The attempted suicide (14043) involved an overdose with buspirone in a patient with pre-existing obsessive-compulsive disorder and depression.

The intentional overdose (1131) involved a patient with pre-existing depression and a previously unknown history of attempted suicide. Following a single ingestion of 150 g of Xyrem overdosing, the patient recovered without sequelae in the ER and was hospitalized for 5 days for psychiatric evaluation.

Thus, this series of 402 patients did not include any fatalities singularly attributable to an overdose with Xyrem, in spite of the huge dose taken by the patient overdosing which was approximately 20 times the maximum proposed total daily dose.

4.8.3.6.2 Scharf Trial

One of the 143 patients reported an AE that coded to the COSTART term suicide attempt, after approximately 2 years on trial medication. This event was reported as verbatim term "attempted suicide by taking an overdose of GHB." The patient had a prior medical history consistent with attempted suicide, including depression with suicide ideation and possible anxiety neurosis. The event was considered serious and definitely related to trial medication, and led to patient discontinuation.

Two of the 143 patients reported AEs that coded to the COSTART term overdose. Both cases were serious and involved overdose with trial medication. One patient (017) overdosed on approximately 18.0 g of trial medication on day 541 reported associated with a sleepwalking episode. This event was considered probably related to trial medication. The patient was unresponsive, was hospitalized, and required intubation. The patient continued on the trial with no further overdose episodes until he died 4.5 years later from cardiopulmonary arrest due to atherosclerotic disease. The second patient (267) was taken to the ER after possibly taking a third dose (of unknown volume) of trial medication on Day 1673. The patient did not recall taking the third dose. The patient awoke after an enuresis episode, and the patient's daughter discovered her walking around in a daze. The patient was taken to the ER; by the time she arrived, she was having no further difficulties. She continued on treatment for 6 months with no further recurrence.

4.8.3.7 Paranoid Reaction

4.8.3.7.1 Updated Integrated Clinical Trial Database

Four (1.0%) of the 402 patients reported AEs that coded to the term paranoid reaction. Patient 0202 admitted to occasionally feeling paranoid at 1 clinic visit and also described two consecutive nights of feeling paranoid at bedtime. These feelings were accompanied by visual and auditory hypnagogic hallucination. Patient 0239 described feeling paranoid on a single occasion, with only 1 day's duration. Patient 0702 described intermittent episodes of feeling fearful.

The paranoid reaction AE in the fourth patient was considered serious (patient 0232). This patient suffered an acute paranoid delusional psychosis that occurred after 15 months on study drug and required overnight hospitalization. The trial medication was discontinued and the patient's mental status improved while being treated on antipsychotic medication. This patient was discontinued from the trial.

4.8.3.7.2 Scharf Trial

One (0.7%) of the 143 patients reported an AE that coded to the COSTART term paranoid reaction. The verbatim description of this event indicated that the patient was "acting very paranoid – carries a bat with him while at home and feels someone is watching him." The event start and stop dates were unknown, but the event was considered not related to study drug. The Investigator reported that the patient had hypnagogic hallucinations. The patient was 16 years of age when he started the trial in June 1986. The patient discontinued the trial in June 1988 due to non-compliance with the diary and clinical lab requirements of the trial. The patient had no previous history of neuropsychiatric events.

4.8.3.8 Coma

4.8.3.8.1 Updated Integrated Clinical Trial Database

Two (0.5%) of the 402 patients were described as having experienced coma while taking trial medication. Patient 0238 was heard to fall and was found unconscious on the floor of the kitchen by his spouse. Paramedics were immediately summoned and found the patient unconscious; he received atropine for bradycardia; naloxone was administered without response. On arrival at the ER, he was intubated to support depressed respiration and was transferred to an ICU, where he soon fully recovered from the event. He later admitted to taking his bedtime dose of sodium oxybate in the kitchen. Intensive neurological and cardiac investigation failed to define a cause for this event and it was proposed to be possibly due to an unidentified cardiac event or to cataplexy with additional head trauma from his head striking the floor. Study drug was discontinued.

Patient 2830 was considered to have experienced coma on 2 occasions while on study drug. In both cases, she fell secondary to cataplexy attack and hit her head, causing loss of consciousness. This patient was known for being non-compliant with the study drug regimen, which probably contributed to her cataplexy.

None of these events qualify as a neuropsychiatric AE

4.8.3.8.2 Scharf Trial

One of the 143 patients experienced an AE with verbatim term "comatose" as part of an overdose (See Table 4.9).

4.8.3.9 Psychosis

Two (0.5%) of the 402 patients in the updated integrated clinical trial database reported AEs that coded to COSTART term psychosis. .

Patient 1101 completed double-blind treatment in the OMC-GHB-2 trial where the dose assignment had been 6.0 g/d sodium oxybate. The patient entered the open-label OMC-GHB-3 trial (1/5/98) at 6.0 g/d. The dose of sodium oxybate was titrated to 7.5 g/d (3/8/98) and then to 9.0 g/d (3/17/98) to achieve optimal clinical benefit. The patient had been taking multiple stimulants to include Dexedrine 15 mg twice daily and Ritalin 10mg three times daily concurrently until this regimen was changed to Adderall 20 mg four times daily approximately two months prior to the adverse event. The patient developed symptoms of acute psychosis beginning 4/27/98 considered of moderate intensity and possibly related to trial medication. Following psychiatric consult both the stimulants and trial medication were discontinued. The adverse event did not resolve. Two weeks following the onset of the adverse event the investigator evaluated all findings and considered the adverse event as not related to study drug by requiring specific other treatment that was contraindicated by the protocol.

Patient 2030 suffered symptoms of psychosis after being on study drug for about 6 months. At that time, he was reported by a family member to be increasingly paranoid and suffering from night terrors and hallucinations. The patient was seen in the ER, where he admitted to increasing his Ritalin dose to facilitate cramming for college examinations. The patient was started on antipsychotic medications and was restarted on study drug after the symptoms of psychosis had resolved. A week later these same symptoms and precipitating circumstance recurred, prompting a hospital admission and discontinuation from the study. This event was considered the result of escalated doses of stimulant medication and sleep deprivation.

No patients in the Scharf trial experienced psychosis.

4.8.3.10 Manic Depressive Reaction

An adverse event of bipolar affective disorder (verbatim term) COSTART coded to manic depressive reaction was reported for 1 patient (0931) in the 402 patient updated integrated clinical trial database. The patient was a 29-year-old female with a previous history of depression. The diagnosis of bipolar affective disorder was made during psychiatric consult following reports of intermittent hallucinations for two weeks and unusual behavior (from delayed response to violent agitation on questioning when found asleep in her automobile). The adverse event was considered severe but unrelated to study drug and the patient was discontinued from the trial. The patient was treated and released from hospital. Present day follow-up showed the patient to be functioning well with continued treatment (Haldol, Cogentin) for underlying disease, which excluded further participation in the trial despite positive response in narcolepsy.

No patients in the Scharf trial experienced manic depressive reaction.

4.8.3.11 Personality Disorder

One patient (1530) in the 402 patients in the updated integrated clinical trial database reported an AE that coded to personality disorder. This 25-year-old woman experienced a personality disorder (investigator term "grief reaction" due to the death of a relative) beginning on Day 139 of the OMC-SXB-6 trial. The event lasted 258 days in trials OMC-SXB-6 and OMC-SXB-7. The event was considered mild in severity, intermittent, and not related to trial medication. No action was taken for the event.

No patients in the Scharf trial experienced personality disorder.

4.8.3.12 Emotional Lability

Ten (7.0%) of the 143 patients in the Scharf trial reported 14 AEs that coded to the COSTART term emotional lability. The majority of the verbatim terms relate to conditions of "laughing" or "crying." The dosages at onset ranged from 3.0 to 9.0 g/d. None of the events was considered serious. One event was considered probably related to trial medication, 2 were possibly related, 9 were not related, and 2 were of unknown relationship. Date of onset ranged from Days 0 to 1078, with the majority of events occurring during the first 100 days on trial medication. Seven events resolved in 3 days or less. One patient who experienced an event of verbatim term "heart aches" had a previous history of depression and recurrent melancholia. One patient (259), who experienced a probably related event of "crying a lot" at the 5.3 g/d dosage, discontinued due to this and other AEs.

4.8.3.13 Thinking Abnormal

Nine (6.3%) of the 143 patients in the Scharf trial reported 13 AEs that coded to the COSTART term thinking abnormal. The verbatim terms included "fogginess," and terms relating to problems with concentration, transposition of numbers, and negative thinking. The dosage at onset for these events ranged from 4.5 to 9.0 g/d; the date of onset ranged from Days 0 to 531. One event ("very talkative after gamma dose") was considered probably related to trial medication, 5 events were possibly related, 3 events were of unknown relationship, and 3 events were considered to be not related. Events where resolution dates were recorded usually represented transient episodes, lasting for a day or less. Four patients had a previous history of traumatic head injury, 1 of whom also had a previously diagnosed frontal lobe lesion.

