| 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 | 5/30/1995 | Adverse Event | Weight loss |
| 01-005 | | F | 45 | 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 7.4.1 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.

### *7.5 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.

#### *7.5.1 Source Of Case Report Forms*

The Case Report Forms for the Scharf study were created by [redacted], a contract organization hired by the sponsor [redacted] 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.

#### *7.5.2 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

*7.5.3 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 capture
- 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

*7.5.4 Deaths And Adverse Event Discontinuations*

*7.5.4.1 Deaths*

None of the deaths listed above were causally attributable to GHB

*7.5.4.2 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.

*7.5.5 Patients Discontinued From Scharf Study For Non-Compliance*

*7.5.5.1 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

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

*7.5.5.2 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)<br><br>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)<br><br>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<br><br>Adverse events including dizziness and other symptoms had resolved |

| 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 |
|---|---|---|---|---|---|---|---|
| | | | | | | | (contacted in March 2001) |
| 01-216 [redacted] | 1/28/98 | 2/22/87 | 2/9/87 | 2/9/87 | 2/5/85 | 2/16/87 | No attempt |
| 01-217 [redacted] | 2/18/98 | 7/19/86 | 7/15/86 | 9/4/85 | 5/6/85 | 7/9/86 | No attempt |
| 01-222 [redacted] | 2/24/98 | 4/21/88 | 2/3/88 | 5/27/88 | No record | 4/18/88 | No attempt but see footnote ******** |
| 01-223 [redacted] | 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<br><br>No subsequent attempt at follow-up |
| 01-240 [redacted] | 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 [redacted] | 2/11/98 | 4/22/87 | 7/14/86 | 1/12/87 | 1/12/87 | 7/16/86 | Not attempted |
| 01-248 [redacted] | 2/17/98 | 10/13/86 | 10/22/86 | No record of laboratory tests | 6/18/86 | 10/10/86 | Not attempted |
| 01-251 [redacted] | 2/27/98 | 11/21/86 | 1/31/85 | 7/29/87 | 4/11/86 | 11/21/86 | Not attempted |
| 01-256 [redacted] | 2/27/98 | 6/30/88 | Not recorded ********** | 3/29/88 | 3/29/88 | 3/13/88 | Not attempted |
| 1-258 [redacted] | 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<br><br>Study coordinator spoke with patient on 1/3/92 to request logs. Unclear whether he was still taking medication at that time.<br><br>Additional follow-up not attempted |
| 01-263 [redacted] | 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 [redacted] | 4/8/98 | 7/31/97 | 1/16/97 | 12/30/97 | 11/30/96 | 5/30/97 | Not attempted |
| 01-268 [redacted] | 3/4/98 | Unknown | 8/96 | 11/3/97 | 4/30/97 | 1/25/97 | Not attempted |
| 01-288 [redacted] | 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

***The last recorded adverse event was during her initial period of treatment with GHB (see narrative in Section 7.5.10.1). 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 7.5.10.5
***********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

### *7.5.6 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.

### *7.5.7 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

### *7.5.8 Patients Continuing In Scharf Study*

#### *7.5.8.1 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.

*7.5.8.2 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

*7.5.9 Patients Subjected To Recent Attempts At Follow-Up*

*7.5.9.1 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**

*7.5.9.2 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) |
|---|---|---|---|
| 01-27. [redacted] | 9/30/95 | Adverse event: Weight loss | Unsuccessful |

### *7.5.9.3 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

### *7.5.10 Unresolved Adverse Events Of Concern*

### *7.5.10.1 Patient # 01-063 (Initials [redacted])*

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.**

### *7.5.10.2 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.

### *7.5.10.3 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 the apparent resolution of the patient's symptoms; 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.**

### *7.5.10.4 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.

### *7.5.10.5 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 entry, on account of non-compliance (failure to return his sleep logs)

### *7.5.10.6 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

### *7.6 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/ | 01-238/ | 01-240. |
| 01-027/ | 01-254/ | 01-268. |
| 01-054/ | 01-259 | 01-256. |
| 01-065. | 01-273 | 01-063. |
| 01-228. | | |
| 01-262 | | |
| 01-269 | | |
| 01-283 | | |

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

## 8. 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 ——— MD, a neurologist in ——— Dr — consultation letter was written on 4/26/89 very soon after the patient was instructed to discontinue GHB (see below).

