverse events that were coded under the COSTART terms of "convulsion" or "convulsion grand mal". These adverse events were as recorded through the NDA cut-off date of May 31, 1999.

In response to the above request the sponsor has performed an analysis of convulsions as follows:

- All patients who had the above COSTART-coded adverse events were selected
- For each patient with such an adverse event the following were determined
  - Dosage of GHB at the onset of each adverse event (calculated using the algorithm in Section 10.2)
  - Start and stop date for each adverse event calculated from the date of the first dose of trial medication in his or her first trial with GHB
  - Investigator terms used

## 12.2 Results Of Analysis

### 12.2.1 Number And Distribution Of Patients With "Convulsion(s)"

9/143 (6.3%) were recorded as having an adverse event that was coded as a "convulsion" or "convulsion grand mal."

Their distribution according to dose and severity is noted in the following table which I have copied from the submission. As the table indicates

- None of these instances lead to death
- This adverse event was serious in 1 patient
- This adverse event lead to study medication discontinuation in 2 patients
- This adverse event did not appear to be dose-related

Neuropsychiatric: All Events	Total *	Sodium Oxybate Oral Solution Dosage (g/d) at Onset <sup>b</sup>				
		3.0	4.5	6.0	7.5	9.0
Number of Convulsion AE's	20					
Patients with at Least 1 AE	9 <sup>c</sup>	0	0	5	2	2
Patients with SAEs	1	0	0	0	0	1
Patients with Related AEs	1	0	0	0	0	1
Patients with Severe AEs <sup>d</sup>	1	0	0	0	0	1
Patient Discontinuation due to an AE	2	0	0	1	1	0
Patient Deaths	0	0	0	0	0	0

\* Patients are counted only once in each category at the highest dose at onset.

<sup>b</sup> Dosage at onset.

<sup>c</sup> 3 patients experienced more than one AE designated as COSTART preferred term Convulsion or Convulsion Grand Mal

<sup>d</sup> 1 patient experienced 3 AEs coded as severe.

### 12.2.2 Investigator Terms

Verbatim investigator terms for all patients recorded to have a "convulsion" or "convulsions" are in the following table copied from the submission.

Patient ID	COSTART Term	Verbatim Term	Dose (g) <sup>a</sup>
043	Convulsion	Excessive cataplexy	6.0
048 <sup>b</sup>	Convulsion	Convulsive-like seizure	8.3
049	Convulsion	Fall, sudden cataplexy	6.0
051	Convulsion	Fell twice, with cataplexy	6.0
064	Convulsion	Seizure	7.5
		Seizure	6.0
		Seizure	6.0
		Seizure during the morning	6.0
		Seizure in the morning	6.0
		Another seizure in afternoon	6.0
		Seizure in the morning	6.0
219	Convulsion	Cataplexy, twice <sup>c</sup>	7.5
247	Convulsion	Seizures, continuous jerking	6.0
255 <sup>d</sup>	Convulsion Grand Mal	Brief grand mal seizure	5.3
257	Convulsion	Violent shaking and vibrations	5.3
		Jerking during cataplexy	9.0
		Bad cataplexy	9.0
		Cataplexy	12.0
		Fall from cataplexy caused him to hit his head on furniture increase in cataplexy resulted.	11.3

<sup>a</sup> Dose recorded is the dose at the onset of the adverse event.

<sup>b</sup> This event was serious and determined to be related to study medication.

<sup>c</sup> Two cataplexy events captured as separate AEs in the data listings.

<sup>d</sup> Patient 255 had a history of seizures of unknown etiology at enrollment.

As the above table indicates

- Adverse events coded to the term "convulsion" were all episodes of cataplexy in the case of 4 patients: #s 01-43, -49, -51 and -219.
- In the case of Patient # 01-257, the majority of the events coded under the term "convulsion" represented attacks of cataplexy
- Based on investigator terms the events in Patients 01-48, -64, -247 and -255 did not appear to be attacks of cataplexy

Narratives are provided below for all patients who had episodes coded as "convulsion"/"convulsion grand mal" that did not appear to be cataplectic attacks. Although the same narratives are provided elsewhere in the review they are reproduced here for convenience

## **12.3 Narratives For Patients With Non-Cataplectic Convulsions**

### **12.3.1 Patient # 01-048**

This patient was a 27 year old woman with a history of febrile seizures at age 2 and of narcolepsy for 8 years. Concomitant medications at study entry included dextroamphetamine, diazepam, flurazepam, methylphenidate (immediate and controlled-release), imipramine and meprobamate.

The day she entered the study, and while taking a dose of 6 g/day she felt dizzy, noted twitching of her face, had palpitations and was laughing continuously. According to the Case Report Form this cluster of adverse events lasted 3 days. This event presumably began after she received the drug as the relationship to the drug is listed in the Case Report Form as being "unknown."

About a week after she entered the study she was reported to be disoriented on a single day; at that time she was also taking GHB in a dose of 6 g/day. Further details of this episode are unavailable. A further week later she was again disoriented/confused on a single day; she was believed to be continuing to take 6 g/day of GHB at that time. Further details of that episode are also unavailable.

About 5 months after study entry she woke sweating, numb, tingling from head to toe, heard a loud roaring, had a dry mouth and felt disoriented, dizzy and was breathing in a "strange" way. She was still taking GHB in a dose of 6 g/day at that time. She called her neurologist who suggested that the episode was an anxiety attack and recommended diazepam (which she did not have available) and re-breathing from a bag that she had expired into

About 11 months after entering the Scharf study and while taking a GHB dose of 7.5 g/day she had an episode of urinary incontinence which occurred on the same date as complaints of "numbness all over", confusion, night sweats, shortness of breath and nausea.

A further 5 years later she reported an episode of urinary incontinence that occurred at the same time (as recorded in a source document) as a "convulsive-like" seizure; she appears to have been receiving GHB in a dose of 8.3 g/day at that time. She was hospitalized and testing revealed a normal EEG and negative urine and serum drug screens.

About 1 ½ years after study entry she was reported to be behaving in a bizarre manner at work: she raised the ambient temperature to 95 degrees F using the thermostat, was continually drinking Coca-Cola®, appeared pale and was noted to stagger and to have hiccups. She was taking GHB in a dose of 6 g/day at that time. Both GHB and triazolam, which she was also taking were discontinued; GHB alone was re-started initially in a dose of 3 g/day with the dose being increased later to 6 g/day. During the period of study drug interruption an EEG was done which was reported to be normal.

The narrative supplied states (apparently on the basis of information in the source document) that about 3 years after she first entered the study a concern was raised by her physician that she was misusing triazolam which he then declined to prescribe, leading to her seeing 2 other physicians within the next 3 months. A further 2 years later she was reported to be taking triazolam, clobazam and propoxyphene-acetaminophen without informing the investigator.

The patient's participation in the Scharf study was terminated by the investigator 2 days after the above "convulsive-like" seizure occurred. A week after termination of participation in the study she informed site personnel that she was taking GHB without permission

### **12.3.2 Patient # 01-064**

This patient (initials \_\_\_\_\_), was 13 years old at the time of study entry. 2 years prior to entering the study she had sustained a fall, was stated to have sustained a concussion and was found on CT scan to have a

left frontal cyst; a burr hole procedure was apparently done at the time she had her head injury. After her fall she began experiencing excessive daytime sleepiness and, later, cataplexy. The narrative states that "polysomnogram testing confirmed the diagnosis of narcolepsy."

Concomitant medications at study entry included slow-release methylphenidate (dose unspecified) and protriptyline 10 mg t.i.d. Her medical history was also remarkable for a scoliosis.

She is believed to have participated in the Scharf study for about 2 years, although the date of her last dose is uncertain. Her dose of GHB during the trial ranged from 3 g/day to 7.5 g/day with the most common dose being 6 g/day.

During the Scharf trial she had 7 "seizures" (investigator term). Descriptions of these episodes are unavailable. Treatment with carbamazepine and divalproex sodium was apparently initiated; both drugs appear to have been used at separate times. After the 7<sup>th</sup> episode she was instructed to stop both divalproex and GHB. An EEG was reported to show "slow discharges" from the "anterotemporal frontal area of the brain (i.e., the region of the brain cyst)" but the narrative does not indicate whether the discharges did in fact originate from the left frontal region.

Headaches and vomiting were among the other adverse events noted during the study. The etiology of these was unclear.

A phone conversation with the patient's mother on 3/21/01, about 12 years after the patient discontinued from the Scharf study, indicated that the patient continued to have seizures of 3 different types, always at night.

Dr Moe's letter indicates that

- Carbamazepine was unhelpful for her seizures and divalproex was used instead
- On one occasion she was found to have a bitten tongue which was presumed to have been due to a seizure
- An EEG on 4/26/99 showed left frontal spike-wave discharges

### 12.3.3 Patient # 01-247

This patient was a 33 year old woman with a preceding history of urinary incontinence and of psychiatric illness with multiple hospitalizations; her psychiatric illnesses apparently included major depression and a suicide attempt. Medications at study entry included L-tyrosine, methylphenidate, temazepam, dextroamphetamine, imipramine, protriptyline, fluoxetine and alprazolam. The Case Report Form indicates that in addition to a diagnosis of narcolepsy, the possibility that she could have had obstructive sleep apnea could not be excluded.

At least 11 episodes of incontinence are documented in the Case Report Form, prior to the episode described in the next paragraph. Details of those episodes are unavailable; no concomitant symptoms are recorded.

About 9 months after study entry and while ostensibly taking a GHB dose of 6 g/day she reported having a "seizure" ("continuous jerking all over"). Although the sponsor's narrative states that this episode occurred in conjunction with an episode of incontinence that is not clearly documented in the Case Report Form.

A source document indicates that although the frequency of her attacks of cataplexy improved with GHB she had increasing difficulty sleeping after her second dose of GHB; her physician felt that she was depressed and treated her with triazolam 0.25 mg daily beginning 2 months before her seizure and after discontinuing temazepam which she was taking earlier. 3 days after withdrawing from triazolam she had a seizure.

She then withdrew from the Scharf trial but over a year later requested that she be enrolled again because of poor control of cataplexy (she was apparently not re-enrolled). At that time she attributed her "seizure" to excessive use of GHB and concomitant alcohol use in the setting of depression and accompanying a failing marriage.

About 2 months after beginning study drug she was reported to have an episode of sleep-walking.

#### **12.3.4 Patient # 01-255**

This patient was a 46 year old man who reportedly had 2 seizures, 7 months and 4 months prior to entry into the Scharf study: details of these seizures are unavailable. He was also paranoid and was reported to have difficulty controlling his temper. Medications at study entry included imipramine, phenytoin, dextroamphetamine, and pemoline. He was recorded as having obstructive sleep apnea in addition to narcolepsy, and impaired vision caused by macular degeneration.

About 10 months after study entry and while taking GHB in a dose of 5.3 g/day he had urinary incontinence in a doctor's office at the same time that he had what was described as a "brief grand mal seizure". Surprisingly the Case Report Form has no record of this episode; neither have any source documents been supplied to substantiate this possibility.

GHB was apparently continued with the patient participating in the study for at least 7 years.

While participating in the study he apparently had multiple episodes of sleep walking. Early in the study he reported nausea, dizziness and periods of depression, as well as a feeling of frustration and panic early one morning. About 7 years into the study he was recorded as having an episode of bedwetting.

#### **12.3.5 Patient # 01-257**

This patient was a 32 year old man. In the year prior to his entry into the Scharf study he was involved in an automobile accident that reportedly resulted in a whiplash injury and a concussion, as well as residual tingling in his hands, and weakness in his upper body. In addition to having narcolepsy he had also been diagnosed to have obstructive sleep apnea. Concomitant medications at study entry included protriptyline, methylphenidate, buspirone and methamphetamine.