4.8.3.14 Depersonalization

Seven (4.9%) of the 143 patients in the Scharf trial reported AEs that coded to the COSTART term depersonalization. Verbatim terms generally related to unusual behavior or feeling unusual. The dosage at onset for these events ranged from 5.3 to 6.8 g/d; date of onset ranged from Days 3 to 513 after initiation of sodium oxybate treatment. Three events were considered probably related to trial mediation (verbatim terms "bizarre behavior," "felt crazy," and "zombie like state"), 2 were of unknown

relationship, and 2 were considered not related. None of the events was considered serious. Duration is recorded for only 3 events, with 2 occurring for 1 day or less and 1 having a duration of 17 days. One patient (259) discontinued the trial due to the AEs she was experiencing.

4.8.3.15 Hostility

Six (4.2%) of the 143 patients in the Scharf trial reported 8 AEs that coded to the COSTART term hostility. Of the 8 events, 3 were considered possibly related, 3 were considered not related, and 2 were of unknown relationship to trial medication. None of the AEs was considered serious or led to patient discontinuation.

Six of the 8 events were related to anger (including terms temper and rage). The dosage at onset for these 6 events ranged from 4.5 to 9.0 g/d; the date of onset ranged from Days 34 to 1078. Only 1 AE (patient 215, rage) had a stop date recorded, with a duration of 1 day. One patient (286) had a previous history of irritability caused by Ritalin, although it is not certain if he was taking Ritalin at the time of the event.

Two additional events coded to the COSTART term hostility, with verbatim terms "feisty" and "frustration." The event termed "feisty" occurred on day 124 at the 9.0 g/d dosage. No resolution date was recorded, but the event was considered possibly related to study drug and was not serious. The event termed "frustration" occurred and resolved on Day 20 at the 4.5 g/d dosage. The patient's history included difficulty controlling his temper. The event was not serious and was considered not related to study drug.

4.8.3.16 Neurosis

Two of the 143 patients in the Scharf trial reported AEs that coded to the COSTART term neurosis. The first event occurred in a female patient on Day 3328 at a 5.3 g/d dosage. The verbatim term (patient's diary description of the event) indicated that she was "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." The patient woke her husband up to help her with the event(s). The event was not serious, not considered related to trial medication, and of unknown duration.

The second event occurred in a male patient on a 6.0g/d dosage starting on Day 3283 and was described by verbatim term "claustrophobia." The patient was instructed to decrease his Ambien dosage, with no resolution. The patient was then instructed to decrease his trial medication dosage from 6.0 to 3.0 g/d, and the event subsequently resolved. The event was not serious and was considered possibly related to trial medication. The patient continued in the trial, usually at a dosage of 6.0 to 6.6g/d, until the data cutoff of May 31, 1999, with no further recurrence.

4.8.4 BLOOD GLUCOSE

The updated integrated clinical trial database was analyzed for any patients who had AEs with the COSTART preferred term of hyperglycemia or diabetes mellitus, and/or

who experienced clinically significant increases in glucose laboratory values (≥ 70% increase over baseline [from earliest trial] and an absolute value of > 200 mg/dL).

Measurement of blood glucose levels was not done on a routine basis in these long-term studies. Non-fasting glucose measurements were used for all tests in the treatment IND protocols (OMC-SXB-6, OMC-SXB-7), while fasting blood collections were specified in the OMC-GHB-2 and OMC-SXB-3 protocols (although this requirement was not always met).

Of the 402 patients, 5 patients (1%) had 9 AEs with the COSTART preferred term of hyperglycemia or diabetes mellitus. Four patients had 1 AE each; patient 1505 had 4 AEs of hyperglycemia and 1 AE of diabetes mellitus. The incidence of hyperglycemia/diabetes did not appear to be dose-related, with 1 patient in each of 3 of the dosage at onset treatment groups (4.5 g/d, 7.5 g/d, and 9.0 g/d), and 2 patients in the 6.0 g/d group.

There were no deaths, no SAEs, and no discontinuations due to these AEs. All AEs of hyperglycemia/diabetes mellitus were of mild to moderate severity. Four patients had AEs considered unrelated to trial drug, while 1 patient (1610 in OMC-GHB-3) had unknown relationship.

Two of the 5 patients had a history of diabetes (0410 and 1505); 2 patients (1505 and 2633) were obese. The other 2 patients had no relevant medical history. Of the 5 patients, 4 (80%) were men, and 3 (60%) were 50 years of age or older (range 36.4 to 65.4 years).

There was no relationship between the incidence of hyperglycemia/diabetes and the length of exposure to sodium oxybate: 1 patient experienced hyperglycemia on Day 15; 3 patients experienced hyperglycemia or diabetes mellitus during Days 31 to 394; and 1 patient experienced 5 AEs during Days 511 to 1064. Two patients had unresolved AEs (1708, diabetes; 2633, hyperglycemia), and the outcome of 1 AE (patient 1505, elevated glucose) is unknown. All other AEs resolved.

Actual investigator terms were:

- "Elevated blood glucose" or "elevated glucose" – 3 patients with 4 events
- "Abnormally high glucose" – 1 patient with 2 events
- "Hyperglycemia" – 1 patient with 1 event
- "Diabetes" or "poorly controlled diabetes" – 2 patients with 2 events

Two of the AEs were associated with clinically significant increases in glucose values – patients 0410 (verbatim term elevated blood glucose) and 1505 (verbatim term poorly controlled diabetes, on day 650). An additional 4 patients had clinically significant increases in glucose values that were not associated with an AE of hyperglycemia or diabetes mellitus. An elevated glucose level not associated with an AE was also seen on Day 278 for patient 1505.

Two of the 4 additional patients had a history of diabetes. The 7 instances of elevated glucose values for all 6 patients occurred on Days 201 to 363 for 3 events, Days 424 to 618 for 3 events, and Day 1070 for 1 event. Absolute levels ranged from 217 to 403 mg/dL; increase from baseline ranged from 70.2% to 140.0%.

4.8.5 DETAILED ANALYSIS OF ELEVATED ANTI-NUCLEAR ANTIBODY AND STUDY DRUG-RELATED LUPUS

4.8.5.1 Scharf Trial

In 1991, a 49-year-old female patient in the Scharf trial developed clinical symptoms of arthritis, after treatment with sodium oxybate 6.0 g/d for more than 5 years. An anti-nuclear antibody (ANA) test and 2 repeat tests were all positive, raising concern for the possibility of study drug-related lupus. She was withdrawn from sodium oxybate with a subsequent fall in ANA titers, followed by an increase again 1 year later.

At the request of the FDA, ANA profiles were collected for all ongoing patients in the Scharf trial until 1999. Over the next 2 years, 19 (29.2%) of 65 patients tested were shown to have ANA elevations ranging from 1:40 to 1:2560. Some of these elevations were intermittent and no correlation was found between positive ANA titer and duration of treatment, age, or sex. Antihistone antibodies (determined for 15 of the 19 ANA-positive patients) showed a "borderline" positive result in only 1 patient. All 65 patients tested were requested to complete a symptom questionnaire, which showed a low overall incidence of symptoms possibly related to lupus and no discernible difference in the subgroup of ANA-positive patients.

No association emerged between the occurrence of positive ANA findings and the development of symptoms consistent with systemic lupus erythematosus (SLE), medication-induced lupus, or any rheumatic disease except for the first patient who had acute arthritis symptoms and a positive ANA when last tested. In medication-induced lupus, positive ANA findings are accompanied by positive antihistone antibodies in more than 90% of cases (Schur 1996). This occurred in only 1 of 15 ANA-positive patients who were tested, and this patient did not display symptoms characteristic of lupus.

These data indicate that long-term use of sodium oxybate may result in ANA elevations without the corresponding increase in antihistone antigens characteristic of most reported cases of medication-induced lupus. In addition, narcoleptic patients with positive ANA findings did not present with or subsequently develop symptoms suggestive of lupus-related disease. Finally, no patients in the Scharf long-term trial have developed SLE during treatment with sodium oxybate for up to 16 years.

Dr. Evelyn Hess, an internationally recognized expert on medication-induced lupus and SLE, concurred with these findings and could find no evidence of either SLE or medication-induced lupus. In her opinion, the most that could be concluded was that sodium oxybate, like some 80 other drugs in the scientific literature, may be associated with low-level increased titers of ANA of no known clinical significance.

4.8.5.2 Updated Integrated Clinical Trial Database

In response to an FDA request for a post-hoc evaluation of the potential for symptoms of drug-induced lupus, the updated integrated clinical trial database was examined in 2 ways. First, the AE listings were visually examined for a combination of potential lupus symptoms occurring within a given patient. Second, the AE database was queried electronically to identify all patients who reported 1 or more of the 9 selected possible drug-related lupus symptoms (as COSTART terms) – arthralgia, arthritis, myalgia, joint disorder, pain, alopecia, fever, malaise, and rash. These COSTART terms were selected following examination of the previously submitted drug-induced lupus review article by Dr. Evelyn Hess (Hess 1991) and a telephone discussion with Dr. Hess on 3/12/01. According to Dr. Hess, patients with drug-related lupus present with multiple symptoms, particularly the articular symptoms (arthritis and/or arthralgia in multiple joints), which occur in over 80% of drug-related lupus patients.