### *8.1 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 7th 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 —— 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

### *8.2 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.

## 9. "Reaction Unevaluable" Adverse Events In Scharf Trial

### *9.1 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.

### *9.2 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 history

  Or 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

### *9.3 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

### *9.4 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 is a provision of more 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

### *9.5 Reviewer's Comments*

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

## 10. Analysis Of Urinary And Fecal Incontinence In Scharf Trial

### *10.1 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 the original submission under Treatment IND —— 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

### *10.2 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

### *10.3 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 |
| 019 | enuresis episode | 08/12/94 | 08/12/94 | sleepwalking episode | 08/12/94 | 08/12/94 |
| 048 | enuresis | 09/13/84 | 09/13/84 | confusion | 09/13/84 | 09/13/84 |
| 048 | | | | numb all over | 09/13/84 | 09/13/84 |
| 048 | urinary incontinence with seizure | 02/07/89 | 02/08/89 | convulsive-like seizure | 02/07/89 | 02/08/89 |
| 201 | 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 |
| 256 | 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 |

### *10.4 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)

#### *10.4.1 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 during 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

### *10.4.2 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.

### *10.4.3 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.

### *10.4.4 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 reported to be 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

### *10.5 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 that 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.

### *10.6 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.

### *10.7 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 13 and 16
- 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 represented 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 11).

- 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.

## 11. Adverse Events Coded As "Confusion" In Scharf Study

### *11.1 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 11.2) 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

### *11.2 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 [a] | Xyrem Oral Solution Dosage (g/d) at Onset[b] | | | | |
|---|---|---|---|---|---|---|
| | | 3.0 | 4.5 | 6.0 | 7.5 | 9.0 |
| Patients with at Least 1 AE | 10[c] | 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[c] | 0 | 0 | 0 |
| Patient Discontinuation due to an AE | 0 | 0 | 0 | 0 | 0 | 0 |
| Patient Deaths | 0 | 0 | 0 | 0 | 0 | 0 |

[a] Patients are counted only once in each category.
[b] Dosage at onset.
[c] 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."

### *11.3 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

### *11.4 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<br>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 |

### *11.5 Narrative For Patient With Confusion As A Serious Adverse Event*

I have read the sponsor's narrative and supplemented it by reading the Case Report Form

#### *11.5.1 Patient 01-012 (Initials [redacted])*

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 ≥ 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.

### *11.6 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.

#### *11.6.1 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 ≤ 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.

#### *11.6.2 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.

#### *11.6.3 Patient 01-048 (Initials —*

A narrative for this patient has been provided in Section 10.4.1

#### *11.6.4 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.

### *11.6.5 Patient 01-235 (Initials [redacted]*

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)

### *11.6.6 Patient 01-248 (Initials [redacted]*

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.

### *11.6.7 Patient 01-251 (Initials [redacted]*

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."

### *11.7 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

## 12. Neuropsychiatric Adverse Events In Scharf Study

### *12.1 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 |

### *12.2 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 12.1. Their distribution by dose and severity is displayed in the following table which I have copied from the submission.

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

[a] Patients are counted only once in each category patients are classified by the highest dose at which a neuropsychiatric AE occurred.

[b] Total number of patients in each dosage group represents the dosage at onset

[c] Patients are classified here by highest dose at which any neuropsychiatric AE occurred

[d] 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

[e] 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

[f] 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

### *12.3 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 |

### *12.4 Specific Neuropsychiatric Adverse Events*

#### *12.4.1 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

#### *12.4.2 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./ Init | Sex/ Age[a] | Dosage at Onset (g/d) | AE Start Date | Trial Day Start | Trial Day Stop | Verbatim Term | Serious | Relationship/ Severity | Relevant Medical History |
|---|---|---|---|---|---|---|---|---|---|
| 001 | M/49.0 | 9.0 | 10/30/86 | 1096 | | 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 |
| 046 | 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 Ache" | No | Not Related/Not Indicated | Narcolepsy, Memory Problems, Depression with Recurrent Melancholia, Dizzy Episodes when Walking and Laying Down |

| Patient No./ Init: | Sex/ Age[a] | Dosage at Onset (g/d) | AE Start Date | Trial Day Start | Trial Day Stop | Verbatim Term | Serious | Relationship/ Severity | Relevant Medical History |
|---|---|---|---|---|---|---|---|---|---|
| 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 laugher | No | Not Related/Not Indicated | |
| 238/ | M/45.2[b] | 22.5[c, d] | | | | Emotional interplay (Reported by Physician on 07/02/85) | No | Possibly Related/Not Indicated | No history available |
| 257/ | M/33.0[b] | 12.0[c] | | | | Tearful | No | Not Related/Not Indicated | Narcolepsy, Whiplash/Concussion, Difficulty left Binocular Foucusing Hard Moving All Positions |

| Patient No./ Initials | Sex/ Age[a] | Dosage at Onset (g/d) | AE Start Date | Trial Day Start | Trial Day Stop | Verbatim Term | Serious | Relationship/ Severity | Relevant Medical History |
|---|---|---|---|---|---|---|---|---|---|
| 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, |