About 1 month after study entry he was recorded as having the following symptoms: excessive sweating, chills, blurred vision, memory loss and violent shaking and vibrations. At that time he was taking GHB in a dose of 5.3 g/day. Although the sponsor maintains that this episode was related to a bout of tonsillitis I am not able to substantiate that from the Case Report Form

About 8 months after he began taking GHB, and while he was receiving a dose of 9 g/day, he was described as being incontinent of urine and stool during events that were described as consisting of "intense body shaking" and "jerking during cataplexy". The patient had however continued to receive GHB since that time at least until 8 years after study entry without any recurrence of the same events. However about 6 years after he began taking the study drug he had episodes of bedwetting and sleep walking at a time when he was taking GHB in a dose of 12 g/day.

About 5 years after study entry he fell on a butcher's knife which penetrated his abdomen and exited from his back injuring his colon. The mechanism of this incident has not been described, but other falls due to attacks of cataplexy have been noted in the Case Report Form.

Among the more common adverse events reported during the study were nausea, headache, feelings of weakness and jitteriness.

His Case Report Form also records an episode, 8 years after he began taking GHB, of "periods of apnea and hypoxemia" leading to an emergency hospitalization and intubation. This adverse event apparently resolved in a day, but further details are unavailable.

As noted above, this patient did not discontinue from the Scharf study

#### **12.4 Reviewer's Comments**

- It appears to be widely recognized that muscle twitching can accompany attacks of cataplexy.
- Assuming that Patient # 01-064 did have seizures, they were in all likelihood related to her left frontal lobe lesion and not to GHB.
- Patient # 01-255 is unlikely to have had true convulsions
- Patients 01-247 and 01-048 may have had seizures. In addition it is possible that the episodes were causally related to GHB use. However
  - In Patient 01247 the reported seizure could have also been related to alcohol or triazolam withdrawal
  - In Patient 01048 the concurrent abuse/withdrawal of other drugs such as benzodiazepines is a possible mechanism for her reported seizure

### **13. Adverse Events Coded As "Confusion" In Integrated Clinical Trials**

#### **13.1 Background and Methods**

At the Division's request adverse events coded using the preferred term "confusion" in the updated Integrated Clinical Trials database (including the 120-Day Safety Update) were characterized further.

The dosage at onset of each adverse event was determined and the start and stop dates for the adverse events recorded.

A tabular summary of all patients who had such an adverse event was prepared. Narrative summaries were prepared for all patients in whom this was a serious adverse event or led to treatment discontinuation.

#### **13.2 Overall Summary**

30/402 (7.5%) GHB-treated patients had at least one adverse event coded under the preferred term "confusion." Their distribution by dose and severity is displayed in the following table which I have copied from the submission.

Confusion: All Events	Total <sup>a</sup>	Placebo	Total <sup>a</sup>	Xyrem Oral Solution Dosage (g/d) at Onset <sup>b</sup>				
				3.0	4.5	6.0	7.5	9.0
Number of patients	402 (100%)	54 (100%)	399 (100%)	97 (100%)	269 (100%)	290 (100%)	133 (100%)	129 (100%)
Patients with at Least 1 AE	30 (7%)	1 (2%)	29 (7%)	4 (4%)	6 (2%)	11 (4%)	6 (5%)	10 (8%)
Patients with SAEs	2 (<1%)	0	2 (<1%)	0	0	1 (<1%)	0	1 (1%)
Patients with Related AEs	29 (7%)	1 (2%)	28 (7%)	3 (3%)	6 (2%)	10 (3%)	6 (5%)	10 (8%)
Patients with Severe AEs	4 (1%)	0	4 (1%)	0	2 (1%)	1 (<1%)	0	1 (1%)
Patient Discontinuation due to an AE	3 <sup>c</sup> (<1%)	0	3 <sup>c</sup> (<1%)	0	0	1 (<1%)	0	2 <sup>c</sup> (1%)
Patient Deaths	0	0	0	0	0	0	0	0

<sup>a</sup> Patients are counted only once in the total column.

<sup>b</sup> Some patients were exposed to more than 1 dosage during the trial(s), so the sum of patients exposed to specific dosages exceeds the total number of patients in the integrated clinical trials.

<sup>c</sup> Patient 2632 (9.0 g/d) discontinued due to "patient request" (confirmed by further medical review); therefore, this patient is not included here. However, the AEs of headache/confusion were contributing factors.

As the table above indicates

- In 2/402 (0.5%) of patients, "confusion" was considered to be a serious adverse event
- In 3/402 (0.7%) of patients, "confusion" led to adverse event discontinuation
- This adverse event did appear to be more common at higher doses of GHB
- In 29/30 patients the investigator felt that this adverse event was drug-related.

Note that a proportion of patients experienced adverse events coded under the term "confusion" on more than one occasion and in more than 1 trial

### 13.3 Verbatim Investigator Terms

The actual investigator terms were in the following categories

Investigator Term	Number of Patients
"Confusion"	15
"Acute confusional state"	
"Confusion on awaking"	
"Disoriented"	14
"Disoriented on awaking"	
"Disorientation"	
"Confusion/disorientation"	1
"Feeling 'drunk' after taking drug"	3
"Dazed feeling"	1
"Couldn't comprehend"	1
"Woozy feeling"	1

Note that individual patients may have had several episodes occurring under the same investigator term or category of investigator term

### 13.4 Tabular Summary

The sponsor has provided a table for all 30 patients who had an adverse event coded using the preferred term "confusion". The table provides the following data: patient ID #, trial #, sex, age, dosage at onset of confusion, start and stop date for adverse event, investigator term, whether serious or not, action taken, frequency, relationship to study drug, severity and relevant medical history.

I have not reproduced the table in this review.

The following items are noteworthy in the table

- The 30 patients had a total of 48 adverse events coded as "confusion"
- The actions taken for these adverse events were as follows
 

No change in dosage	37
Adjustment in dosage	4
Temporary discontinuation of GHB	4
Permanent discontinuation of GHB	3

This 67 year old man was enrolled in Study OMC-SXB-6. His past medical history was remarkable for a stomach ulcer, gastroesophageal reflux disease, and a cholecystectomy. Concomitant medications at study entry included clomipramine, methylphenidate, paroxetine, imipramine and modafinil.

He took Xyrem® in a dose of 4.5 g/day for 12 days and 9 g/day for 106 days. After having been on a stable dose of 9 g/day for 106 days he awoke about 1 hour after his second nightly dose feeling dizzy and confused. On getting out of bed he felt nauseated and vomited after reaching the bathroom. He felt a sensation of "shut down" and difficulty breathing, crawled from the bathroom to lie down in the hallway until he felt well enough to return to bed about 1 ½ hours after the episode began. Frequent cataplexy attacks apparently accompanied the episode. After returning to bed he slept soundly and awoke the next morning feeling well. The same day he contacted the Principal Investigator and withdrew from the study. He was never hospitalized or seen in an emergency room.

At the time the episode occurred his concomitant medications included a multivitamin, DGL (a herbal preparation), an unspecified medication for gastroesophageal reflux and methylphenidate.

The episode occurred on 7/27/99. A follow-up phone call from the study coordinator on 3/19/01 indicated that no further such episodes had occurred.

### **13.7 Narratives For Patients With Confusion As An Adverse Event Warranting Permanent Discontinuation Of GHB**

I have read the sponsor's narratives supplemented by Case Report Forms when needed

#### **13.7.1 Patient 0207 (Initials**

See Section 13.6.1

#### **13.7.2 Patient 0231 (Initials**

See Section 13.6.2

#### **13.7.3 Patient # 0702 (Initials**

This 59 year old woman participated in Study OMC-GHB-2. She had a past history of narcolepsy with cataplexy, cirrhosis and a left facial palsy. Concomitant medications included ipratropium bromide and albuterol.

She received OMC-GHB-2 in a dose of 9 g/day. 20 days later she began experiencing confusion, hallucinations and forgetfulness followed in the next 2 days by nausea and paranoia. Study medication was discontinued when these symptoms began and her symptoms resolved 5 days later.

### **13.8 Reviewer's Comments**

- As records for contemporaneous formal mental status examinations for patients with "confusion" are unavailable it is unclear if all patients coded as having this adverse event were really confused, as the term is conventionally understood. Investigator terms suggest that at least some patients may not have been confused
- Nevertheless, the information available 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

- (e.g., 3 g/day) 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 surprising for a sedative drug.

## 14. Neuropsychiatric Adverse Events In Integrated Clinical Trials

### 14.1 Background

At the Division's request neuropsychiatric adverse events in the updated Integrated Clinical Trials database (including the 120-Day Safety Update) were characterized further by the sponsor. The cut-off date for the 120-Day Safety Update was 9/30/00.

The sponsor's methods were as follows:

- Adverse events coded under the following preferred terms were selected from the above: overdose, coma, death, depression, hallucinations, intentional overdose, manic depressive reaction, overdose, paranoid reaction, personality disorder, psychosis, stupor, suicide, and suicide attempt.
- Source documents, Case Report Forms and data listings were reviewed for the above patients
- Tabular and narrative summaries of events were then constructed. Narratives were prepared for deaths, serious adverse events and adverse event discontinuations.
- A review of the literature relevant to the incidence of neuropsychiatric adverse events in narcolepsy was completed
- The dosage at onset of each adverse event was determined and the start and stop dates for the adverse events recorded.

### 14.2 Overall Summary

50/402 (12.4%) GHB-treated patients had at least one adverse event coded under one or more of the neuropsychiatric adverse event terms outlined in Section 14.1. Their distribution by dose and severity is displayed in the following table which I have copied from the submission.

Possible Neuropsychiatric AEs	Total <sup>a</sup>	Placebo <sup>b</sup>	Xyrem Oral Solution Dosage (g/d) at Onset <sup>c</sup>				
			3.0	4.5	6.0	7.5	9.0
Number of patients	402 (100%)	54 (100%)	97 (100%)	269 (100%)	290 (100%)	133 (100%)	129 (100%)
Patients with ≥ 1 AE	50 (12%)	1 (2%)	5 (5%)	6 (2%)	24 (8%)	4 (3%)	14 (11%)
Patients with SAEs	7 (2%)	0	0	2 (1%)	2 (1%)	0	3 (2%)
Patients with related AEs	26 (6%)	1 (2%)	1 (1%)	3 (1%)	11 (4%)	0	12 (9%)
Patients with severe AEs	0 (2%)	0	0	3 (1%)	4 (1%)	0	3 (2%)
Patients discontinued due to AEs	10 (2%)	0	0	3 (1%)	2 (1%)	0	5 (4%)
Patient deaths due to AEs	1 (1%)	0	0	0	1 (1%)	0	0

<sup>a</sup> Patients are counted only once in each total column.

<sup>b</sup> Patients were on placebo for a short time (4 weeks) relative to the long-term exposure of those treated with Xyrem. Some patients were exposed to more than 1 dosage during the trial(s), so the sum of patients exposed to specific dosages exceeds the total number of patients in the integrated clinical trials.

As the table above indicates

- 1 death was associated with a neuropsychiatric adverse event
- 7/402 (1.7%) patients had a serious neuropsychiatric adverse event
- 10/402 (2.5%) patients discontinued treatment on account of a neuropsychiatric adverse event

- Such adverse events did appear to have their highest incidence at the 9 g/day dosage

Note that 2 prominent neuropsychiatric adverse events were not included in the above table

- Patient # 14043, participating in Study OMC-SXB-7, who had obsessive compulsive disorder survived a suicide attempt. This patient was not included in the table as the suicide attempt was, based on an incorrectly entered date in a Case Report Form, mistakenly considered to have occurred about 6 weeks after treatment ended. In fact she was still a participant in the trial when the suicide attempt was made
- Patient # 0936, participating in Study OMC-SXB-7, who had a previous history of depression **died** from what was believed to be an overdose of multiple drugs. The event occurred on 2/24/01, 5 months after the cut-off date for the 120-Day Safety Update.

### 14.3 Distribution Of Individual Neuropsychiatric Adverse Events

The distribution of individual COSTART-coded neuropsychiatric adverse events is as illustrated in the following table

Note that patients may have had adverse events in more than one category

COSTART Term	Number Of Patients
Total	50
Depression	27
Stupor	6
Suicide Attempt (including Overdose and Intentional Overdose)	4
Paranoid Reaction	4
Coma	2
Psychosis	2
Manic Depressive Reaction	1
Personality Disorder	1

### 14.4 Specific Neuropsychiatric Adverse Events

#### 14.4.1 Depression

The sponsor has provided a table summarizing all patients coded to have the COSTART preferred term "depression."