Alopecia was reported on 5 occasions but did not occur in any of the 402 patients in conjunction with any of the other 8 possible drug-related lupus symptoms. Thus, alopecia was dropped from further evaluation and consideration in the analysis.

As expected, the COSTART term "pain" (not otherwise specified) was the most common AE, occurring 168 times in 46 of the 402 patients. In 22 of these 46 patients, nonspecific pain was the only lupus-related symptom reported on 2 or more occasions. Nonspecific pain was generally not associated with the more specific lupus symptom terms of arthralgia, arthritis, joint disorder, and myalgia.

The database was re-examined to identify only those patients who reported one of the 7 remaining drug-related lupus symptoms on more than 1 occasion or more than 1 of the 7 symptoms.

A total of 19 patients were identified with 2 or more of these events. Seven of these 19 patients reported only 1 of the 7 selected symptoms on multiple occasions – 2 patients with 6 events for myalgia, 2 patients with 5 events for fever, 1 patient with 2 events for joint disorder, 1 patient with 3 events for malaise, and 1 patient with 2 events for rash. Since no other symptoms suggestive of possible drug-related lupus were recorded for these 7 patients, no further analysis was indicated.

The remaining 12 patient case records were reviewed in detail to determine if any patient developed AEs suggestive of possible drug-related lupus. For 11 of the patients, there was no convincing evidence of symptoms consistent with a possible diagnosis of drug-related lupus. For the twelfth patient (1633), symptoms of joint pain developed while on treatment, persisted for several months, and disappeared within 2 months after stopping the drug. Follow-up 1 year later indicated no recurrence of joint pain. Thus, drug-related lupus cannot be totally ruled out. However, in the absence of any supportive laboratory measures (such as positive ANA and antihistone antibodies) and any other symptoms of lupus, the diagnosis of drug-induced lupus cannot be established.

In conclusion, none of the 402 patients in the updated integrated clinical trial database developed SLE or were diagnosed with drug-induced lupus during participation in any of the 5 trials. A systematic review of the AE data collected on these 402 patients definitively excluded symptoms suggestive of drug-induced lupus in all but 1 patient.

4.8.6 DETAILED ANALYSIS OF INCONTINENCE AES AND RELATIONSHIP TO SEIZUROGENESIS

Animal studies have shown that high dosages of sodium oxybate may be associated with EEG changes and symptomatology representing absence-seizure-like states. This has been developed as a model for absence seizures in primates (Snead 1978), using high dosages of IV sodium oxybate. Myoclonus has also been described as a frequent accompaniment of anesthesia induction with IV sodium oxybate.

4.8.6.1 Updated Integrated Clinical Trial Database

In their review of the OMC-GHB-2 clinical trial report (submitted October 10, 1998), the FDA requested an analysis of a potential relationship between incontinence and seizurogenesis. Our investigation included:

- A questionnaire to all affected investigators to review any observed abnormal nocturnal observations suggestive of seizures, urological history preceding oxybate therapy, and any new neurological symptoms
- Correlation between CNS AEs that could be related to seizures and incontinence (either urinary or fecal)
- Overnight full-montage EEG recording in 6 patients with a prior history of incontinence during sodium oxybate treatment (at a Xyrem dosage of 9 g/d)
- Review of the data by an independent expert (Dr. Nathan Crone, Johns Hopkins University Medical Center)

In review of the data, there was no evidence to support seizurogenesis in our clinical trials. An analysis of all AEs reported in OMC-GHB-2 and OMC-GHB-3 suggestive of incontinence (66 events), as well as CNS anomalies, showed no relationship between the two. The analysis noted that "episodes of neurological dysfunction, including tremor, incoordination, focal sensory loss and/or confusion (83 events), were simultaneous with enuresis on only 4 occasions."

Over the clinical experience of approximately 750 patient-years with sodium oxybate, the analysis noted, most of the patients had bed partners, none of whom reported behavior suggestive of seizures. Since the seizures that most commonly cause urinary incontinence are generalized tonic-clonic seizures, these would be expected on at least some occasions to awaken a bed partner.

The analysis described 15 events of enuresis or urinary incontinence in 8 of the 136 patients in OMC-GHB-2, and 51 events in 13 of the 118 patients in OMC-GHB-3. A single patient (0819) in OMC-GHB-3 accounted for 15 events. One additional patient in each trial experienced fecal incontinence. Two patients in each trial experienced urinary incontinence and a CNS anomaly simultaneously. No events suggestive of seizure occurred in either of the patients (0124 and 0702) in OMC-GHB-2, or in either of the patients (0219 and 0819) in OMC-GHB-3.

In the full-montage EEG studies, 1 patient had urinary incontinence during the recording. There was no EEG evidence of seizure activity in any of the 6 patients.

Overall, in the updated integrated clinical trial database, 36 of the 402 patients (9.0%) experienced incontinence urine or urinary incontinence; 2 patients (0.2%) experienced fecal incontinence.

One subject (003) from the 8 pharmacokinetic trials experienced an adverse event of "labored respiration" coded to the COSTART term "apnea". Two hours post-dosing (with a single 4.5 g dose) the subject experienced a second event of respiratory stridor which was accompanied by fecal incontinence. The subject was arousable, and responded to verbal commands. The event resolved and two hours later the subject consumed a lunch.

4.8.6.2 Scharf Trial

We conducted a similar analysis on the 143 patients enrolled in the long-term clinical (Scharf) trial, in which 33 of the 143 patients (23.1%) experienced urinary incontinence, and 1 patient (0.7%) experienced fecal incontinence.

The analysis included 2 independent examinations of all AE terms suggestive of incontinence. AE terms suggestive of CNS anomalies were also carefully examined. There was 1 observation of fecal incontinence in 1 patient, 140 observations of urinary incontinence or enuresis in 33 patients, and 704 observations of any nervous system anomaly in 104 patients (42 specific terms).
An analysis to identify those patients in whom fecal or urinary incontinence or enuresis occurred in temporal association with any nervous system anomaly (which could suggest seizurogenesis) revealed 10 incontinence events and 12 CNS events in 7 patients (Table 4.21).

Table 4.21 Patients Exhibiting Enuresis, Urinary Incontinence, or Fecal Incontinence and CNS Anomalies – Scharf Trial

Patient Number	Enuresis, Urinary Incontinence, or Fecal Incontinence AEs			CNS 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
	Enuresis episode	08/12/93	08/12/93	Sleepwalking episode	08/12/93	08/12/93
048	Enuresis	09/11/84	09/11/84	Confusion	09/11/84	09/11/84
				Numb all over	09/11/84	09/11/84
	Urinary incontinence with seizure	02/07/89	02/08/89	Convulsive-like seizure	02/07/89	02/08/89
207	Wet the bed	03/22/85	03/22/85	Sleepwalking	03/22/85	03/22/85
247	Enuresis	04/27/90	04/27/90	Seizure (continuous jerking all over)	04/27/90	04/27/90
255	Urinary incontinence	02/21/91	02/21/91	Brief grand mal seizure (while at Dr.'s office)	02/21/91	02/21/91
257	Loss of bowel control	01/26/91	01/26/91	Intense body shaking	01/26/91	01/26/91
	Loss of bladder control	01/26/91	01/26/91	Jerking during cataplexy	01/26/91	01/26/91
262	Bedwetting (3 episodes)	01/24/96	01/31/96	Dizzy	01/24/96	01/25/96
				Felt like head rolling around	01/24/96	01/25/96

Analysis of these 7 cases revealed 6 occurrences of enuresis that were deemed probably related to study drug and were associated with sleepwalking, confusion, and dizziness, also believed to be related to study medication. None of these CNS events supported seizure activity relating to the incontinence event. Four additional observations were possibly associated with seizure activity:

- One patient (255) experienced a witnessed major motor seizure; however, he also had a history of seizures prior to taking study drug. It was determined to be unlikely that the study drug was responsible for this event.

- In 3 other instances, fecal (1) or urinary incontinence or enuresis (2) occurred with coincident CNS anomalies that were suggestive of seizures:

- Patient 048 reported urinary incontinence that occurred in conjunction with a "convulsive-like seizure." Although the patient's EEG was normal, these events were felt to be possibly related to the study drug.

- Patient 247 had 1 case of enuresis (probably related to study drug) associated with "continuous jerking all over"; this patient had 10 other episodes of enuresis that were not associated with any CNS anomaly. While the relationship between the continuous jerking and the study drug is unknown, seizure activity cannot be excluded.

