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

14.5 "Confusion" In Study OMC-GHB-2

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

The distribution of this adverse event by dose group, based on the sponsor's table described in Section 14.4 was as follows

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

The sponsor has drawn attention to the following:

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

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

14.6 Narratives For Patients With Confusion As A Serious Adverse Event

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

14.6.1 Patient 0207 (Initials —)

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

She received Xyrem® 6 g daily. On Day 4 of treatment she developed nausea. Beginning Day 5 she became very talkative with pressured speech, and the next day was noted to be disoriented, agitated and to sleep poorly. She was seen at an emergency room where neurological examination was remarkable for hyperreflexia. Xyrem® was discontinued, the patient was treated with haloperidol and by the next day her confusion had resolved. An EEG was normal and a CT scan of the head showed minor temporal lobe asymmetry. The study drug was permanently discontinued.

14.6.2 Patient 0231 (Initials —)

This patient's narrative is also reproduced in Section 18.2

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

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

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

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

14.7 Narratives For Patients With Confusion As An Adverse Event Warranting Permanent Discontinuation Of GHB

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

14.7.1 Patient 0207 (Initials —

See Section 14.6.1

14.7.2 Patient 0231 (Initials —)

See Section 14.6.2

14.7.3 Patient # 0702 (Initials . —

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

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

14.8 Reviewer's Comments

- As records for contemporaneous formal mental status examinations for patients with "confusion" are unavailable it is unclear if all patients coded as having this adverse event were really confused, as the term is conventionally understood. Investigator terms suggest that at least some patients may not have been confused
- Nevertheless, the information available does suggest that GHB is capable, at therapeutic doses, of causing a confusional state which may be accompanied by psychotic symptoms. The incidence and seriousness of such adverse events may be slightly more pronounced at higher doses, and especially if higher doses are administered without titration. However a confusional state also appears to be capable of occurring at lower and even sub-therapeutic

(e.g., 3 g/day) doses of GHB, and after maintenance treatment for several months.

- The presence of true confusion in patients taking GHB could lead to their taking GHB in a manner other than as prescribed.
- The symptoms that have been subsumed under the COSTART term "confusion" are not surprising for a sedative drug.

15. Neuropsychiatric Adverse Events In Integrated Clinical Trials

15.1 Background

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

The sponsor's methods were as follows:

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

15.2 Overall Summary

50/402 (12.4%) GHB-treated patients had at least one adverse event coded under one or more of the neuropsychiatric adverse event terms outlined in Section 15.1. Their distribution by dose and severity is displayed in the following table which I have copied from the submission.

Possible Neuropsychiatric AEs	Total[a]	Placebo[b]	Xyrem Oral Solution Dosage (g/d) at Onset[c]				
			3.0	4.5	6.0	7.5	9.0
Number of patients	402 (100%)	54 (100%)	97 (100%)	269 (100%)	298 (100%)	133 (100%)	129 (100%)
Patients with ≥ 1 AE	50 (12%)	1 (2%)	5 (5%)	6 (2%)	24 (8%)	4 (3%)	16 (12%)
Patients with SAEs	7 (2%)	0	0	2 (1%)	2 (1%)	0	3 (2%)
Patients with related AEs	26 (6%)	1 (2%)	1 (1%)	3 (1%)	11 (4%)	0	12 (9%)
Patients with severe AEs	8 (2%)	0	0	3 (1%)	4 (1%)	0	3 (2%)
Patients discontinued due to AEs	10 (2%)	0	0	2 (1%)	2 (1%)	0	5 (4%)
Patient deaths due to AEs	1 (1%)	0	0	0	1 (1%)	0	0

[a] Patients are counted only once in each total column.
[b] Patients were on placebo for a short time (4 weeks) relative to the long-term exposure of those treated with Xyrem.
[c] Some patients were exposed to more than 1 dosage during the trial(s), so the sum of patients exposed to specific dosages exceeds the total number of patients in the integrated clinical trials.

As the table above indicates

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

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

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

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

15.3 Distribution Of Individual Neuropsychiatric Adverse Events

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

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

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

15.4 Specific Neuropsychiatric Adverse Events

15.4.1 Depression

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

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

I have not reproduced the table in this review.

In regard to the table the following are noteworthy

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

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

15.4.2 Hallucinations

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

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

I have not reproduced the table in this review.

In regard to the table the following are noteworthy

- 9 patients had adverse events that were coded as hallucinations. In all 9 the investigator term also indicated that they had hallucinations.
- All 9 patients were receiving GHB at the time this adverse event appeared
- In 4/9 the hallucinations, based on the investigator term used, were hypnagogic hallucinations. In a further patient the hallucinations ceased with an increased dose of GHB and were therefore presumed to be hypnagogic hallucinations.
- The hallucinations were characterized in 4 patients (these were not patients with hypnagogic hallucinations): the hallucinations were auditory in 3 and visual in 1.
- In only 1 patient were hallucinations a reason for medication discontinuation. This patient has already been described (see Section 14.7.3)

15.4.3 Stupor

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

This table is below

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