The table provides the following data: patient ID #, trial #, sex, age, dosage at onset of confusion, start and stop date for adverse event, investigator term, whether serious or not, action taken, frequency, relationship to study drug, severity and relevant medical history.

I have not reproduced the table in this review.

In regard to the table the following are noteworthy

- Verbatim investigator terms included "depression", "depressed mood", "situational depression", "down in the dumps", and "dysphoria". The sponsor points out that the COSTART term "depression" as used in this particular context is not equivalent to a psychiatric diagnosis of Major Depressive Disorder using DSM-IV criteria.
- 27 patients experienced a total of 30 adverse events coded as depression
- 26/27 patients were receiving GHB at the time of this adverse event and 1/27 placebo

- 3 patients had a recorded previous history of depression or bipolar disorder
- In none of the instances was depression considered a serious adverse event
- GHB was permanently discontinued in 2 patients and temporarily stopped in 2 additional patients
- 5 patients received antidepressant medication to control depressive symptoms
- No patient who attempted to or committed suicide is listed in the table

#### 14.4.2 Hallucinations

The sponsor has provided a table summarizing all patients coded to have the COSTART preferred term "hallucinations."

The table provides the following data: patient ID #, trial #, sex, age, dosage at onset of confusion, start and stop date for adverse event, investigator term, whether serious or not, action taken, frequency, relationship to study drug, severity and relevant medical history.

I have not reproduced the table in this review.

In regard to the table the following are noteworthy

- 9 patients had adverse events that were coded as hallucinations. In all 9 the investigator term also indicated that they had hallucinations.
- All 9 patients were receiving GHB at the time this adverse event appeared
- In 4/9 the hallucinations, based on the investigator term used, were hypnagogic hallucinations. In a further patient the hallucinations ceased with an increased dose of GHB and were therefore presumed to be hypnagogic hallucinations.
- The hallucinations were characterized in 4 patients (these were not patients with hypnagogic hallucinations): the hallucinations were auditory in 3 and visual in 1.
- In only 1 patient were hallucinations a reason for medication discontinuation. This patient has already been described (see Section 13.7.3)

#### 14.4.3 Stupor

The sponsor has provided a table summarizing all patients who had an adverse event coded using the preferred term stupor.

This table is below

Patient No.	Trial	Sex/Age (yr)	Dosage at Onset (g/d)	Trial Start	Day* Stop	Investigator Term	Serious/ Action Taken W/Study Drug	Frequency/ Relationship/ Severity	Relevant Medical History
0122	OMC-GHB-3	F/25.4	6.0	34	34	Felt drunk	No/no change	Intermittent/ unknown/mild	Narcolepsy, cataplexy <sup>c</sup>
0203	OMC-GHB-3	M/35.5	9.0 <sup>b</sup>	55	55	Intoxicated feeling	No/ temporarily stopped	Continuous/ probably related/ moderate	Narcolepsy, cataplexy <sup>c</sup>
0220	OMC-GHB-3	F/55.4	9.0	46	46	Like being drunk	No/no change	Continuous/ probably related/ moderate	Narcolepsy, cataplexy <sup>c</sup>
0222	OMC-GHB-3	F/25.7	6.0	39	39	Felt drunk after first dose	No/no change	Continuous/ possibly related/mild	Narcolepsy, cataplexy <sup>c</sup> Non-specific headaches
0814	OMC-GHB-3	M/55.7	4.5	56	56	Alcohol intoxication feeling	No/no change	Continuous/ possibly related/mild	Narcolepsy, cataplexy <sup>c</sup>
1279	OMC-GHB-3	F/49.7	6.0 <sup>b</sup>	66	66	Felt intoxicated	No/ temporarily stopped	Continuous/ possibly related/mild	Narcolepsy, cataplexy <sup>c</sup>

\* Day relative to first dose of Xyrem in first trial in the integrated database.  
<sup>b</sup> Dosage was carried forward from last known entry.  
<sup>c</sup> From OMC-GHB-2 medical history; no history was taken at entry into OMC-GHB-3.

Note that

- "Stupor" occurred in 6 patients, all of whom had only 1 episode of this adverse event
- Investigator terms suggested that all 6 patients did not have "stupor" in the sense in which the term is conventionally used in the medical literature (i.e., obtunded)
- In no patient was the adverse event serious or a reason for permanent study drug discontinuation
- As the sponsor has pointed out, such an adverse event is not unexpected given the sedative properties of GHB

14.4.4 Suicide Attempt

A total of 4 GHB-treated patients attempted to commit, or successfully committed suicide. These patients are summarized in the following table.

Patient ID #	Study	Sex/Age (years)	Duration Of Treatment With GHB At Time Of Adverse Event	GHB Dose At Time Of Adverse Event	Investigator Term And Details Of Episode	Pre-Existing Psychiatric History	Action Taken
0531	OMC-SXB-7	F/46.5	394 days	6 g/day	Death (suicide)	Bipolar Disorder	Not applicable
0936	OMC-SXB-7	F/52	18 months	6 g/day	Death from multiple drug overdose (suicide)	None recorded at time of study entry. During study was diagnosed to have bipolar disorder	Not applicable
1131	OMC-SXB-7	F/46.2	280 days	9 g/day	Conscious overdose (suicide attempt)	Depression, previous suicide attempt	Study drug discontinued
14043	OMC-SXB-7	F/26	11 years	9 g/day	Overdose (suicide attempt)	Obsessive-compulsive disorder	Study drug discontinued

The nature of the overdose in the case of the above patients was as follows

Patient ID #	Nature Of Overdose
0531	Multiple drugs including, possibly, GHB
0936	Multiple drugs including GHB
1131	GHB only
14043	Bupirone

The sponsor points out that neither of the above fatalities was due to an overdose of GHB alone

#### 14.4.5 Paranoia

The sponsor has provided a table summarizing all patients coded to have the COSTART preferred term "paranoia."

These patients are summarized in the following table which I have copied from the submission

Patient No.	Trial	Sex/ Age (yr)	Dosage at Onset (g/d)	Trial Day <sup>a</sup>		Investigator Term	Serious/ Action Taken W/Study Drug	Frequency/ Relationship/ Severity	Relevant Medical History
				Start	Stop				
0202	OMC-GHB-3	F/ 61.7	6.0	431	433	Mild paranoia due to hypnagogic hallucinations	No/no change	Intermittent/ unknown/mild	Narcolepsy, cataplexy <sup>b</sup>
	OMC-GHB-3	F/ 61.7	6.0	444		Complained of "feeling paranoid" <sup>c</sup>	No/no change	Intermittent/ possibly related/mild	Narcolepsy, cataplexy <sup>b</sup>
0232	OMC-SXB-7	F/ 44.4	9.0	476	489	Acute paranoid delusional psychosis	Yes/ discontinued	Continuous/ probably related/ severe	Narcolepsy, cataplexy, headache and migraine
0239	OMC-SXB-6	F/33.1	4.5	17	18	Feeling paranoid	No/no change	Continuous/ not related/ moderate	Narcolepsy, cataplexy, Depression, anxiety,
0702	OMC-GHB-2	F/59.7	9.0	22	24	Paranoia	No/ discontinued	Intermittent/ probably related/mild	Narcolepsy, cataplexy, headache, Thyroid surgery; cold nodule removed, Rowan replacement thyroid hormone

<sup>a</sup> Day relative to first dose of Xyrem in first trial in the integrated database.  
<sup>b</sup> From OMC-GHB-2 medical history; no history was taken at entry into OMC-GHB-3.  
<sup>c</sup> This AE was also recorded at trial entry for OMC-SXB-7.

As is evident from the above table

- 4/402 (1%) of patients experienced paranoia as an adverse event: in each instance the COSTART term matched the investigator term
- In only 1 patient was this adverse event serious and sufficient to lead to treatment discontinuation
- A previous history of depression and anxiety was present in one patient

#### 14.4.6 Coma

The 2 patients who were coded as having this adverse event are summarized in the following table which I have copied from the submission

Patient No.	Trial	Sex/Age	Dosage at Onset (g/d)	Trial Day <sup>a</sup>		Investigator Term	Serious/Action Taken W/Study Drug	Frequency/Relationship/Severity	Relevant Medical History
				Start	Stop				
0238	OMC-SXB-6	M/64.3	4.5	170	170	Non-responsive	Yes/discontinued	Continuous/probably related/severe	Narcolepsy, cataplexy
2830	OMC-SXB-6	F/41.9	6.0	106	106	Knocked out	No/no change	Isolated/possibly related/severe	Narcolepsy Depression
	OMC-SXB-6	F/41.9	6.0	173	173	Knocked out	No/no change	Isolated/possibly related/severe	See history above

<sup>a</sup> Day relative to first dose of Xyrem in first trial in the integrated database.

The following additional observations can be made

- Only one 1 patient was this adverse event serious and sufficient to lead to GHB discontinuation
- Patient # 2830 is described as falling repeatedly due to cataplexy, striking her head against an object and losing consciousness

The sponsor points out that neither of these adverse events could be considered a neuropsychiatric adverse event

#### 14.4.7 Psychosis

The 2 patients for whom the COSTART term "psychosis" was used are summarized in the following table which is copied from the submission

Patient No.	Trial	Sex/Age (yr)	Dosage at Onset (g/d)	Trial Day <sup>a</sup>		Investigator Term	Serious/Action Taken W/Study Drug	Frequency/Relationship/Severity	Relevant Medical History
				Start	Stop				
1101	OMC-GHB-3	M/39.4	4.5	156		Acute psychosis	No/discontinued	Continuous/possibly related/moderate	Narcolepsy, cataplexy, Congenital exotropia, Headaches, Bizarre dreams, Poor concentration and attention <sup>c</sup> schizophrenia <sup>d</sup>
2030	OMC-SXB-7	M/18.3	9.0 <sup>b</sup>	202	202	Brief reactive psychosis	No/no change	Intermittent/definitely related/moderate	Narcolepsy
	OMC-SXB-7	M/18.3	9.0 <sup>b</sup>	207	214	Brief reactive psychosis	Yes/discontinued	Continuous/possibly related/severe	Narcolepsy

<sup>a</sup> Day relative to first dose of Xyrem in first trial in the integrated database.  
<sup>b</sup> Dosage was carried forward from last known entry.  
<sup>c</sup> From OMC-GHB-2 medical history; no history was taken at entry into OMC-GHB-3.  
<sup>d</sup> Not disclosed at screening.

As the table indicates

- The COSTART term matched the investigator term in each instance
- Both patients discontinued GHB on account of this adverse event; in one patient the adverse event was considered serious
- One patient had a pre-existing history of schizophrenia

#### 14.4.8 Manic Depressive Reaction

The single patient who had this adverse is summarized in the next table

- Medical conditions that the sponsor felt be relevant to the adverse event of "confusion" were present in 7/30 patients: these included multiple sclerosis, hypothyroidism, sleep apnea, and previous head injury.
- 20/30 (66.7%) were over 50 years of age
- 26 such adverse events occurred during the first 60 days of treatment
- All such adverse events eventually resolved

### **13.5 "Confusion" In Study OMC-GHB-2**

In this randomized, double-blind, placebo-controlled trial of 4 weeks' duration 10 patients receiving GHB and 1 patient receiving placebo experienced confusion

The distribution of this adverse event by dose group, based on the sponsor's table described in Section 13.4 was as follows

Dose Group	Total Number Randomized	Number of Patients with Confusion	Percentage of Patients with Confusion	Number (%) Permanently Discontinuing Treatment On Account Of Confusion
Placebo	34	1	2.9%	0 (0%)
3 g/day	34	3	8.8%	0 (0%)
6 g/day	33	1	3.0%	1 (3.0%)
9 g/day	35	6	17.1%	1 (2.9%)

The sponsor has drawn attention to the following:

- The highest incidence of confusion was at the 9 g/day dose
- 6/10 GHB-treated patients (4/6 patients treated with 9 g/day) developed confusion during the first week of drug exposure
- 7/10 GHB-treated patients with confusion were > 50 years of age

The sponsor attributes the high incidence of confusion in this short trial to the assignment of patients to fixed doses of GHB without titration.