- The fecal and urinary incontinence associated with "body shaking" and "jerking during cataplexy" experienced by patient 257 were considered unrelated to study drug. The inclusion of this patient may reflect a coding error, since this patient experienced events where the COSTART term "convulsions" was used for verbatim terms of "cataplexy," "bad cataplexy," "fall from cataplexy," and "violent shaking and vibrations." In addition, fecal incontinence is known to occur secondary to narcolepsy and cataplexy (Vgontzas 1996).

In all other instances of urinary incontinence or enuresis, there was no correlation between any CNS observations; it is likely that the incontinence was due to the narcolepsy disease state (Sher 1996).

Thus, despite the appearance of absence-seizure-like states in primates at IV dosages far exceeding the human therapeutic dosage, there is no support, in the updated integrated clinical trial database, the long-term (Scharf) clinical trial, or in the literature reporting human experience in therapeutic dosages, for a relationship between incontinence and seizures.

4.8.7 SUMMARY OF DISCONTINUED PATIENTS - SCHARF TRIAL

From the time of study initiation in 1983 to the time of study closure in 2000, a total of 143 patients participated in the Scharf trial. As of the data cutoff of May 31, 1999, 63 (44%) of these patients had transferred into the Orphan Medical Treatment IND protocol OMC-SXB-7. Of the remaining 80 patients, 8 continued to participate in the Scharf trial under the Investigator IND, 71 patients had discontinued from the Scharf trial prior to the cutoff date, and 1 was a screen failure.

Comparison of age and gender at trial entry for the 80 patients that did not enroll in OMC-SXB-7 as of May 31, 1999, and the 63 patients who entered Orphan Medical trial OMC-SXB-7 showed no differences between the 2 groups. The mean age at trial entry for 79 of the 80 patients (1 patient who was a screen failure [211] was not included in the calculations) who did not enroll in OMC-SXB-7 was 47.0 years, compared with 44.3 years for the 63 patients who transferred into OMC-SXB-7. Male patients accounted for 57% of the patients in both population subsets.

Table 4.22 summarizes the reasons for discontinuation for the 71 patients who discontinued prior to the data cutoff. The majority of the discontinued patients were terminated from the trial due to non-compliance or cost (37 of 71, 52.1%). Only 6 of the discontinuations were due to possibly or probably related AEs. Of the remaining AE discontinuations, the 10 deaths were due to cardiovascular and neoplastic diseases, none of which was considered related to trial medication. Four patients discontinued because of lack of efficacy, and 1 patient who cited the cost of the drug as a reason for discontinuation also noted a lack of efficacy.

Table 4.22 Patient Disposition – Scharf Clinical Trial

Patient Disposition	Number of Patients
Patients screened	143
Patients treated	142
Continued treatment	71
Ongoing treatment (OMC-SXB-7)	63
Ongoing treatment (Scharf)	8
Discontinued treatment	71
Non-compliance	24
Failure to provide diaries	22
Failure to follow dosing instructions	2
AEs	23
Death (coded as an SAE)	10
Other AE	13
Cost of medication	13
Patient request/withdrawal of consent	5
Lack of efficacy	4
Protocol deviation	1
Other (transfer to fibromyalgia study)	1

[a] In the initial Scharf Report, 11 deaths were reported, however, one patient (202) died in a boating accident seven months following discontinuation of study medication. The case report form lists patient request as the reason for discontinuation.

Patient non-compliance was the most common reason for patient discontinuation. The majority (22 of 24) of patient non-compliance discontinuations were the result of patients' failure to complete and return the patient daily diary sleep logs and/or questionnaires as required by the protocol. The other 2 non-compliance discontinuations were due to patients not conforming to the study drug dosing regimen.

Of the 23 discontinuations due to AEs, 10 patients died. An additional patient (202) died in a boating accident approximately 7 months after discontinuing study drug. Although the CRF listed the death as an SAE, the reason for discontinuation should properly be listed as patient request. None of the deaths was considered possibly or probably related to study medication. It should be noted that the Scharf clinical trial report indicated that 19 patients, not 23, were discontinued due to an AE. On review of source documents, case report forms, and data listings for the 80 patients that did not enroll into OMC-SXB-7 as of May 31, 1999, 4 additional patients were found to have discontinued

due to an adverse event. Of these patients, 2 died (017 – cardiopulmonary arrest due to atherosclerotic disease; 241 – small cell carcinoma of the lung), 1 (006) experienced an event of stimulant-induced rage, and 1 (270) became pregnant. None of these events was considered to be related to trial medication.

Of the remaining 13 AE discontinuations, 6 were considered possibly or probably related to study drug, including: attempted suicide by sodium oxybate overdose (patient 019, who had a previous history of depression and suicide ideation); high ANA titer/possible drug-induced lupus (patients 066 and 244, neither of whom ever manifested the symptoms of lupus); possible pulmonary toxicity (patient 254); depersonalization, emotional lability, hypertonia, and pain chest (patient 259); and swelling of ankles and feet (patient 271). Three of the 6 probably or possibly related AE discontinuations were reported in the Scharf clinical trial report. The remaining 3 were the result of a review of the 80 aforementioned patients in response to the FDA request and data was derived from primary source clinical records and possible patient contact to expand and clarify the data. These patients were, 066, 244, and 254.

The cost of medication, which was communicated to patients prior to study entry in the informed consent document of the Scharf trial, was the reason for discontinuation for 13 patients. Unlike most investigational drug studies, patients treated in the Scharf trial were required to pay a fee of $1,000 per year ($250 paid quarterly) to partially defray the costs incurred by the investigator in providing the study drug. This requirement was clearly specified in the written informed consent statement signed by each patient prior to beginning the trial. It is noteworthy that except for the initial limited funding provided by the FDA Orphan Drug grant, Dr. Scharf conducted this large clinical study independently for over 10 years, without any additional grant support or external funding beyond the stated patient contributions.

Table 4.23 summarizes the 80 patients who did not enroll in OMC-SXB-7 by the data cutoff (sorted by reason for discontinuation).

Table 4.23 Summary of 80 Scharf Patients Who Were Not Enrolled in OMC-SXB-7 as of Data Cutoff (May 31, 1999)

Patient No.	Sex/Age at Trial Entry (yr)	Date Started Sodium Oxybate Treatment	Date of Last Dose	Comments
Reason for Discontinuation: AE – Patient Death				
001	M/46	11/17/1983	7/31/1989	Metastatic colon carcinoma
009	M/58	11/28/1984	11/30/1994	Arteriosclerotic cardiovascular disease
014	M/41	4/13/1987	10/31/1995	Cardiac arrhythmia and severe coronary atherosclerosis
017	M/62	2/7/1989	2/28/1995	Cardiopulmonary arrest due to atherosclerotic disease
032	F/64	7/25/1984	10/19/1994	Lung cancer
053	M/47	3/29/1984	7/31/1994	Myocardial infarction
200	M/66	5/22/1985	9/30/1990	Lung cancer
232	M/64	6/16/1987	3/13/1992	Myocardial infarction secondary to bladder carcinoma
241	M/55	2/27/1985	5/26/1989	Small cell carcinoma of the lung
243	M/58	6/20/1984	2/28/1989	Myocardial infarction
Reason for Discontinuation: AE				
005	F/49	11/16/1987	7/12/1992	Increased difficulty sleeping
006	M/14	7/24/1985	12/31/1992	Stimulant-induced rage
019	M/41	7/12/1987	7/30/1989	Attempted suicide by GHB overdose
064	F/13	6/16/1987	5/00/89	Increased seizure activity
066	F/44	3/25/1985	4/20/1991	High ANA titer/possible drug-induced lupus
238	M/45	11/30/1983	10/20/1985	Decrease in short-term memory (COSTART term "amnesia")
244	F/55	6/21/1988	5/3/1989	High ANA titer/possible drug-induced lupus
247	F/33	7/25/1989	4/30/1990	Seizure
254	F/61	5/2/1988	6/26/1989	Possible pulmonary toxicity
259	F/41	6/3/1987	7/15/1987	Depersonalization, emotional lability, hypertonia, and pain chest
270	F/24	1/16/1994	4/22/1999	Patient became pregnant
271	M/46	10/24/1994	4/30/1995	Swelling of ankles and feet
273	F/59	11/6/1994	9/30/1995	Weight loss
Continued in the Scharf IND Protocol				
004	M/61	1/21/1988	NA	
027	F/55	3/28/1984	NA	
054	M/63	2/10/1987	NA	

(continued)

Table 4.23 Summary of 80 Scharf Patients Who Were Not Enrolled in OMC-SXB-7 as of Data Cutoff (May 31, 1999)

