13.10.2 Patient # 0232

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

13.10.3 Patient # 0931

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

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

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

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

13.10.4 Patient # 1131

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

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

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

13.10.5 Patient # 14043

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

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

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

13.10.6 Patient # 2030

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

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

13.11 Adverse Event Discontinuations

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

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

13.11.1 Patient 1305

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

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

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

14.1.2 Drug Product Kit

The drug product kit will consist of

- The drug product, a clear solution, in a ——— amber bottle with a closure mechanism that is child-resistant
- The Press-In-Bottle-Adapter (PIBA Well) which will be inserted into the bottle by the pharmacist

- An Exacta-Med Dispenser which allows the patient to withdraw the appropriate dose of drug
- Two child-resistant dosing cups, one for each of 2 nightly doses. The first dose will be consumed just prior to lying down at bedtime and the second dose will be placed at the bedside, and sealed with a childproof lid until consumed by the patient 2.5 to 4 hours later.
- A package insert which includes a patient information sheet*

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

*The patient information sheet includes the following information

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

14.1.3 Xyrem® Physician Success Program

This program consists of a videotape and printed material.

14.1.3.1 Distribution

This program will be distributed as follows

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

14.1.3.2 Videotape

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

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

14.1.3.3 Printed Materials

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

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

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