### **13.6 Narratives For Patients With Confusion As A Serious Adverse Event**

I have read the sponsor's narratives and supplemented them with Case Report Forms when needed.

#### **13.6.1 Patient 0207 (Initials)**

This 53 year old woman participating in OMC-GHB-2 had a past medical history of narcolepsy with cataplexy, and fibromyalgia. Several close family members had died shortly prior to her entering the Scharf trial. The patient's father was reportedly a manic-depressive. Concomitant medications included imipramine, estrogen and testosterone, progestin, methylphenidate and a laxative.

She 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. She was seen at an emergency room where neurological examination was remarkable for hyperreflexia. 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.

#### **13.6.2 Patient 0231 (Initials)**

This patient's narrative is also reproduced in Section 17.2

Patient No.	Trial	Sex/Age (yr)	Dosage at Onset (g/d)	Trial Day*		Investigator Term	Serious/ Action Taken w/Study Drug	Frequency/ Relationship/ Severity	Relevant Medical History
				Start	Stop				
0931	OMC-SXB-7	F/28.9	4.5	284	400	Bipolar affective disorder	Yes/ discontinued	Continuous/ not related/ severe	Narcolepsy Migraine <sup>b</sup> Depression <sup>c</sup>

\* Day relative to first dose of Xyrem in first trial in the integrated database.  
<sup>b</sup> From OMC-SXB-6 medical history.  
<sup>c</sup> Not disclosed at screening.

Note that this patient had a prior history of depression

#### 14.4.9 Personality Disorder

The patient outlined in the next table experienced a prolonged grief reaction (coded using the COSTART term of "personality disorder") following the death of a relative. The event appears to have resolved without cessation of study medication.

Patient No.	Trial	Sex/Age (yr)	Dosage at Onset (g/d)	Trial Day*		Investigator Term	Serious/ Action Taken w/Study Drug	Frequency/ Relationship/ Severity	Relevant Medical History
				Start	Stop				
1530 <sup>b</sup>	OMC-SXB-6	F/25.1	6.0	139	430	Grief reaction	No/no change	Intermittent/ not related/mild	Narcolepsy, cataplexy, Skin hurts (in random patches)

\* Day relative to first dose of Xyrem in first trial in the integrated database.  
<sup>b</sup> This AE was also recorded (as COSTART preferred term depression) at trial entry for OMC-SXB-7.

### 14.5 Narratives For Deaths Associated With Neuropsychiatric Adverse Events, Serious Neuropsychiatric Adverse Events, and Discontinuations Due To Neuropsychiatric Adverse Events

These narratives are below

#### 14.5.1 Patient # 0932 (Initials)

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

#### 14.5.2 Patient # 0531 (Initials)

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 6<sup>th</sup> 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%

#### 14.5.3 Patient # 0936 (Initials)

This 52 year old woman participated first in Study OMC-SXB-6, and then in OMC-SXB-7. She has a past medical history of narcolepsy with cataplexy, surgery for obesity and depression.

She received Xyrem® for a total of about 18 months. About 3 days before her death she saw a psychiatrist who diagnosed a possible bipolar disorder and prescribed lithium and paroxetine.

She was found dead in her home. Based on what remained of her supply of GHB she was believed to have consumed about 600 mL over 3 days. Prescription bottles for lithium (which should have contained about 60 tablets of uncertain strength), paroxetine (which should have contained about 45 tablets of uncertain strength) and oxycodone-acetaminophen were found to be empty. A full medical examiners report is pending but she was felt by the investigator to have died of an overdose of multiple drugs.

Earlier during the study she had been hospitalized twice on account of kidney stones. Other medications prescribed during the study were cephalexin and iron supplements

#### 14.5.4 Patient # 1131 (Initials)

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®.

#### 14.5.5 Patient # 14043 (Initials)

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.

#### **14.5.6 Patient # 0232 (Initials)**

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.

#### **14.5.7 Patient # 0238 (Initials)**

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 around midnight, 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.

#### **14.5.8 Patient # 2030 (Initials)**

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.

#### **14.5.9 Patient # 0931 (Initials)**

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.

#### **14.5.10 Patient # 0204 (Initials)**

This 60 year old woman received GHB in OMC-GHB-3. At the time of her entry into the study, and prior to receiving GHB she was irritable, depressed and had difficulty awaking. Her only concomitant medication included acetaminophen.

During her participation in the trial she reported continued depression and insomnia. She received GHB initially in a dose of 6.0 g/day and later in a dose of 9 g/day. 19 days after first entering the study she discontinued participation on account of a lack of efficacy

#### **14.5.11 Patient # 0213 (Initials)**

This 60 year old man participated in OMC-GHB-3 prior to which he had received GHB for about 4 months. He did not have a past medical history of depression.

He entered the OMC-GHB-3 study on a dose of 6 g/day. While in this study his dose was increased to 9 g/day; it was later reduced to 3 g/day on account of a depressed mood and excessive tiredness. After temporary interruptions of treatment to see if he improved, he eventually discontinued taking the drug permanently following which these adverse events resolved

#### **14.5.12 Patient # 0702 (Initials)**

This 59 year old woman participated in Study OMC-GHB-2. She had a past history of narcolepsy with cataplexy, cirrhosis and a left facial palsy. Concomitant medications included ipratropium bromide and albuterol.

She received OMC-GHB-2 in a dose of 9 g/day. 20 days later she began experiencing confusion, hallucinations and forgetfulness, followed in the next 2 days by nausea and paranoia. Study medication was discontinued when these symptoms began and her symptoms resolved 5 days later.

#### **14.5.13 Patient # 1101 (Initials)**

This 39 year old man participated in Study OMC-GHB-3. At the time of entry into the study he was receiving dextroamphetamine and methylphenidate, both of which had been taken for about a year.

He received GHB for about 6 months, last in a dose of 4.5 g/day. After 6 months of treatment he developed an "acute psychosis" leading to discontinuation of all stimulant drugs. About 2 months prior to that, methylphenidate had been discontinued and amphetamine-dextroamphetamine substituted. GHB was discontinued 2 weeks later.

4 years later the patient remained psychotic.

### **14.6 Experience With Neuropsychiatric Adverse Events In Controlled Clinical Trial OMC-GHB-2**

This section was created by the reviewer and is not part of the sponsor's presentation.

As noted earlier this was a 4-week randomized, double-blind, placebo-controlled, parallel-arm study comparing 3 doses of GHB with placebo. I have chosen this study as it constitutes the only parallel-arm

Adverse events that could be considered neuropsychiatric are summarized in the following table. Percentages are in parentheses. As the table indicates the number of neuropsychiatric adverse events seen in this study was too small, and without a clear overall pattern in relation to study drug/dose, to draw inferences.

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)
Anxiety	1 (2.9)	1 (2.9)	0	2 (5.7)
Dream Abnormal	0	0	3 (9.1)	1 (2.9)
Thinking Abnormal	0	1 (2.9)	0	2 (5.7)
Insomnia	1 (2.9)	0	0	0
Depression	0	1 (2.9)	0	0
Nervousness	3 (8.8)	1 (2.9)	2 (6.1)	3 (8.6)
Paranoid Reaction	0	0	0	1 (2.9)
Hostility	0	0	1 (3.0)	0
Hallucinations	0	0	1 (3.0)	1 (2.9)
Emotional Lability	2 (5.9)	2	0	0
Euphoria	0	0	1 (3.0)	0

Adverse events that could be considered neuropsychiatric and led to treatment discontinuation are summarized in the next table

Patient ID #	Patient Age and Gender	Treatment Group	Adverse Event (COSTART Term)	Duration of Treatment at Onset of Adverse Event	Outcome
818	53 F	Placebo	Insomnia	3 weeks	Resolved
605	20 M	GHB 9 g	Somnolence, thinking abnormal	8 days	Resolved
702	59 F	GHB 9 g	Confusion, hallucinations, amnesia, nausea and paranoid reaction	19 days	Resolved

### 14.7 Psychopathology In Narcolepsy

The sponsor has reviewed medical publications that describe the association between narcolepsy and neuropsychiatric symptoms.

Based on these publications the sponsor has drawn attention to the following

- A higher incidence of psychopathology, including depression, may be present in narcoleptic patients than in controls, based on retrospective case-control studies. Depressive symptoms have been reported to be present in about 50% of narcoleptics
- Psychiatric morbidity in narcoleptics may also be related to high-dose stimulant therapy.

The sponsor considers that in patients with narcolepsy, patient status (i.e., psychiatric status) is a “complicated and dynamic representation” of the following

- Disease-associated psychosocial morbidity.
- Stimulant-induced personality changes.
- Stress variations in daily life.

- Treatment-related co-morbidities.

#### **14.8 Reviewer's Comments**

- I agree that in the majority of patients who developed neuropsychiatric adverse events 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 above.

### **15. Adverse Events Coded As "Convulsions" In Integrated Clinical Trials**

#### **15.1 Background**

The following request was made to the sponsor by the Division  
10 patients are listed as having had "convulsions" (preferred term) in the Integrated Clinical Trials  
Please identify these patients

What were the investigator terms used in these instances?

What additional information is available about these episodes?

In response to the above request the sponsor has performed an analysis of convulsions as follows:

- All patients who had adverse events with the COSTART preferred term of "convulsion" or "convulsions" in the 5 Integrated Clinical Trials (OMC-GHB-2, OMC-GHB-3, Scrima, OMC-SXB-6 and OMC-SXB-7) were included in the analysis; the cut-off date for inclusion was 9/30/00 which was also the cut-off date for the 120-Day Safety Update
- For each patient with such an adverse event the following were determined
  - Dosage of GHB at the onset of each adverse event
  - Start and stop date for each adverse event calculated from the date of the first dose of trial medication in his or her first trial with GHB
  - Investigator terms used

#### **15.2 Results Of Analysis**

##### **15.2.1 Number And Distribution Of Patients With "Convulsion(s)"**

14 out of 402 patients (3%) were recorded as having an adverse event that was coded as a "convulsion" or "convulsions." All occurred during treatment with GHB

Their distribution according to dose and severity is noted in the following table which I have copied from the submission. As the table indicates none of these instances led to death, serious adverse events or adverse event discontinuations.

	Xyrem Oral Solution Dosage (g/d) at Onset							
	Total *	Placebo	Total *	3.0	4.5	6.0	7.5	9.0
Number of patients	402 (100%)	54 (100%)	399 (100%)	97 (100%)	269 (100%)	290 (100%)	133 (100%)	129 (100%)
Patients with ≥ 1 AE of convulsion	14 (3%)	0	14 (4%)	0	3 (1%)	5 (2%)	0	6 (5%)
Patients with convulsion SAEs	0	0	0	0	0	0	0	0
Patients with related convulsion AEs	7 (2%)	0	7 (2%)	0	1 (<1%)	4 (1%)	0	2 (2%)
Patients with severe convulsion AEs	2 (<1%)	0	2 (1%)	0	1 (<1%)	1 (<1%)	0	0
Patients discontinued due to convulsion AE	0	0	0	0	0	0	0	0
Patient deaths due to convulsion AE	0	0	0	0	0	0	0	0

\* Patients are counted only once in each category.

### 15.2.2 Investigator Terms

Verbatim investigator terms for all 14 patients recorded to have a “convulsion” or “convulsions” are in the following table copied from the submission.

Patient Number	COSTART Term	Verbatim Term
0221	Convulsion	Increase in major cataplexy attacks
0231	Convulsion	Increased duration of cataplectic events
0243	Convulsion	Increase partial cataplexy
0545	Convulsion	Increase in cataplexy <sup>a</sup>
0608	Convulsion	Increased cataplexy
0814	Convulsion	Seizures
0835	Convulsion	Increased cataplexy/ cataplexy <sup>b</sup>
1130	Convulsion	Cataplexy
1302	Convulsion	Increased cataplexy (significant) <sup>a</sup>
1306	Convulsion	Increase in cataplexy
1509	Convulsion	Multiple cataplexy attacks for 10 mins. (due to protocol violation of patient: got out of bed to use bathroom 1 and ½ hrs. after taking 1 <sup>st</sup> dose of GHB)
1703	Convulsion	Bit tongue/hit temple against furniture (due to falling faster to ground: cataplexy) <sup>c</sup>
2936	Convulsion	Cataplexy
3937	Convulsion	Cataplexy

<sup>a</sup> This patient had two separate events with the same verbatim term.