Patient No.	Sex/Age at Trial Entry (yr)	Date Started Sodium Oxybate Treatment	Date of Last Dose	Comments
065	F/39	11/16/1983	NA	
228	M/16	2/17/1986	NA	
262	F/63	3/27/1991	NA	
269	M/50	7/8/1993	NA	
283	M/56	12/3/1997	NA	
Reason for Discontinuation: Cost				
013	M/47	1/18/1988	3/26/1988	
016	M/29	2/19/1986	1/31/1989	
023	F/34	4/18/1984	12/31/1992	
029	F/40	1/11/1984	2/28/1989	
204	M/49	6/27/1984	11/27/1984	
205	F/54	4/1/1985	9/25/1986	
214	M/53	7/25/1985	11/1/1985	
224	F/45	2/20/1987	4/20/1988	
239	F/59	11/30/1984	11/11/1985	
242	M/40	2/1/1984	8/12/1985	
245	M/49	4/18/1984	8/18/1985	
252	M/61	6/27/1984	11/27/1984	
285	M/43	8/14/1991	11/30/1994	Also noted lack of efficacy
Reason for Discontinuation: Lack of Efficacy				
007	M/54	8/13/1985	3/16/1991	Started on Anafranil to control cataplexy
208	M/51	10/17/1984	11/13/1984	Patient's chief complaint was excessive daytime sleepiness
221	F/43	5/23/1984	6/17/1984	
253	F/75	9/30/1987	12/26/1987	
Reason for Discontinuation: Non-Compliance				
048	F/27	10/26/1983	2/28/1989	
063	F/26	5/6/1988	5/31/1997	
201	F/47	10/26/1983	12/31/1983	
203	F/39	4/18/1984	5/14/1984	
207	F/32	2/1/1984	3/31/1985	
209	F/30	6/27/1984	10/2/1984	
210	M/30	10/5/1984	5/3/1985	
212	M/58	7/29/1985	11/16/1985	
213	F/45	6/3/1985	12/23/1985	

(continued)

Table 4.23 Summary of 80 Scharf Patients Who Were Not Enrolled in OMC-SXB-7 as of Data Cutoff (May 31, 1999)

Patient No.	Sex/Age at Trial Entry (yr)	Date Started Sodium Oxybate Treatment	Date of Last Dose	Comments
215	F/46	10/26/1983	10/30/1988	
216	M/49	11/26/1984	2/22/1987	
217	M/52	1/27/1986	7/19/1986	
222	F/72	3/5/1987	4/21/1988	
223	M/45	7/15/1986	1/24/1987	
240	M/42	1/5/1988	7/5/1988	
246	M/59	7/15/1986	4/22/1987	
248	M/73	7/17/1986	10/13/1986	
251	M/65	4/18/1984	11/21/1986	
256	M/16	6/10/1986	6/10/1988	
258	M/54	11/14/1990	Unknown	
263	M/61	1/30/1991	5/31/1991	
267	F/61	4/29/1992	7/31/1997	
268	M/22	7/11/1993	3/00/97	
288	F/27	7/10/1998	10/31/1998	
Reason for Discontinuation: Other				
279	F/35	9/13/1996	6/20/1998	Patient transferred to fibromyalgia study
Reason for Discontinuation: Patient Request				
012	M/74	8/20/1984	8/31/1994	
036	M/31	2/6/1989	10/00/98	
202	M/55	12/20/1984	3/8/1986	Patient died in boating accident approximately 7 months after discontinuing study drug
206	F/53	1/13/1984	8/26/1984	Patient concerned about smoking while sleepwalking
218	F/40	5/26/1984	6/00/84	
Reason for Discontinuation: Protocol Deviation				
276	M/31	12/12/1995	2/26/1996	Failed to meet inclusion criteria (not a narcoleptic)
Screen Failure				
211	F/NA	NA	NA	Patient did not receive study drug

4.8.8 EVALUATION OF "REACTION UNEVALUABLE" PATIENTS (SCHARF TRIAL)

At FDA request, Orphan Medical sought to provide explanation for a total of 75 Adverse Events in the Scharf trial which were initially coded as "reaction unevaluable." Table 4.24 summarizes these 75 events. The description of the AE is based on a review of the documentation (eg, source records, CRFs). The events were categorized as follows:

- Treatment – The event was a treatment procedure or medication for one of the following:
  - A previously described AE
  - Conditions described in the patient's medical history
  - A treatment that was entered in the CRF in place of the AE(s) that precipitated the need for treatment
- Diagnostic Procedure – The patient underwent diagnostic testing because of an AE (eg, angiography performed for an AE of chest pain)
- Elective Surgery – Patient underwent elective surgery
- Not an AE – The event was captured in the CRF, but was not an AE (eg, the prophylactic use of aspirin for prevention of cardiovascular disease)
- Unknown Medication – Patient diary or CRF noted that patient took a drug, but there was no indication listed for the drug

Table 4.24 Summary of "Reaction Unevaluable" AEs – Scharf Trial

Event Type	Number of Events
Total	75 (100%)
Treatment	44 (58.7%)
Diagnostic Procedure	16 (21.3%)
Not an AE	7 (9.3%)
Elective Surgery	6 (8.0%)
Unknown Medication	2 (2.7%)

Of the 75 "reaction unevaluable" events analyzed, the review process clarified 73 events; 2 events (2.7%) were for medications taken for unknown conditions, and could not be resolved.

Fifteen (20%) of the 75 events were considered serious. Only 2 of the "reaction unevaluable" events were considered "probably related" to study drug. These 2 events, both coding to COSTART term "overdose," were among the 15 SAEs.

4.8.9 ADVERSE EVENTS: COMPARISON OF SODIUM OXYBATE AND PLACEBO IN CONTROLLED TRIALS

Table 4.25 summarizes AEs occurring in ≥ 5% of any group for sodium oxybate (all dosages combined) and placebo in the 3 double-blind, randomized, 4-week, placebo-controlled trials with washout periods (no treatment for cataplexy) of 1 to 7 weeks (OMC-GHB-2, Scrima, and Lammers) and for the double-blind, randomized, 2-week, placebo-controlled trial with a 2-week lead-in of single-blind Xyrem (OMC-SXB-21).

In the 3 trials with washout periods, 69% of the sodium oxybate-treated patients experienced 1 or more AEs, compared with 49% of the placebo-treated patients. The most frequently reported AEs for sodium oxybate-treated patients were dizziness (23%), headache (20%), and nausea (16%). For placebo-treated patients, headache was the most frequently reported AE (15%); all other AEs occurred in less than 10% of placebo patients.

In OMC-SXB-21, 12% of the sodium oxybate-treated patients experienced 1 or more AEs, compared with 31% of the placebo-treated patients. No AE was reported by more than 1 patient (4%) in the sodium oxybate group. For placebo-treated patients, headache and anxiety were the most frequently reported AEs (2 patients, 7% each); all other AEs occurred in only 1 patient (3%).

Table 4.25 AEs Occurring in ≥ 5% of Any Group, by Body System, COSTART Preferred Term, and Treatment Group (Active or Placebo) — Controlled Trials

Body System / COSTART Preferred Term	OMC-GHB-2, Scrima, and Lammers			OMC-SXB-21		
	Total[a]	Placebo	Sodium Oxybate	Total	Placebo	Sodium Oxybate
Number of Patients	**226 (100%)**	**79 (100%)**	**147 (100%)**	**55 (100%)**	**29 (100%)**	**26 (100%)**
Patients with ≥ 1 AE	130 (58%)	39 (49%)	101 (69%)	12 (22%)	**9 (31%)**	3 (12%)
Body as a Whole	79 (35%)	24 (30%)	60 (41%)	4 (7%)	3 (10%)	1 (4%)
Headache	39 (17%)	12 (15%)	29 (20%)	2 (4%)	2 (7%)	0
Infection	11 (5%)	1 (1%)	10 (7%)	0	0	0
Pain	19 (8%)	3 (4%)	17 (12%)	0	0	0
Cardiovascular System	11 (5%)	2 (3%)	9 (6%)	1 (2%)	1 (3%)	0
Digestive System	46 (20%)	9 (11%)	37 (25%)	0	0	0
Dyspepsia	14 (6%)	5 (6%)	9 (6%)	0	0	0
Nausea	28 (12%)	4 (5%)	24 (16%)	0	0	0
Vomiting	10 (4%)	1 (1%)	9 (6%)	0	0	0
Musculoskeletal System	9 (4%)	1 (1%)	8 (5%)	0	0	0
Nervous System	80 (35%)	17 (22%)	66 (45%)	5 (9%)	5 (17%)	0
Anxiety	5 (2%)	1 (1%)	4 (3%)	2 (4%)	2 (7%)	0
Confusion	12 (5%)	1 (1%)	11 (7%)	0	0	0
Dizziness	36 (16%)	2 (3%)	34 (23%)	1 (2%)	1 (3%)	0
Nervousness	12 (5%)	6 (8%)	7 (5%)	0	0	0
Sleep disorder	15 (7%)	2 (3%)	13 (9%)	1 (2%)	1 (3%)	0
Somnolence	24 (11%)	7 (9%)	17 (12%)	1 (2%)	1 (3%)	0
Respiratory System	20 (9%)	6 (8%)	14 (10%)	2 (4%)	1 (3%)	1 (4%)
Skin	15 (7%)	4 (5%)	11 (7%)	2 (4%)	1 (3%)	1 (4%)
Special Senses	10 (4%)	3 (4%)	7 (5%)			
Urogenital System	24 (11%)	7 (9%)	18 (12%)	1 (2%)	0	1 (4%)
Incontinence, urine	8 (4%)	0	8 (5%)	0	0	0