[a] Age at AE start date.
[b] Age at trial start date.
[c] Highest dose of sodium oxybate taken during the trial.
[d] 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

### *12.4.3 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[a] | 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 197. with 1 week amnesia |
| 044/ | F/34.2 | 4.5 | 11/00/87[b] | 152 | | Mixes things up- transposes numbers i.e. thinks 280 but writes 208 | No | Unknown/Not Indicated | Narcolepsy, Concussion 4/85; Frontal lobe lesion |
| 203/ | F/32.1 | 6.0 | 02/01/94 | 0 | 0 | Incoherence | No | Probably Related/Not Indicated | Narcolepsy |
| 215/ | F/46.2 | 7.5 | 11/01/89 | 6 | | Very talkative- after gamma dose | No | Possibly Related/Not Indicated | Skull Fractures, 1978 |
| | F/46.3 | 7.5 | 12/08/93 | 43 | | Fogginess | No | Unknown/Not Indicated | |
| | F/46.3 | 7.5 | 02/01/94 | 100 | 100 | Fogginess lasted couple of hours | No | Possibly Related/Not Indicated | |
| 218/ | F/40.3[b] | 7.5[c] | | | | Being in a fog | No | Possibly Related/Not Indicated | Narcolepsy |

| Patient No./ Initials | Sex/ Age[a] | Dosage at Onset (g/d) | AE Start Date | Trial Day | | Verbatim Term | Serious | Relationship/ Severity | Relevant Medical History |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Start | Stop | | | | |
| 218/ | M/45.7 | 9.0 | 06/25/94 | 208 | 209 | Can't seem to concentrate | No | Possibly Related/Not Indicated | No History Available |
| 218/ (Contd.) | M/45.9 | 7.5 | 09/04/94 | 279 | 280 | Negative thinking | No | Possibly Related/Not Indicated | No History Available |
| 257/ | M/33.0[b] | 12.0[c] | | | | Problem concentrating | No | Not Related/Not Indicated | Narcolepsy, Whiplash / Concussion, Obstructive Sleep Apnea |
| 267/ | F/61.4 | 4.5 | 05/00/92[b] | 16 | | Foggy and Lightheaded feeling | No | Not Related/Not Indicated | Narcolepsy Sleep apnea |
| 279/ | F/37.5 | 5.4 | 02/20/98 | 531 | | Foggy Minded | No | Not Related/ Moderate | |
| | F/37.2 | 2.3 | 05/15/98 | 609 | 617 | Inability to Concentrate | No | Not Related/ Severe | |

[a] Age at AE start date.
[b] No start date indicated for this AE so age at study start is used for age at onset of AE
Event onset date calculated from the midpoint of the known period (i.e. the 15th of the month).
[c] 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 11.6.4
- This adverse event was not considered serious in any patient and did not lead to medication discontinuation

### *12.4.4 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[†] | 12/00/93[‡] | 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.
† Dose at onset determined from the highest dose of the known period.
‡ 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 12.5.2) discontinued treatment on account of this adverse event.

### *12.4.5 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[a] | Dosage at Onset (g/d) | AE Start Date | Trial Day Start | Trial Day Stop | Verbatim Term | Serious | Relationship/ Severity | Relevant Medical History |
|---|---|---|---|---|---|---|---|---|---|
| 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[b] | 06/00/87 | 34[c] | | 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[b] | 06/00/87 | 34[c] | | Short tempered | No | Unknown/Not Indicated | |
| 215/— | F/46.6 | 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[a] | Dosage at Onset (g/d) | AE Start Date | Trial Day Start | Trial Day Stop | Verbatim Term | Serious | Relationship/ Severity | Relevant Medical History |
|---|---|---|---|---|---|---|---|---|---|
| 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 |

[a] Age at AE start date.
[b] Dose at onset determined from the highest dose of the known period.
[c] 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

### *12.4.6 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[a] | Dosage at Onset (g/d) | AE Start Date | Trial Day Start | Trial Day Stop | Verbatim Term | Serious | Relationship/ Severity | Relevant Medical History |
|---|---|---|---|---|---|---|---|---|---|
| 012/__ | M/76.8 | 7.5 | 9/15/86 | 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 |
| 207/__ | 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[a] | Dosage at Onset (g/d) | AE Start Date | Trial Day Start | Trial Day Stop | Verbatim Term | Serious | Relationship/ Severity | Relevant Medical History |
|---|---|---|---|---|---|---|---|---|---|
| 257/__ | M/33.0[b] | 12.0[c] | | | | 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 |

[a] Age at AE start date.
[b] No start date indicated for this AE so age at study start is used for age at onset of AE
[c] 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.