<sup>b</sup> This patient had two separate events, one of “increased cataplexy” and one of “cataplexy”

<sup>c</sup> This patient had two events, one of “Bit tongue (due to falling faster to ground: cataplexy)” and one on the same day of “hit temple against furniture (due to falling faster to ground: cataplexy)”

As the table above indicates, in 13 out of 14 patients the verbatim investigator term, based on which the patient was coded as having a “convulsion” or “convulsions”, indicated that the “convulsion(s)” represented cataplexy.

In the remaining patient (# 0814) the verbatim investigator term used was "seizures". A more detailed narrative for this patient is in the next section.

### **15.2.3 Narrative For Patient # 0814 (Initials)**

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

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

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

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

### **15.3 Reviewer's Comments**

- It does appear that all but one of the 14 patients in the Integrated Clinical Trials who were listed as having "convulsion(s)" in fact had cataplexy
- The remaining patient (# 0814) was considered to have a fugue state, the etiology of which is unclear. While partial complex seizures can be the cause of such states, a primary psychiatric disorder may also be responsible. Further details of this patient's episodes are unavailable and it is therefore not possible to make a determination whether he did have partial seizures. In addition it is somewhat difficult to understand the following
  - The reason why the principal investigator felt these were episodes of cataplexy (attacks of narcolepsy can, however, be associated with automatic behavior)
  - The reason why his neurologist chose to treat him with what was almost certainly an inadequate dose of phenytoin.

## **16. Abnormalities Of Blood Glucose And Transaminases In Integrated Clinical Trials**

### **16.1 Abnormalities Of Blood Glucose**

#### **16.1.1 Background And Sponsor's Methods**

The Division had asked for further information with hypoglycemia and hyperglycemia depicted in a table that I have already displayed in Section 4.3.1.

The questions, all of which pertained to the Integrated Clinical Trials only, were as follows

- Patients 0810, 0815 and 0820 had exceptionally low post-baseline blood glucose estimations (ranging from 12 to 24 mg/dL).  
Are these results accurate?  
Is there an explanation for their apparent hypoglycemia?  
What were their symptoms, if any, when hypoglycemic?
- A number of patients had hyperglycemia (mainly post-baseline). Were they known diabetics or are there any other explanations for their hyperglycemia?

In responding the sponsor has discussed the instances of hypoglycemia and hyperglycemia separately.

For the 3 patients with apparent hypoglycemia, laboratory records were examined and both tabular and narrative analyses prepared.

To answer the Division's questions about hyperglycemia the sponsor identified such patients using the following criteria

- Adverse events recorded using the COSTART terms of hyperglycemia or diabetes mellitus
- Blood glucose levels ("clinically significant elevated blood glucose levels") corresponding to the following

Either

A blood glucose that was > 70% higher than at baseline

Or

A blood glucose > 200 mg/dL

The sponsor has indicated that

- Fasting blood glucose measurements were specified for protocols OMC-GHB-2 and OMC-GHB-3, although this requirement was not always met
- "Non-fasting" blood glucose measurements were used in Protocols OMC-SXB-6 and OMC-SXB-7

Information in this amendment was supplemented by a telephone conversation with the sponsor held on 4/6/01

### 16.1.2 Hypoglycemia

The 3 patients with hypoglycemia are described further below

#### 16.1.2.1 Patient # 0815 (Initials)

This 43 year old woman had no history of diabetes mellitus or any metabolic-endocrine disease and was not receiving concomitant medications capable of causing hypoglycemia.

Her fasting blood glucose levels, dates on which the respective blood samples were drawn, and concurrent Xyrem® doses are listed in the table below which I have copied from the submission

Protocol	Dose	Collection Date	Blood Glucose (Normal 60-115)
OMC-GHB-2	0	4/28/97	83
	0	5/20/97	62
	0	6/9/97	67
	9g	6/23/97	69
	9g	7/11/97	24
	9g	7/22/97	73

During the study a number of adverse events were recorded. These included disorientation, diaphoresis, unstable gait, malaise, and a smothering sensation. However these were recorded on dates when blood glucose levels were normal. On the date when she had a blood glucose of 24 mg/dL, the following adverse events were recorded: stomach cramps and diarrhea; no symptoms or physical signs consistent with hypoglycemia were recorded. The sponsor presumes that the blood glucose level of 24 mg/dL was a laboratory error.

#### 16.1.2.2 Patient # 0820 (Initials)

This 37 year old woman had no history of diabetes mellitus or any metabolic-endocrine disease and was not receiving concomitant medications capable of causing hypoglycemia.

Her fasting blood glucose levels, dates on which the respective blood samples were drawn, and concurrent Xyrem® dose are listed in the table below which I have copied from the submission.

Protocol	Dose	Collection Date	Blood Glucose (Normal 60-115)
OMC-GHB-2	0	7/1/97	49
	0	7/8/97	44
	0	7/29/97	42
	0	8/14/97	16
	0	8/19/97	76
OMC-GHB-3	0	8/28/97	42
	6g	3/6/98	47
	6g	6/24/98	15
Discontinued From Study			

As the table indicates all her blood glucose levels across Studies OMC-GHB-2 and OMC-GHB-3 were low, with one exception (a reading of 76 mg/dL during OMC-GHB-2). During the OMC-GHB-2 study the only adverse event recorded was malaise but the date on which this was recorded is unclear; the sponsor states that "no hypoglycemic symptomatology was reported" even in association with the blood glucose level of 16 mg/dL. It is noteworthy that during this study she received placebo.

During Study OMC-GHB-3 she continued to have low fasting blood glucose levels with the lowest being recorded on 6/24/98 (15 mg/dL): according to the sponsor "there were no symptoms suggestive of acute hypoglycemia at the time of this visit but because of a large number of reported adverse events and in the best interests of the patient she was discontinued from the study at that time."

The sponsor has supplied adverse event listings for this patient for the OMC-GHB-3 study alone. On 6/24/98 the adverse events recorded included dizziness, lightheadedness, left hand "shakey", body shaking, shakiness in legs, upset stomach, headache, hallucinations ("hearing voices"), dyspnea and lack of energy. During the entire study the patient experienced the above, as well as numerous other adverse events that included numbness (including facial numbness), "down in dumps", snoring, cessation of breathing while asleep, nightmares, leg cramps, confusion, vomiting, hand and arm pain, finger cramps, depression, malaise, listlessness, nervousness, feeling cold and muscle weakness.

The sponsor has also supplied a clinical summary by the principal investigator dated 3/25/98 on which date the patient had attended a scheduled OMC-GHB-3 follow-up visit. On the afternoon of the previous day the patient had laid down for an afternoon nap when here breathing appeared "funny" and she was not responsive; she had last taken GHB at 2AM the same day. When an ambulance crew was summoned she was found to have a "stable respiratory pattern" and to respond when catheterized. After being transferred to an emergency room she became increasingly responsive over the next 2 hours. A drug screen (urine?) was reported to show traces of GHB. Electrolytes were normal. The episode was attributed to marital stress and GHB withheld the same night.

The sponsor states that no post-study blood glucose levels were drawn.

**16.1.2.3 Patient # 0810 (Initials)**

This 49 year old woman had no history of diabetes mellitus or any metabolic-endocrine disease and was not receiving concomitant medications capable of causing hypoglycemia.

Her blood glucose levels (fasting in OMC-GHB-2 and OMC-GHB-3), dates on which the respective blood samples were drawn, and concurrent Xyrem® dose are listed in the table below which I have copied from the submission.

Protocol	Dose	Collection Date	Blood Glucose (Normal 70-115)
OMC-GHB-2	0	4/4/97	58
	0	4/16/97	63
	0	4/30/97	57
	3g	5/13/97	49
	3g	5/28/97	58
OMC-GHB-3	3.8g	12/4/97	12
	4.5g	1/29/98	65
	4.5g	11/19/98	75
	4.5g	4/1/99	65
OMC-SXB-7	9.0g	11/10/99	57
	9.0g	5/10/00	77

There were reportedly no adverse events recorded on the same dates that she had blood glucose levels of 49 mg/dL and 12 mg/dL. She did have insomnia, dizziness and heart burn on 6/19/97, "sick" on 9/26/98, and a urinary tract infection in December 1998.

The sponsor presumes that her blood glucose of 12 mg/dL on 12/4/97 was a laboratory error for the following reasons

- There were no adverse events, or abnormalities of physical examination recorded on the same day
- Her blood glucose was normal 2 months later and subsequently

**16.1.3 Hyperglycemia**

In keeping with the sponsor's method of analysis, this phenomenon is discussed under 2 headings

**16.1.3.1 Adverse Events Of Hyperglycemia Or Diabetes Mellitus**

5 patients with such adverse events occurred among the 402 patients treated with Xyrem® in the Integrated Clinical Trials, through the cut-off date of 9/30/00 for the 120-Day Safety Update. Further information about these adverse events is as follows

- All such adverse events occurred during treatment with GHB; none occurred during periods of treatment with placebo (54 patients).
- None of these adverse events were serious, severe, or led to study drug discontinuation or death
- The distribution of these patients by dosage at onset was as follows

Dose	Number of Patients
3.0 g/day	0
4.5 g/day	1
6.0 g/day	2
7.5 g/day	1
9.0 g/day	1

- 2 patients were recorded to have diabetes mellitus at the time of study entry.
- The outcome of the adverse event was described as follows
 

Resolved	2 patients
Unresolved	1 patient

Outcome unknown 1 patient

### 16.1.3.2 Clinically Significant Elevated Blood Glucose Levels

Using the criteria described in Section 16.1.1 the sponsor has identified 6 patients with such blood glucose levels among the 402 enrolled in the Integrated Clinical Trials

- 7 such episodes occurred in these 6 patients
- All such episodes occurred during treatment with GHB; none occurred during periods of treatment with placebo (54 patients).
- The distribution of these patients by dosage at onset was as follows

Dose	Number of Patients
3.0 g/day	0
4.5 g/day	1
6.0 g/day	2
7.5 g/day	2
9.0 g/day	1

- 4/6 patients were recorded to have diabetes mellitus at the time of study entry.
- 2 of these patients were also recorded to have adverse events coded as hyperglycemia or diabetes mellitus

### 16.1.4 Teleconference With Sponsor: 4/6/01

A teleconference was held with the sponsor today to discuss the above review of hypoglycemia, and, briefly, that of hyperglycemia as well.

The following items of information were conveyed/confirmed by the sponsor

- All blood glucose levels during OMC-GHB-2 and OMC-GHB-3 were done at a single central laboratory (Premier Research Laboratories, Philadelphia, PA).
- All 3 patients with hypoglycemia described above were from a single center (Martha Hagaman, MD, Nashville, TN)
- The blood glucose readings of 24 mg/dL (for Patient # 0815), 16 mg/dL and 15 mg/dL (for Patient # 0820), and 12 mg/dL (for Patient # 0820) were all drawn at formal study visits. At the time of these visits, physical examinations recorded in the Case Report Forms, and Dr Hagaman's recollection of their condition as confirmed during recent telephone contacts with the sponsor, indicated that these patients were normal and not exhibiting the symptoms of hypoglycemia that would have been expected at those blood glucose levels; as a result those blood glucose values were considered laboratory errors by Dr Hagaman.
- Dr Hagaman asked Patient # 0820 to return for a follow-up visit after she discontinued taking study medication: the patient declined to do so. Dr Hagaman later confirmed with the patient's primary care physician that the patient was well; there is no evidence that the patient has been investigated for an underlying metabolic-endocrine disorder.
- In 5/9 patients with hyperglycemia there was no record of pre-existing diabetes mellitus in the entries made to the Case Report Form at the screening visit

### 16.1.5 Dr James Knudsen's Review Of Hypoglycemia

Dr James Knudsen of this Division's Safety Team was requested to determine if

- There were cases of GHB-associated hypoglycemia in the Adverse Events Reporting System (AERS)
- There were reports of GHB-associated hypoglycemia in the medical literature

Please refer to Dr Knudsen's review for full details of the analysis conducted by him.