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

4.9 Other Safety Information

4.9.1 ANALYSIS OF ADVERSE EVENT DOSE-RESPONSE INFORMATION

4.9.1.1 Dosage Justification

4.9.1.1.1 Historical Clinical Experience

At the time the first controlled clinical trial contained in this application was initiated (Scrima trial report, Scrima 1989, 1990), information was available on suitable dosage ranges for sodium oxybate from published reports of open-label clinical trials (Broughton 1979, 1980; Scharf 1985; Mamelak, 1986) that suggested that nightly dosages of 3.0 to 9.0 g/d, usually taken in divided nightly doses, were effective in reducing cataplexy and other symptoms of narcolepsy and were well tolerated. Mamelak (1981) reported a single case study in which sodium oxybate at a dosage of approximately 5 g/d was effective and well tolerated in the treatment of narcolepsy. Since that time, an additional paper by Bédard (1989), using EEG measures, demonstrated the efficacy of sodium oxybate in improving the disrupted sleep architecture (decreasing REM latency, time awake after sleep onset, and duration of stage 1 sleep; and increasing the number of sleep-onset REM periods, amount of REM, and REM efficiency) of patients with narcolepsy at a dosage of 2.25 g/d (single nightly dose).

4.9.1.1.2 Dosage Justification

In the long-term, open-label clinical trial (Scharf, begun in 1983), 6.0 g/d as a divided dose was the most frequent dosage.

The Scrima trial (begun in 1986) employed a dosage based on body weight (50 mg/kg), approximately equivalent to a dosage of 3.5 g/d for a 70-kg person. Based on the actual body weights of patients enrolled in the study, the mean dosage actually administered was 4.2 g/d (ranging from 3.0 g/d to 5.7 g/d for individual patients).

The Lammers trial (begun in 1987) employed a slightly higher dosage, also on a per-kilogram basis (60 mg/kg; 4.2 g/d for a 70-kg person). Based on the actual body weight of the patients enrolled in the study, the mean dosage actually administered was 4.7 g/d (ranging from 3.7 g/d to 5.5 g/d for individual patients).

For the OMC-GHB-2 trial (begun in 1997), the above-cited studies were used as a basis for selecting the dosage, as was expert opinion solicited by Orphan Medical. At the request of FDA (August 1995), higher and lower dosages (3 g/d and 9 g/d) were also included in the study design to look for evidence of dose-responsiveness: the 3 g/d dosage was selected as being marginally below what was thought to be the minimum effective dosage, and 9 g/d was selected to approximate a maximum tolerated dosage.

Final dosages in open-label studies OMC-GHB-3 (begun in 1997), OMC-SXB-6 (begun in 1999), and OMC-SXB-7 (begun in 1999) were arrived at by titration to optimal clinical effect. Patients began at a dosage of either 6.0 g/d (OMC-GHB-3) or 4.5 g/d

(OMC-SXB-6) and investigators titrated patients' dosages up or down to maximize therapeutic benefit while minimizing any potentially drug-related adverse experiences. This dosage-selection procedure was intended to more closely resemble actual clinical practice, in which patients will be recommended to begin treatment at 4.5 g/d and increase or reduce their dosage in 1.5 g/d (0.75 g per individual dose) increments at intervals of 2 weeks to maximize clinical benefit.

The distribution of final dosages in OMC-GHB-3, OMC-SXB-6, and OMC-SXB-7 (through the data cutoff of September 30, 2000) is summarized in Table 4.26.

Table 4.26 Distribution of Final Dosages — Open-Label Studies (OMC-GHB-3, OMC-SXB-6, and OMC-SXB-7)

Trial	Total	Sodium Oxybate Last Dosage (g/d)				
		3.0	4.5	6.0	7.5	9.0
OMC-GHB-3	117[a]	15 (13%)	20 (17%)	37 (32%)	25 (21%)	20 (17%)
OMC-SXB-7	185	4 (2%)	52 (28%)	73 (40%)	27 (15%)	29 (16%)
OMC-SXB-6	236	5 (2%)	39 (17%)	76 (32%)	59 (25%)	57 (24%)

[a] Does not include the 1 patient who did not receive sodium oxybate.

Dosages employed in the clinical trials included in the updated integrated clinical trial database, and in OMC-SXB-21, ranged from 3 to 9 g/d, taken in divided nightly doses.

4.9.1.2 Adverse Event Dose-Response Analysis

In the updated integrated clinical trial database, a higher incidence of AEs was seen with the patients taking 9.0 g/d sodium oxybate. This was true for patients with at least 1 AE (78% for 9.0 g/d, compared with 51% to 62% for the other 4 dosage at onset groups), patients with related AEs (55% for 9.0 g/d, vs. 28% to 40% for the other 4 dosage at onset groups), patients with severe AEs (16% for 9.0 g/d, vs. 3% to 12% for the other 4 dosage groups), and discontinuations due to AEs (12% for 9.0 g/d, vs. 2% to 6% for the other 4 dosage groups). Interestingly, the incidence for the patients in the placebo group with at least 1 AE (70%) and patients with related AEs (57%) was similar to that for the 9.0 g/d group for patients. No similar trend was apparent for patients with SAEs.

For the most frequently reported AEs, there were no apparent differences in incidence of headache and pain among the 6 dosage at onset groups, including placebo and the 5 sodium oxybate groups. There was a higher incidence (23%) of nausea in the 9.0 g/d group, compared with 7% for placebo and 8% to 11% for the other 4 sodium oxybate groups. A higher incidence of dizziness was seen in the 3.0 g/d and 9.0 g/d groups (16% and 17%, respectively), compared with 4% for placebo and 6% to 12% for the other 3 sodium oxybate groups. No inferential statistical analyses were performed for the integrated database.

A slight dose-related effect was seen in the OMC-GHB-3 trial for nausea ($p = 0.021$) and viral infection ($p < 0.001$), with a 16.7% incidence for both AEs in the 9.0 g/d sodium oxybate dosage group, compared with 9.8% and 3.3%, respectively, in the 3.0 g/d

sodium oxybate dosage group. In the OMC-GHB-2 trial where doses were assigned in a blinded, randomized fashion, a dose-related effect was apparent for dizziness ($p = 0.0178$), infection ($p = 0.0338$), nausea ($p = 0.0045$), urinary incontinence ($p = 0.0143$), and vomiting ($p = 0.0475$).

4.9.2 LONG-TERM ADVERSE EVENTS

As discussed in Section 4.2, of the 399 patients in the updated clinical trial database, 296 patients took Xyrem for $\geq$ 6 months, 223 patients took Xyrem for $\geq$ 1 year, and 48 patients took Xyrem for $\geq$ 2 years. Of the 479 patients in the combined experience from the updated integrated clinical trial database and the Scharf trial, 360 patients took Xyrem for $\geq$ 6 months, 286 patients took Xyrem for $\geq$ 1 year, and 150 patients took Xyrem for $\geq$ 2 years.

Analyses comparing AEs in different time periods were carried out in the OMC-GHB-3 trial (first 12 months vs. entire 24 months) and the Scharf trial (first 6 months vs. remainder of trial). In OMC-GHB-3, almost all AEs appeared to initiate within the first 12 months of the trial. Only 15 additional COSTART terms were reported during the second 12 months, only 3 of which occurred in more than 1 patient – GI distress (3 patients), bilirubinemia (2 patients), and increased alkaline phosphatase (2 patients). Only 1 patient experienced urinary incontinence during the second 12 months. In the Scharf trial, 95.1% of the 143 patients experienced 1 or more AE at any time during the trial; 87.4% of the patients experienced an AE during the first 6 months, again supporting the conclusion that few new AEs are seen after the first 6 to 12 months of treatment.

The profile of SAEs in the Scharf trial (with an incidence of 37.8%) was consistent with the serious illnesses that would be expected in a patient population of older adults. The most frequent SAEs were related to cardiovascular disease and narcolepsy. The incidence of serious accidental injury was not unexpected in patients with cataplexy. Several contributing factors could account for the incidence of SAEs, including:

- The increasing age of the patients during the trial (from a mean of 45.3 years of age at entry to a mean of 61 years of age), which would be associated with the development of chronic illness
- Underlying cardiovascular abnormalities, which were present in approximately 20% of patients at baseline, and the expected age-related progression and presentation of cardiovascular morbidities
- Possible maladaptive patterns of behavior for some patients as a result of long-standing disease (average time from diagnosis of narcolepsy to trial entry, 9.5 years)

4.9.3 WITHDRAWAL EFFECTS

To determine if REM rebound effects (ie, rebound cataplexy) occur on abrupt withdrawal of sodium oxybate, the incidence of AEs suggestive of REM rebound (increased cataplexy attacks, sleep disturbance, hallucinations, and abnormal dreams) during the

period of up to 5 days prior to Visit 6 (end of treatment period) was compared with that during the period of 3 to 5 days after Visit 6 during which no oxybate treatment was given in the OMC-GHB-2 trial. There was no evidence of acute rebound cataplexy and no exacerbation of AEs suggestive of REM rebound effects, suggesting that REM rebound effects do not appear when sodium oxybate is withdrawn for 3 to 5 days.