### *12.4.7 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[a] | Dosage at Onset (g/d) | AE Start Date | Trial Day Start | Trial Day Stop | Verbatim Term | Serious | Relationship/ Severity | Relevant Medical History |
|---|---|---|---|---|---|---|---|---|---|
| 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 |
| 235/1__ | M/58.0 | 6.0 | 9/00/93 | 3283[b] | 3405 | Claustrophobia | No | Possibly Related/Not Indicated | Narcolepsy, Depression |

[a] Age at AE start date.
[b] Start day calculated as 3/15/93, 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.

### *12.4.8 Overdose*

The sponsor has included the following patients in this listing.

- Patient 01-017 (see Section 12.5.4)
- Patient 01-267 (see Section 12.5.5)

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 12.5.1) in this section. This patient also took a drug overdose but was coded as making a suicide attempt.

### *12.4.9 Suicide Attempt*

A single patient (#01-019) was coded as making a suicide attempt during this study. This patient is further described in Section 12.5.1. As noted in the narrative he had a history of multiple psychiatric conditions including schizophrenia and depression prior to entry into the Scharf trial

### *12.4.10 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[a] | 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 |

[a] Age at AE start date.

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

### *12.4.11 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[a] | Dosage at Onset (g/d) | AE Start Date | Trial Day | | Verbatim Term | Serious | Relationship/ Severity | Relevant Medical History |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Start | Stop | | | | |
| 256/1 | M/16.4[b] | 4.5[c] | | | | 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 |

[a] Age at AE start date.
[b] No start date indicated for this AE so age at study start is used for age at onset of AE
[c] Highest dose of sodium oxybate taken during the trial.

A narrative for this patient is below

### *12.4.11.1 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)

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

These narratives are below

### *12.5.1 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.

### *12.5.2 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.

### *12.5.3 Patient 01-012 (Initials —)*

See Section 11.5.1

### *12.5.4 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.

### *12.5.5 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 during participation in the study.

## *12.6 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

### *12.6.1 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.

### *12.7 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 15.7.

### *12.8 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 15.8

## 13. Adverse Events Coded As "Convulsions" In Scharf Study

### *13.1 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 11.2)
  - 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

## *13.2 Results Of Analysis*

### *13.2.1 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 [a] | Sodium Oxybate Oral Solution Dosage (g/d) at Onset[b] | | | | |
|---|---|---|---|---|---|---|
| | | 3.0 | 4.5 | 6.0 | 7.5 | 9.0 |
| Number of Convulsion AE's | 20 | | | | | |
| Patients with at Least 1 AE | 5[c] | 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[d] | 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 |

[a] Patients are counted only once in each category at the highest dose at onset.
[b] Dosage at onset.
[c] 3 patients experienced more than one AE designated as COSTART preferred term Convulsion or Convulsion Grand Mal
[d] 1 patient experienced 3 AEs coded as severe.

### *13.2.2 Investigator Terms*

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

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

| Patient ID | COSTART Term | Verbatim Term | Dose (g)[a] |
|---|---|---|---|
| 043 | Convulsion | Excessive cataplexy | 6.0 |
| 048[b] | 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[c] | 7.5 |
| 247 | Convulsion | Seizures, continuous jerking | 6.0 |
| 255[d] | 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 |

[a] Dose recorded is the dose at the onset of the adverse event.
[b] This event was serious and determined to be related to study medication.
[c] Two cataplexy events captured as separate AEs in the data listings.
[d] 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

## 13.3 Narratives For Patients With Non-Cataplectic Convulsions

### 13.3.1 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 during 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 during 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

### 13.3.2 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 7th 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 ⟶ 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

### *13.3.3 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, 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.

### *13.3.4 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.

### *13.3.5 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

### *13.4 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

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

### *14.1 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.

### *14.2 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[a] | Placebo | Total[a] | Xyrem Oral Solution Dosage (g/d) at Onset[b] | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 3.0 | 4.5 | 6.0 | 7.5 | 9.0 |
| Number of patients | 402 (100%) | 54 (100%) | 355 (100%) | 97 (100%) | 265 (100%) | 250 (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[c] (<1%) | 0 | 3[c] (<1%) | 0 | 0 | 1 (<1%) | 0 | 2[c] (1%) |
| Patient Deaths | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

[a] Patients are counted only once in the total column.

[b] 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.

[c] 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

### *14.3 Verbatim Investigator Terms*

The actual investigator terms were in the following categories

| Investigator Term | Number of Patients |
|---|---|
| "Confusion"<br>"Acute confusional state"<br>"Confusion on awaking" | 15 |
| "Disoriented"<br>"Disoriented on awaking"<br>"Disorientation" | 14 |
| "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

### *14.4 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 |