#### *16.1.5.1 GHB-Associated Hypoglycemia In AERS*

Among the 301 adverse event reports of GHB-exposure in AERS no cases of hypoglycemia (defined arbitrarily as a blood glucose  $\leq$  2.2 mmol/L) were identified.

#### *16.1.5.2 GHB-Associated Hypoglycemia In Medical Literature*

There were no published reports of hypoglycemia associated with GHB exposure in any of the 15 databases searched.

#### *16.1.6 Reviewer's Comments*

##### *16.1.6.1 Hypoglycemia*

- Adverse events recorded on specific dates may not have occurred on those dates; therefore, attempts to correlate low blood glucose readings on specific dates with symptoms recorded on those dates could be misleading
- Patient # 0820 had a number of symptoms that were compatible with hypoglycemia during her participation in the Orphan drug trials; her blood glucose levels were almost consistently low at baseline and across her period of treatment with both placebo and GHB. While her hypoglycemia does not appear to be causally linked to GHB use, it is unlikely that a total of 7 low blood glucose readings all represented laboratory errors, and in view of her symptoms it is especially surprising that these abnormalities were investigated further while she was participating in the study. I understand, however, that efforts are underway at the present time to subject her to further medical testing in this regard.
- Patients 0810 and 0815 were not recorded to have adverse events compatible with hypoglycemia at any time during study participation despite having exceptionally low blood glucose levels (12 mg/L and 24 mg/L, respectively) which might have been expected to have been always associated with pronounced symptoms. The lack of appropriate adverse events, and the reportedly normal physical examination at or around the time the blood samples were drawn does support the sponsor's contention that these laboratory readings were erroneous; yet, erroneously low blood glucose readings, are in this reviewer's experience, quite uncommon and it is especially noteworthy that all 3 such readings were from patients at a single center.
- There are no instances of GHB-associated hypoglycemia in AERS or in the medical literature, based on Dr Knudsen's review.

##### *16.1.6.2 Hyperglycemia*

- In at least 4/9 of the instances listed by the sponsor, diabetes mellitus appears to have been present and the likely mechanism of the hyperglycemia
- In the remaining patients the explanation for the hyperglycemia is not clear, but it is conceivable that at least some of these patients did have diabetes mellitus but the diabetes was not documented. Even assuming that all those

with hyperglycemia had diabetes mellitus the prevalence of that condition in this population is not in excess of that in the general population.

## 16.2 Abnormalities Of Transaminases

### 16.2.1 Background

The Division had asked for further information about 4 patients who had post-baseline transaminase elevations depicted in a table that I have already displayed in Section 4.3.1: #s 0202, 0507, 1610 and 1709. The Division asked whether these abnormalities were followed up and whether they had resolved.

The sponsor states that these laboratory tests were performed centrally for these trials. The reference ranges are as in the following table

Trial	Laboratory	Reference Range	
		AST (IU/L)	ALT (IU/L)
OMC-GHB-2	Premier	2-40	2-53
OMC-GHB-3			
OMC-SXB-7	Covance	9-34	6-34

### 16.2.2 Sponsor's Description Of Individual Cases

#### 16.2.2.1 Patient # 0202 (Initials)

This patient was a 62 year old woman who participated consecutively in Studies OMC-GHB-2, OMC-GHB-3 and OMC-SXB-7. Her transaminase results are tabulated below; the table is the sponsor's

Protocol	Dose	Sample Date	AST (9-34)	ALT (6-34)
OMC-GHB-2	0	2/24/97	16	17
	0	3/03/97	19	19
	0	3/17/97	27	29
	3g	3/31/97	13	15
	3g	4/14/97	12	16
OMC-GHB-3	4.5g	5/27/97	15	14
	0.0g	7/28/97	14	13
	4.5g	10/2/97	13	11
	4.5g	4/6/98	11	7
	6.0g	10/7/98	18	17
	3.0g	1/14/99	19	23
OMC-SXB-7	3g	4/20/99	19	38
	6g	7/20/99	19	18
	6g	10/21/99	36	262
	6g	10/26/99	21	90
	6g	2/17/00	19	21
	6g	5/25/00	19	19
	6g	11/16/00	23	20

The sponsor reports that accompanying the elevation in ALT on 10/21/99 the patient complained of nausea, vomiting and upper abdominal pain. As the table indicates the ALT abnormality had improved 5 days later and her transaminases remained normal for at least a further year despite continuing the same dose of GHB (dosing with this drug was never interrupted). Other liver function tests-alkaline phosphatase, LDH and total bilirubin remained normal.

#### 16.2.2.2 Patient # 0507 (Initials)

This 34 year man participated consecutively in Studies OMC-GHB-2, OMC-GHB-3 and OMC-SXB-7. His transaminase results are tabulated below; the table is the sponsor's

Protocol	Dose	Sample Date	AST	ALT
GHB-2	0	4/30/97	38	65
	0	5/17/97	31	36
	0	5/28/97	24	38
	0	5/31/97	25	39
	9g	6/13/97	29	37
	9g	6/27/97	24	28
OMC-GHB-3	3g	1/5/98	29	51
	3g	7/20/98	52	109
	7.5g	2/15/99	35	67
OMC-SXB-7	7.5g	5/10/99	49	86

As the table above indicates, this patient had a mild elevation of ALT at screening and mild elevations, mainly of ALT, during Studies OMC-GHB-3 and OMC-SXB-7. Adverse events recorded (but not necessarily present) on the same days as the elevations in ALT and AST included "flu" and "heartburn/reflux". "Malaise-generally not feeling well" was recorded on 3/2/98.

The patient discontinued after the first visit of OMC-SXB-7 and did not attend a closeout visit. No blood tests were done after 5/10/99.

### 16.2.2.3 Patient # 1610 (Initials)

This patient was a 26 year old woman who participated consecutively in Studies OMC-GHB-2, OMC-GHB-3 and OMC-SXB-7. Her transaminase results are tabulated below in a table copied from the submission

Protocol	Dose	Sample Date	AST	ALT
OMC-GHB-2	0	8/8/97	22	17
	0	9/19/97	31	119
	0	9/25/97	32	48
	0	10/3/97	28	26
	3g	10/17/97	47	49
	3g	10/31/97	34	36
OMC-GHB-3	9g	5/6/98	24	23
	9g	5/15/98	18	22
	9g	11/4/98	76	248
	9g	11/11/98	17	42
	9g	1/4/99	16	11
OMC-SXB-7	9g	3/3/99	14	9

After an isolated elevation in ALT was noted prior to receiving GHB, an elevation in ALT, AST and alkaline phosphatase was noted about 1 year after beginning GHB. All enzyme elevations resolved spontaneously without discontinuation of GHB and without any adverse events contemporary with the enzyme abnormalities being recorded

### 16.2.2.4 Patient # 1709 (Initials)

This patient was a 26 year old woman who participated consecutively in Studies OMC-GHB-2, OMC-GHB-3 and OMC-SXB-7. Her transaminase results are tabulated below in a table copied from the submission

Protocol	Dose	Sample Date	AST	ALT
OMC-GHB-2	0	10/3/97	22	15
	0	10/10/97	19	18
	0	10/22/97	27	23
	9g	11/5/97	23	24
	9g	11/19/97	24	25
OMC-GHB-3	6g	5/13/98	17	13
	3g	11/11/98	30	76
	4.5g	4/26/99	34	38
OMC-SXB-7	4.5g	7/15/99	24	18

This patient had a single isolated elevation in ALT which was not contemporaneous with any recorded adverse events and resolved despite continuing GHB for at least another 8 months

### **16.2.3 Sponsor's Comments**

- In all 4 of the above instances the sponsor was unable to find an explanation for the liver function abnormalities
- In all 4 instances the sponsor believed that it was unlikely that the study drug was responsible for the abnormalities

### **16.2.4 Reviewer's Comments**

I agree with the sponsor's contention that GHB is unlikely to have been responsible for the transaminase elevations noted above

## **17. Patient 0231**

### **17.1 Background**

This patient (initials ) participated in the open-label study OMC-SXB-6 and was described in some detail earlier in this reviewer's NDA Safety Review.

The sponsor was asked whether this patient was hospitalized. In this submission a complete narrative has been provided. I have summarized the narrative below

### **17.2 Narrative**

This 67 year old man was enrolled in Study OMC-SXB-6. His past medical history was remarkable for a stomach ulcer, gastroesophageal reflux disease, and a cholecystectomy. Concomitant medications at study entry included clomipramine, methylphenidate, paroxetine, imipramine and modafinil.

He took Xyrem® in a dose of 4.5 g/day for 12 days and 9 g/day for 106 days. After having been on a stable dose of 9 g/day for 106 days he awoke about 1 hour after his second nightly dose feeling dizzy and confused. On getting out of bed he felt nauseated and vomited after reaching the bathroom. He felt a sensation of "shut down" and difficulty breathing, crawled from the bathroom to lie down in the hallway until he felt well enough to return to bed about 1 ½ hours after the episode began. Frequent cataplexy attacks apparently accompanied the episode. After returning to bed he slept soundly and awoke the next morning feeling well. The same day he contacted the Principal Investigator and withdrew from the study. He was never hospitalized or seen in an emergency room.

At the time the episode occurred his concomitant medications included a multivitamin, DGL (a herbal preparation), an unspecified medication for gastroesophageal reflux and methylphenidate.

The episode occurred on 7/27/99. A follow-up phone call from the study coordinator on 3/19/01 indicated that no further such episodes had occurred.

### **17.3 Reviewer's Comments**

- It is clear from the above narrative that the patient was not hospitalized.
- It is possible that the episode of nausea, vomiting, dizziness and other sensations was caused by Xyrem® although it is unclear why the episode occurred after the patient had been on a stable dose for over 3 months

## **18. Drug-Induced Lupus In Integrated Clinical Trials**

### **18.1 Background**

A limited number of patients participating in the open-label Scharf study had antinuclear antibody testing done and a proportion of these patients had positive

tests. While there were no definite cases of drug-induced lupus in that study, the sponsor was asked to analyze the safety data for the 402 patients participating in the Integrated Clinical Trials to determine if there were any patients who had clinical symptoms and signs suggestive of drug-induced lupus.

A detailed review of the section of the Amendment dealing with this matter was performed by Dr Tarek Hammad of the Safety Team. Please refer to Dr Hammad's review for full details. The following summary is based entirely on Dr Hammad's review

**18.2 Sponsor's Methods**

Antinuclear antibody testing was not done in the Integrated Clinical Trials. To identify possible cases of drug-induced lupus the sponsor therefore used a symptom-based case definition that was developed in consultation with Dr Evelyn Hess, a rheumatologist, who was earlier consulted regarding the positive antinuclear antibody tests in the Scharf trial.

The sponsor's case definition required that a patient experience two of the nine following symptoms: arthralgia, arthritis, myalgia, joint disorder, pain, alopecia, fever, malaise and rash.

The sponsor reviewed adverse event data for all 402 patients participating in the Integrated Clinical Trials. A total of 12 patients were eventually identified who had 2 or more of the symptoms subsumed under the above case definition: 10 of these patients had these symptoms while under treatment with GHB and 2 patients had these symptoms while being treated with placebo. The 10 GHB-treated patients who met the case definition are summarized in the following table which I have copied from Dr Hammad's review.