In the OMC-SXB-21 trial, abrupt double-blind discontinuation of long-term Xyrem treatment at therapeutic dose range for 2 weeks led to an increase in cataplexy attacks (median increase 21.0, compared with 0.0 for the Xyrem group), but did not appear to result in an increase in AEs that would indicate physical dependence or withdrawal syndrome.

4.10 Safety Summary

In dosages between 3.0 and 9.0 g/d in nightly divided doses, sodium oxybate was generally well tolerated in the 5 trials included in the updated integrated clinical trial database, the Lammers trial, the Scharf trial, and the OMC-SXB-21 trial, with side effects that were usually mild and most frequently included nausea, dizziness, and headache, with occasional urinary incontinence (enuresis) and somnambulism (sleepwalking).

Of the 399 patients in the updated clinical trial database, 296 patients took Xyrem for $\geq$ 6 months, 223 patients took Xyrem for $\geq$ 1 year, and 48 patients took Xyrem for $\geq$ 2 years. Of the 479 patients in the combined experience from the updated integrated clinical trial database and the Scharf trial, 360 patients took Xyrem for $\geq$ 6 months, 286 patients took Xyrem for $\geq$ 1 year, and 150 patients took Xyrem for $\geq$ 2 years. Total exposure to sodium oxybate was 329.89 patient-years in the updated integrated clinical trial database, 2.08 patient-years in the Lammers trial, and 996.15 patient-years in the Scharf trial, or a total of 1,328.12 patient-years.

Of the 402 narcolepsy patients included in the updated integrated clinical trial database, 331 (82%) experienced at least 1 AE. As expected, a higher incidence (95%) was seen in the long-term (16-year) clinical trial (Scharf); however, the incidence of AEs during the first 6 months of treatment with sodium oxybate was similar in the OMC-SXB-6, OMC-GHB-3, and Scharf trials.

Related AEs were seen for 247 of the 402 patients (61%) in the updated integrated clinical trial database. Severe AEs were seen for 82 of the 402 patients (20%). In the Scharf trial, severe AEs were seen for 21 of the 143 patients (14.7%) during the first 6 months on sodium oxybate.

SAEs were experienced by 27 of the 402 patients (7%) in the updated integrated clinical trial database and 54 of the 143 patients (37.8%) in the long-term (16-year) Scharf trial. Two deaths (0.5%) were reported in the OMC-SXB-7 trial, including patient 0936 who died after the data cutoff, and 11 [7.7%] deaths were reported in the Scharf trial over 16 years. None of these deaths was considered related to trial medication. Fifty-two patients (13%) discontinued due to 1 or more AEs in the updated integrated clinical trial database and 23 patients (16.1%) in the long-term (Scharf) trial. Of these patients,

42 (10%) in the updated integrated clinical trial database and 3 (2%) in the Scharf trial discontinued due to AEs considered to be related to trial medication.

In the updated integrated clinical trial database, the most frequently reported AEs included headache (29%), nausea (23%), dizziness (19%), and pain (18%). In the Scharf trial, the most frequently reported AEs (nearly all of which would be expected in a long-term trial and were associated with common intercurrent illnesses) included viral infection (56.6%), headache (52.4%), pain (48.3%), accidental injury (42.0%), nausea (40.6%), flu syndrome (38.5%), pharyngitis (37.8%), rhinitis (36.4%), increased cough (34.3%), sleep disorder (sleepwalking; 31.5%), diarrhea (28.0%), dizziness (27.3%), fever (26.6%), abdominal pain (26.6%), sinusitis (26.6%), and dyspepsia (25.2%).

Overall, a slight dose-response relationship was seen for the incidence of patients with 1 or more AEs in the updated integrated clinical trial database. Statistical analysis showed a dose-response relationship for specific AEs in 2 trials (dizziness, infection, nausea, urinary incontinence, and vomiting in OMC-GHB-2; nausea and viral infection in OMC-GHB-3). Examination of the data in the long-term (up to 16 years) clinical trial (Scharf) for AEs (during the first 6 months, and during the remainder of the study) showed no strong evidence of a dose-response relationship.

Special analyses showed no evidence of seizurogenesis (based on an analysis of incontinence AEs) or of medication-induced lupus (based on an analysis of increased ANA levels).

An analysis of the 3 placebo-controlled trials with washout periods of 1 to 7 weeks (OMC-GHB-2, Scrima, and Lammers) showed a higher incidence of patients with 1 or more AEs for sodium oxybate (69%) than for placebo (49%). The most frequently reported AEs for sodium oxybate-treated patients were dizziness (23%), headache (20%), and nausea (16%). For placebo-treated patients, headache was the most frequently reported AE (15%); all other AEs occurred in less than 10% of placebo patients.

In the placebo-controlled OMC-SXB-21 trial (with a 2-week lead-in of single-blind Xyrem), the incidence of patients with 1 or more AEs was 12% for sodium oxybate, compared with 31% for placebo. No AE was reported by more than 1 patient (4%) in the sodium oxybate group. For placebo-treated patients, headache and anxiety were the most frequently reported AEs (2 patients, 7% each); all other AEs occurred in only 1 patient (3%).

Laboratory evaluations for the integrated clinical trial database and the Scharf trial included blood chemistry, hematology, and urinalysis. The only potentially significant laboratory abnormality was hypocalcemia. Although this was present in 23 of the 132 patients tested in the 5 integrated clinical trials, it was a variable measure in 15 patients, with a return to normal during treatment. In all cases, the reduction in calcium levels was minor, and not of clinical significance.

4.11 Overall Conclusion

Safety information collected for this orphan indication from clinical trials is intrinsically limited. The safety data collected for Xyrem (sodium oxybate) suggests an acceptable safety profile as summarized herein and represented in greater detail in the NDA application on file with FDA.

SECTION 5
PHARMACOKINETICS, DRUG INTERACTIONS, AND PHARMACODYNAMICS

5.0 PHARMACOKINETICS, DRUG INTERACTIONS, AND PHARMACODYNAMICS

5.1 Human Pharmacokinetics and Drug Interactions Summary

Eight (8) Phase I clinical pharmacokinetic studies of sodium oxybate were sponsored. The first was a pilot study that evaluated the single-dose pharmacokinetics of sodium oxybate in narcoleptic patients who had been taking oxybate for 2 to 13 years (OMC-GHB-4). Thereafter, the pharmacokinetics of sodium oxybate were evaluated after single and repeated (8-week) administration in oxybate-naïve narcoleptic patients (OMC-SXB-10). Dose-proportionality (OMC-SXB-9), sex-related differences (OMC-SXB-8), and effects of food (OMC-SXB-11) on sodium oxybate pharmacokinetics were assessed in 3 studies in healthy volunteers. The potential for interaction between sodium oxybate and 3 classes of drugs (hypnotics, antidepressants, and stimulants) commonly used in the treatment of narcoleptic symptoms were assessed in 3 studies in healthy volunteers using zolpidem (Ambien®) (OMC-SXB-12), protriptyline (Vivactil®) (OMC-SXB-14), and modafinil (Provigil®) (OMC-SXB-17). Potential for drug interactions through inhibition of cytochrome P450 (CYP) isoenzymes was also assessed *in vitro* (Covance Study No. 6627-129).

Since Xyrem (sodium oxybate) is a true solution for oral administration and is not a solid dosage form, absolute bioavailability studies and/or bioequivalence studies are not required for New Drug Application (NDA) submission in the United States. At a meeting between Orphan Medical and FDA in August 1998, the Agency concurred that no bioequivalence studies are required for this application and none were performed.

5.1.1 NARRATIVE SUMMARIES FOR XYREM (SODIUM OXYBATE) ORAL SOLUTION BIOPHARMACEUTIC STUDIES

The 8 clinical pharmacokinetic studies and one *in vitro* study sponsored by Orphan Medical Inc. are summarized below. Several features were common to the 8 clinical pharmacokinetic studies. All were open label single center studies and none used biomarkers or surrogate end-points. With the exception of the pilot study (OMC-GHB-4), all the pharmacokinetic studies used a Xyrem (sodium oxybate) oral solution[1] identical to the one to be released to the market upon NDA approval. The pilot study used a powder formulation[2] that was readily dissolved in a small volume of water before ingestion by study subjects as an oral solution.