Case ID/ Study #	Sex/ age	Time to onset (d = days)	Symptoms	Outcome/ recurrence	Sodium oxybate status	Comments
1633/SXB-6	F/56 y	70 d	Myalgia, stiff & sore joints, difficulty concentrating, diarrhea, loss of taste, shortness of breath on exertion and weight gain.	Resolved after drug discontinuation/ no recurrence	Dose 9 g/night. Drug discontinued after five months of treatment due to persistent symptoms.	Patient improved within two weeks of drug discontinuation. A follow up, 14 months later, showed that symptoms disappeared completely after two months with no new medical problems.
0211/GHB-3	F/56 y	45 d	Arthralgia in three joints	Resolved/no recurrence	Dose 6 g/night. Treatment continued.	History of arthritis. Miscoded as three episodes of arthralgia.
0240/SXB-6	M/59 y	18 d	Rash on arm	Resolved/no recurrence	Dose 4.5 g/ night. Treatment continued.	None
		123 d	Joint pain	Intermittent	Dose 6 g/night Treatment continued	
0608/GHB-2, GHB-3, SXB-7	F/48 y	301, 352, 397, & 508 d	Four episodes of arthralgia and/or pain	Resolved/no recurrence	Dose 4.5 g/night. Treatment continued.	History of "long-standing" fibrositis and osteoarthritis (back, hip & knees).
0815/GHB-2	F/43 y	54, 56, & 58 d	Fever and "achiness"	NA	Dose 3 g /night. Treatment continued.	History of arthritis since 1985 & chronic fatigue syndrome. The episode diagnosed as "chronic fatigue immune dysfunction syndrome."
1302/GHB-2, GHB-3, SXB-7	F/55 y	31 d	Fever	Resolved/no recurrence.	Dose 9 g/ night. Treatment continued.	History of joint and back pain for seven years and "familial ankle swelling."
		282 d	Arthritis			
		346 d	"Severe hammer toe"			

Case ID/ Study #	Sex/ age	Time to onset (d = days)	Symptoms	Outcome/ recurrence	Sodium oxybate status	Comments
		854 d	"Unspecified pain"			
1305/GHB-2, GHB-3, SXB-7	F/73 y	Four occasions between 247-324 d	Arthritic symptoms in left knee or hip	Resolved/no recurrence	NA	History of arthritis since 1980.
1603/GHB-2, SXB-7	F/48 y	268 & 318 d	Arthralgia and myalgia	Resolved/no recurrence	Dose 4.5 g/ night. Treatment continued.	Positive ANA two years prior to GHB exposure. History of fibromyalgia since 1966, chronic fatigue, abdominal & pelvic pain, and hair loss.
		581 & 645 d	Shoulder pain	NA	NA	
1608/ GHB-3	F/42 y	43,68, & 86 d	Arthralgia (wrist joint)	Resolved/no recurrence	Dose 6 g/ night. Treatment continued.	Pain started after physical activity on day 528.
		503, 536, & 541 d	Low back pain and myalgia			
1612/GHB-2, GHB-3	F/48 y	1 d	Wrist pain	Resolved/no recurrence	Dose 6 g/night. Treatment continued	History of low back, shoulder and hip pain
		101 d	Arthralgia and alopecia		Dose 7.5 g/night. Treatment continued.	
		108, 120, 128, 153, 156, 187, 374, & 481 d	Muscle or leg pain			

After reviewing each of the above cases Dr Hammad is of the opinion that only Patient # 1633 participating in OMC-SXB-6 had symptoms and signs consistent with drug-induced lupus. However in the absence of antinuclear or antihistone antibody testing the diagnosis cannot be confirmed.

### 18.3 Sponsor's Conclusions

"None of the 402 patients in the Integrated Clinical Trials developed systemic lupus erythematosus or was diagnosed with drug-induced lupus during, participation in any of the five trials. A systematic review of the adverse effect data collected on these 402 patients definitively excluded symptoms suggestive of drug-induced lupus in all but one patient."

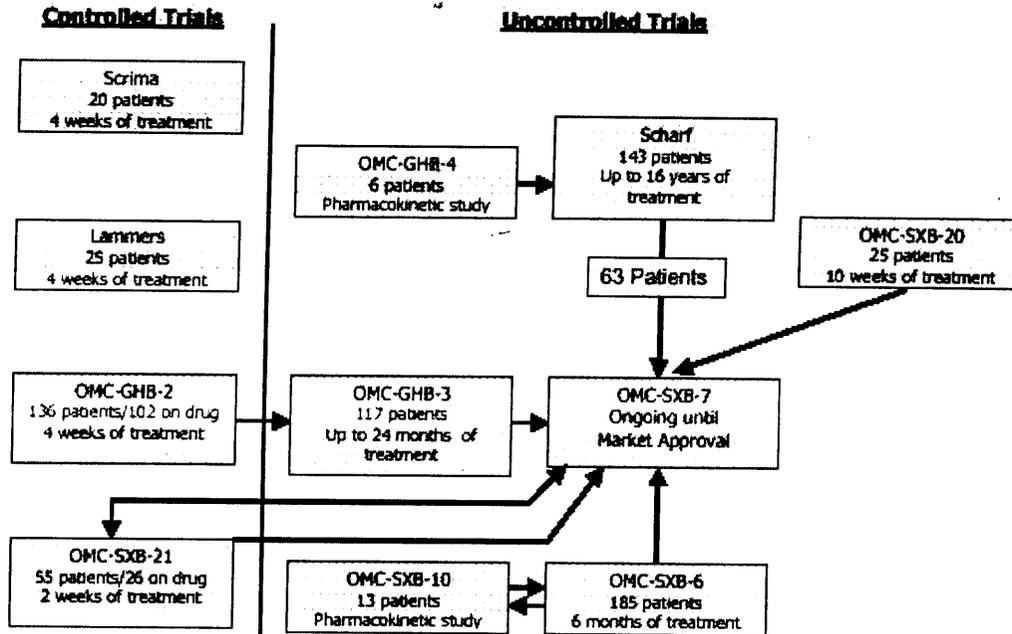
### 18.4 Reviewer's Comments

- I agree that there is no firm evidence that any patient participating in the Integrated Clinical trials had drug-induced lupus; however, in the absence of appropriate antibody testing, which was not performed at all in this cohort, it is hard to see how firm evidence of that diagnosis could have been obtained
- I also agree that at least one patient participating in the Integrated Clinical Trials had symptoms that may have been suggestive of drug-induced lupus.

## 19. Exposure Tables

### 19.1 Overall Schematic For Clinical Trials In Narcoleptic Patients Included In NDA

This schematic is copied from the submission and is included in this section by me for convenience.



## 19.2 Tables

### 19.2.1 Sponsor's Methods For Creating Tables

Tables were created for 2 different groups of patients

- The updated Integrated Clinical Trials database which included the following studies through the cut-off date for the 120-Day Safety Update (9/30/00): OMC-GHB-2, OMC-GHB-3, OMC-SXB-6, OMC-SXB-7 and Scrima
- All patients subsumed by the above bullet plus the Scharf study

The sponsor used the following methods for creating these tables

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

Patient Dose g/day	"Standard" Dose Group Category g/day
0 to 3.5	3
> 3.5 to 5.5	4.5
> 5.5 to 7.0	6.0
> 7.0 to 8.5	7.5
> 8.5	9.0

- Each patient's exposure to these 5 standard doses was calculated for both groups of patients and the number of patients at each dose level for each duration of exposure recorded in the tables. Assignment of patients to a dosing category was made based on continuous exposure time in that dosing category
- For the "overall duration of exposure" category each patient's time of exposure was calculated regardless of dose.
- Patients who received placebo only were not included in the tables
- Duration of exposure was calculated based on a 28-day month

- Since each patient could be represented in more than one dose category for the specified duration of exposure the overall exposure numbers do not represent arithmetical summations of the numbers in individual dose categories

### 19.2.2 Tables

The sponsor has presented tables for different durations of exposure

#### 19.2.2.1 Duration of Exposure $\geq$ 6 Months

The sponsor's table is presented below

Patients	3.0 g/d	4.5 g/d	6.0 g/d	7.5 g/d	9.0 g/d	Overall
ISS Only	9	50	115	59	62	296
ISS + Scharf	25	87	171	83	70	360

#### 19.2.2.2 Duration of Exposure $\geq$ 12 Months

The sponsor's table is presented below

Patients	3.0 g/d	4.5 g/d	6.0 g/d	7.5 g/d	9.0 g/d	Overall
ISS Only	5	27	60	26	34	223
ISS + Scharf	12	55	114	50	42	286

#### 19.2.2.3 Duration of Exposure $\geq$ 24 Months

The sponsor's table is presented below

Patients	3.0 g/d	4.5 g/d	6.0 g/d	7.5 g/d	9.0 g/d	Overall
ISS Only	2	4	13	9	13	48
ISS + Scharf	6	26	66	34	23	150

#### 19.2.2.4 Sponsor's Comments About Above Tables

The sponsor has drawn attention to the following:

- The most commonly used dose of GHB across the 3 durations of exposure was 6 g/day regardless of whether data from the long-term Scharf trial were included or excluded
- The vast majority of patients used doses ranging from 4.5 to 9 g/day, across durations of exposure. The sponsor has proposed a starting dose of 4.5 g/day with a range of 3 to 9 g/day after titration
- Even if patients from the Scharf study are excluded patient exposures are currently sufficient to meet ICH guidelines for the 6 and 12 month periods

### 19.3 Sponsor's Overall View Of Adequacy Of Exposure

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

Study Pool	Integrated Clinical Trials Plus Scharf		Integrated Clinical Trials Only	
	Patients	Healthy Subjects*	Patients	Healthy Subjects*
Any Exposure	528	125	448	125
Exposure $\geq$ 6 Months	376	0	296	0
Exposure $\geq$ 12 Months	303	0	223	0
Patient-Years Of Exposure	1265	Not calculated	269	Not calculated

\*Healthy subjects were exposed to single doses only

- The entire database contains sufficient patient exposure sufficient to meet the ICH guidelines at 6 months (> 300 patients) and 1 year (> 100 patients)
- "Since this is an Orphan Drug FDA has proposed a number of about 500 total subjects exposed to meet the requirement for overall exposure." The database includes over 500 subjects exposed to GHB even if the Scharf dataset is not included.

#### **19.4 Reviewer's Comments**

- The size of the Xyrem® NDA database (with the 120-Day Safety Update included) does meet ICH guidelines for drug exposure for 6 months and a minimum of 1 year if one assumes that the effective dose ranges from 3 to 9 grams/day. The ICH guidelines are met even if the Scharf study is excluded
- However if one concludes (from the efficacy studies) that the 9 g/day dose is the only effective dose and is that to be recommended for general use the number of those exposed to Xyrem® 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."

- 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.
- There are no ICH guidelines that address exposure requirements for Orphan Drugs. While the sponsor's statement *that "since this is an Orphan Drug, FDA has proposed a number of about 500 total subjects exposed to meet the requirement for overall exposure"* is technically incorrect (the number was proposed by the sponsor and judged acceptable by the Division), the total number of patients exposed to Xyrem® may be appropriate for an Orphan Drug; that may be especially true if the sponsor's estimate that the number of diagnosed/treated cataplexy patients in the United States is in the range of 20,678-22,917 is correct (this estimate was conveyed to this Division at a meeting held on 2/28/01)

## **20. Reviewer's Summary Of "Sleepwalking"**

### **20.1 Background**

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. The COSTART preferred term under which this entity has been coded is "sleep disorder."

The sponsor has not discussed this adverse event, either in the original NDA submission or in this Amendment. Given the frequency and potential/actual consequences of this adverse event (see below) I have chosen to discuss it further briefly

In most instances of "sleepwalking" in this NDA, a detailed description of patient behavior during that adverse event is not available.

The medical term "sleepwalking" refers to a non-REM parasomnia classified as an arousal disorder. During episodes patients exhibit complex behaviors including automatic and semi-purposeful motor activities: sitting up in bed, walking, climbing stairs, opening and closing windows and even more complex tasks, such as preparing food, may be features. Acts that are destructive or harmful may be seen, such as throwing objects, and climbing out through a window. During and immediately following episodes patients are confused; they have amnesia for the episodes. It is not at all clear that the term "sleepwalking" has a similar connotation when used in this NDA, or that it refers to a single clinical entity. In the majority of instances of sleepwalking in the Scharf study, this term appears to be derived from daily logs maintained by patients

Based on a literature search there does not appear to be an association between narcolepsy and typical sleepwalking, as defined in the paragraph above. However about 50% of narcoleptic patients have periods of automatic behavior that are described as memory lapses or blackouts; patients have amnesia for their activities during these episodes. Semi-purposeful activity is possible during such episodes which may manifest with phenomena such as walking into objects, getting lost while driving, and writing unintelligibly. Such episodes are believed to be due to micro-sleeps that intrude into wakefulness, and are most frequent in the mornings. Again there is no information supplied with the NDA that would strongly suggest that any of the "sleepwalking" episodes correspond to automatic behavior occurring as part of narcolepsy.

## **20.2 Incidence Of "Sleepwalking" In Xyrem® NDA**

### **20.2.1 Controlled Clinical Trial OMC-GHB-2**

The incidence of adverse events coded under the COSTART preferred term "sleep disorder" is as follows among the 4 treatment groups

Dose Group	Total Number Randomized	Number of Patients with "Sleep Disorder" (COSTART)	% of Patients with "Sleep Disorder" (COSTART)
Placebo	34	1	2.9
3 g/day	34	2	5.9
6 g/day	33	4	12.1
9 g/day	35	5	14.3

The sponsor has attempted to characterize the term "sleep disorder" further in the following table which I have copied from the OMC-GHB-2 clinical trial report

Description	Placebo	GHB		
		3g	6g	9g
Prolonged sleep paralysis	1	1	2	5
Sleep walking	0	0	0	2
Poor sleep maintenance/ frequent arousal	0	1	2	1
Microsleep	0	0	1	0

### 20.2.2 Integrated Clinical Trials

Note that OMC-GHB-2 is a component of this group of trials.

“Sleep disorder” (COSTART) occurred in 46/402 (11.4%) of patients participating in these trials. There was no dose-response seen and the sponsor has not characterized this adverse event further except in the case of those participating in OMC-GHB-2. Thus it is unclear how many patients recorded as having a “sleep disorder” (COSTART) might have been considered to have “sleepwalking”

### 20.2.3 Scharf Trial

Based on my review of all the Case Report Forms for this study, 45/143 (31.5%) of patients were listed as having one or more episodes of “sleepwalking.” A single patient (# 01-042, initials \_\_\_\_\_, is described as having 346 episodes, and many patients had multiple episodes.

The patients listed as having “sleepwalking” constitute the entire cohort of those coded under the COSTART preferred term “sleep disorder” in this study

### 20.3 Characterization Of “Sleepwalking” Episodes

As already indicated the sponsor has not provided more detailed descriptions of patient behavior during these episodes except in a very small number of instances.

I have not attempted to characterize the “sleepwalking” episodes in regard to patient demographics, duration, severity and seriousness of episodes, GHB dose at onset, concomitant medications and illnesses, outcome and other parameters. I currently lack both the time and resources to perform such an analysis. The sponsor should, however, be required to perform such an analysis prior to approval. Such episodes, regardless of their etiology, have had serious consequences as outlined below.

### 20.4 Consequences Of “Sleepwalking” In Xyrem® NDA

Narratives are provided below for patients who were reported to have events of serious or potentially serious consequence during episodes of “sleepwalking.” These consequences include taking an overdose of GHB as well as other

actions. Several of these narratives are elsewhere in this review but are reproduced here for convenience. All instances occurred in the Scharf study.

#### **20.4.1 Patient 01-215 (Initials)**

This 46 year old woman with narcolepsy, who sustained a skull fracture 5 years prior to study entry, took GHB in a variable dose of 4.5 to 10.5 g/day in 2 or 3 divided doses despite being prescribed 7.5 g/day (this is not consistent with what has been entered in the medication logs in the Case Report Form. About 4 months after entering the study she reported symptoms of nausea, a tipsy feeling, blurred vision, and a swollen face and hands. These symptoms persisted for 14 days, no action was taken, and her doses subsequently were variable and as high as 10.5 g/day. She continued in the study for a further 4 years when she was discontinued on account of non-compliance which involved not submitting daily sleep log diaries and modifying dosing schedules without prior consultation with Dr Scharf.

A number of unexplained fits of laughter (termed "hysterical" in one instance, and "uncontrollable" at other times), and **episodes of "sleepwalking" (during one of which she tried to drink nail polish remover)**. Episodes of headache, nausea, dizziness, blurred vision, enuresis, "fogginess", "stumbling around-unsure of self on feet after gamma", "drugged effect, vision blurred, unsteady on feet", "drunken stupor; rage", other similar events, and sleeplessness, were also noted during the study.

A telephone contact with the patient 12 ½ years after she discontinued from the study indicated that her neurological adverse events, with the exception of blurred vision, had resolved once GHB was discontinued.

#### **20.4.2 Patient 01-017 (Initials)**

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.

### **20.4.3 Patient 01-267 (Initials)**

This 65 year old woman had a history of obesity, sleep apnea on treatment, and narcolepsy. She began taking GHB in a dose of 4.5 g daily.

**About 4 ½ years after study entry she was reported to have taken an overdose of GHB, consuming a third nightly dose instead of merely two doses. The patient's daughter reported that the patient was shortly afterward incontinent of urine, awoke and (for unclear reasons) was covered with spaghetti sauce. She also appeared dazed and confused. Her diaries are unavailable for that period and it is therefore unclear what her regular dose of GHB was at the time. She was taken to an emergency room but had recovered by that time. She was reported to have continued GHB after that episode but ceased returning any daily diaries at all beginning about 5 ¼ years after study entry and was therefore recorded as having left the study on account of non-compliance. Repeated letters to the patient from the study center were reportedly unanswered. Further information about this patient is unavailable.**

**During her participation in the study she was also recorded to have multiple episodes of sleepwalking and multiple additional episodes of urinary incontinence, not apparently occurring contemporaneously. She was also seen at an emergency room for an episode of somnolence which was felt to be related to her sleep apnea. She reported swollen ankles and wrists, and pain, numbness and tingling in her feet.**

(It is not clear from the above or from the Case Report Form whether the overdose occurred during an episode that would have been considered to represent "sleepwalking")

### **20.4.4 Patient 01-206 (Initials)**

This 62 year old woman had a history of narcolepsy, hypertension and heavy smoking. She began taking GHB in a dose of 3 g/day.

**While participating in the trial she had 7 episodes of sleep walking. 2 episodes which occurred, separated by a 2-day interval, 7 ½ months after she entered the study, led to her discontinuing GHB. During each of these episodes she was found by her husband with a burning cigar or cigarette in her hand, apparently not aware of having been smoking. On one of these occasions she was found in a room other than their bedroom asleep with a cigar in her hand. On the second occasion the cigarette was found to be burning her nightgown; her husband threatened at that point to end their marriage unless she stopped taking GHB. The patient's entries in her daily sleep log indicate that she was unaware of her actions during these episodes and had no personal recollection of them subsequently .**

### **20.5 Reviewer's Comments**

- In the absence of adequate clinical descriptions in most instances it is unclear what the investigator term "sleepwalking" represents, or whether it refers to single or multiple entities.
- Regardless of what the term "sleepwalking" means in the context of this NDA, it is clear that such episodes are common; almost one-third of patients participating in the long-term Scharf safety study did have one or more such occurrences, and a single patient is recorded as having as many as 346 episodes. The incidence of this adverse event in the entire Integrated Clinical Trials grouping is unknown (except for a single study, OMC-GHB-2)
- The few clinical descriptions of this adverse event that are available in this NDA suggest that during "sleepwalking" episodes patients may be confused

and may act in a manner that could be prejudicial to their own safety and that of others.

- The sponsor has not, so far, attempted to analyze this adverse event as an entity
- The fairly high incidence and potential consequences of such episodes make it essential that the sponsor should be asked to better characterize the instances of sleepwalking in this NDA prior to the drug being approved for marketing.
- In this reviewer's opinion (and on a largely speculative basis) it is possible that the term "sleepwalking" as used in this entity could be describing one or more of the following entities
  - An acute confusional state induced by GHB
  - Automatic behavior of narcolepsy
  - Partial complex seizures (these are unlikely to be caused by GHB)
  - Prolonged absence seizures (such seizures have been reported to be induced by other drugs in the past)
  - An arousal disorder akin to true sleepwalking
- It is certainly possible that some instances of sleepwalking in patients with are not very different in their manifestations from the episodes of confusion or fugue state or reported in others

## 21. Overall Comments

- 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 been "accounted for" although the basis for doing so is less-than-optimal in a significant number. Further efforts need to be made by the sponsor to account fully for 11 of the remaining 16 (unsuccessful recent efforts have been made to contact 5 patients out of those 16). The 11 patients are listed below. Adverse events that were ongoing at the time of discontinuation are reasons for obtaining further follow-up in at least some of these 11 patients

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

- None of the "adverse events" in the "unevaluable" category that occurred in the Scharf study appear to be attributable to GHB
- Urinary and fecal incontinence both appear to be unusually common adverse events in patients taking GHB and the key issues are whether such episodes are accompaniments of unrecognized convulsions, and whether GHB is

capable of causing convulsions at therapeutic doses. Currently the evidence that the vast majority of episodes of incontinence in the entire NDA are related to unrecognized convulsions is weak. There does appear to be at least 1 patient in the Scharf study in whom incontinence clearly accompanied a true convulsion.

- While there are clearly a few patients (n = 2) in the entire NDA safety database who experienced, or may have experienced, convulsions while taking GHB, the presence of confounding factors (e.g., possible benzodiazepine withdrawal) makes it difficult to link the convulsions causally to GHB. Whether GHB is capable of causing other types of seizures, e.g., absence or partial complex, is even less clear
- In this NDA, and especially in the Scharf Study, the term “sleepwalking” has been used as a verbatim (investigator) term for a common adverse event. Detailed clinical descriptions of such episodes are not available for the majority of patients and their mechanism has not been delineated. A separate analysis of these episodes has not been performed by the sponsor and it is not clear how common they are in the Integrated Clinical Trials grouping, but such episodes have been associated with serious consequences (e.g., overdose, pyrogenesis, consuming toxic chemicals) in patients enrolled in the Scharf study
- The information available in this NDA does suggest that GHB is capable, at therapeutic doses, of causing a confusional state (which may be accompanied by psychotic symptoms). The incidence and seriousness of such adverse events may be slightly more pronounced at higher doses, and especially if higher doses are administered without titration. However a confusional state also appears to be capable of occurring at lower and even sub-therapeutic doses of GHB, and after maintenance treatment for several months. The presence of true confusion in patients taking GHB could lead to their taking GHB in a manner other than as prescribed. The symptoms that have been subsumed under the COSTART term “confusion” are not unusual for a sedative-hypnotic drug.
- In the majority of patients who developed “neuropsychiatric” adverse events (e.g., paranoia, hallucinations, anxiety, stupor, etc) while taking GHB in Integrated Clinical Trials it is not possible to attribute causality for the adverse event to GHB. Pre-existing psychiatric illness, and concomitant medications such as stimulants, as well as other factors, could be contributory. Even in patients in whom there was no recorded premorbid history of psychiatric illness the extent to which they were screened for such illness is not clear. However the occurrence of neuropsychiatric adverse events in patients taking GHB, even if not directly caused by the drug, could place them at risk of intentional or accidental overdose, as is suggested by the narratives in this review
- There is no firm evidence that any patients participating in the Integrated Clinical Trials had drug-induced lupus. However antinuclear antibody and antihistone antibody testing was not performed for patients participating in this study

- There is no evidence suggesting a causal link to GHB for the small number of hypoglycemic and hyperglycemic blood test readings in the NDA; several of the apparently hypoglycemic readings could in fact have represented laboratory errors. Neither is there firm evidence in AERS or in the medical literature that GHB is capable of causing hypoglycemia.
- GHB is unlikely to have been the cause of transaminase elevations seen in a few patients in the Integrated Clinical Trials.
- 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  $\geq 12$  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."

## 22. Conclusions

Deferred

## 23. Recommendations

Deferred

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Ranjit B. Mani, M.D.  
Medical Reviewer

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

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