Blood for determination of plasma oxybate concentrations was taken at varying times after sodium oxybate administration. A liquid chromatography atmospheric pressure

[1]In addition to sodium oxybate (500 mg/mL), the liquid formulation contains malic acid, FCC NF, sodium hydroxide, NF, and purified water, USP.
[2]Unit doses of the powder formulation were packaged in twin pouches: one containing sodium oxybate and the other the flavor excipient. The contents were dissolved in two ounces of water before ingestion. The powder formulation was also used in clinical trials OMC-GHB-2 and OMC-GHB-3.

ionization tandem mass spectrometry (LC/MS/MS) analytical method with a limit of quantification (LOQ) of 5 µg/mL oxybate for a 0.1 mL aliquot of plasma was used in all studies except the pilot study, which used a gas chromatographic method with mass selective detection (LOQ 7.02 µg/mL for a 1.0 mL aliquot of plasma).

In all studies, plasma oxybate concentration versus time data from each subject following dosing were subjected to non-compartmental analysis using WinNonlin (version 1.1) and SAS (versions 6.11 and 8) and the following pharmacokinetic parameters determined: peak plasma concentration (C_{max}), corresponding peak time (T_{max}), elimination half-life ($T_{1/2}$), area under the curve from time zero to time infinity (AUC_{inf}), plasma clearance divided by absolute bioavailability (CL/F), and volume of distribution divided by absolute bioavailability (V_z/F). The mean and coefficient of variation (CV) for each parameter was calculated from the individual subject data.

5.1.1.1 Pharmacokinetics of Sodium Oxybate in Oxybate-Experienced Narcoleptic Patients (OMC-GHB-4)

This was a pilot Phase I open label pharmacokinetic study of orally administered sodium oxybate in 6 narcoleptic patients who had been receiving nightly doses of oxybate for 2 to 13 years. Patients received 2 consecutive 3-g doses of sodium oxybate, the first just prior to bedtime and the second 4 hours later. Unit doses of sodium oxybate (and flavoring excipient) were dissolved in 2 ounces of water and the resultant solution ingested by study subjects as a liquid formulation.

The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 6 patients.

First 3-g Dose		Second 3-g Dose		$T_{1/2}$	AUC_{inf}	CL/F	V_z/F
C_{max} µg/mL	T_{max} hour	C_{max} µg/mL	T_{max} hour	hour	µg·hr/mL	mL/min·kg	mL/kg
62.8 ± 43%	0.67 ± 15%	91.2 ± 28%	0.59 ± 19%	0.88 ± 36%	295 ± 27%	4.2 ± 21%	307 ± 18%

Capacity limited elimination kinetics was observed in 3 of 6 patients following two consecutive 3 g oral doses of sodium oxybate. From a pharmacokinetic perspective, dividing the nightly sodium oxybate dose into 2 portions and administering the 2 portions at a 2.5- to 4-hour interval is rational because the elimination half-life of sodium oxybate in narcoleptic patients is short (< 1 hour). The pharmacokinetics of sodium oxybate in narcoleptic patients (who had been ingesting this agent nightly for years) appears to be comparable to that observed in healthy human subjects (Palatini 1993) and in alcohol dependent patients (Ferrara 1992).

5.1.1.2 Pharmacokinetics of Sodium Oxybate After Single and Chronic (8-week) Dosing in Oxybate-naïve Narcoleptic Patients (OMC-SXB-10)

This study was to examine the pharmacokinetics of Xyrem (sodium oxybate) oral solution in narcoleptic patients after a single 4.5 g dose and after 8 weeks of nightly dosing with 4.5 g. Each dose was taken just before bedtime. Subjects were 13 (3 male, 10 female) oxybate naïve narcoleptic patients.

The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 13 patients.

Time of Determination	C_{max} µg/mL	T_{max} hour	$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg
First dose	90.0 ± 34%	0.75[a]	0.67 ± 25%	226 ± 33%	4.0 ± 28%	226 ± 29%
8-weeks	104 ± 30%	0.50[a]	0.67 ± 31%	254 ± 31%	3.5 ± 31%	197 ± 34%

[a]median

On average, the nightly treatment with Xyrem for 8 weeks resulted in a 13% increase in systemic exposure to oxybate based on AUC_{inf} and a 16% increase in peak plasma concentration. While the changes were statistically significant ($P<0.05$; paired t-test of log transformed values), these modest increases are not considered to be clinically significant. It was also concluded that chronic Xyrem treatment did not result in auto-induction (self-induction of metabolism).

5.1.1.3 Pharmacokinetics of Sodium Oxybate in Healthy Male and Female Volunteers (OMC-SXB-8)

This study examined the pharmacokinetics of Xyrem (sodium oxybate) oral solution in 18 male and 18 female healthy adult volunteers who received a single 4.5 g dose just before bedtime. Urine levels of oxybate, for determination of the extent of renal excretion of unchanged oxybate, were also assessed in this study.

The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 18 males and 18 females.

Sex	C_{max} µg/mL	T_{max} hour	$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg
Male	88.3 ± 24%	1.25 ± 53%	0.65 ± 35%	241 ± 34%	3.8 ± 34%	202 ± 30%
Female	83.0 ± 23%	1.14 ± 43%	0.61 ± 20%	233 ± 35%	4.2 ± 38%	218 ± 40%

There was no difference in the systemic exposure to oxybate between male and female subjects. Based on unpaired t-test or Wilcoxon rank sum test (T_{max} only), there was no significant difference ($P > 0.05$) between male and female volunteers for log-transformed AUC_{inf}, log transformed C_{max}, T_{max}, CL/F (per kg), $T_{1/2}$, percentage of dose excreted unchanged in urine, or apparent renal clearance. The $T_{1/2}$ of Xyrem was 39 min in men and 37 min in women, resulting in very low plasma concentrations by 6 hours after a 4.5 g dose. Urinary excretion of unchanged oxybate was a minor elimination pathway (1% – 7%) in both sexes.

5.1.1.4 Dose Proportionality of Sodium Oxybate (OMC-SXB-9)

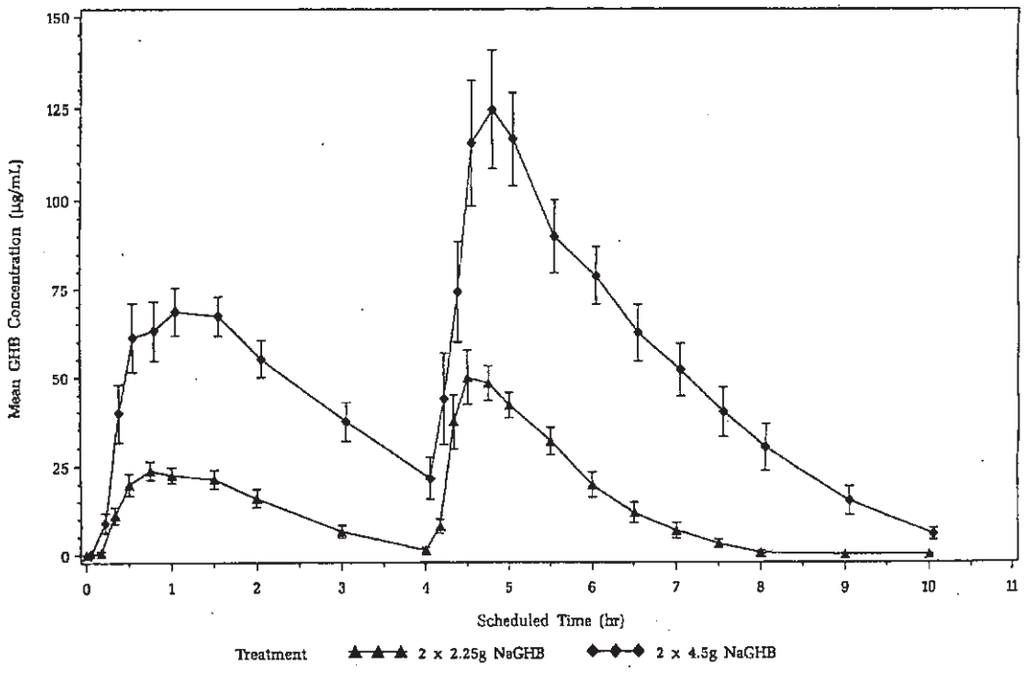
This was a 2-way crossover study that examined the pharmacokinetics of Xyrem (sodium oxybate) oral solution in 10 male and 3 female healthy adult volunteers. Each subject received two treatments with sodium oxybate, one at a dose of 4.5 g and the other at a dose of 9.0 g. For each treatment, doses were divided (2 x 2.25 g or 2 x 4.5 g), with the first half being given just before bedtime and the second 4 hours later. A 7-day washout separated the two treatments. Urine levels of oxybate, for determination of the extent of renal excretion of unchanged oxybate, were also assessed in this study.

The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in the 12 volunteers who completed the study.

Xyrem Dose g	First Nightly Dose		Second Nightly Dose		$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg
	C_{max} µg/mL	T_{max} hour	C_{max} µg/mL	T_{max} hour				
4.5 (2 x 2.25)	26.6 ± 32%	0.85 ± 42%	60.1 ± 29%	0.64 ± 49%	0.59 ± 22%	138 ± 36%	6.6 ± 32%	325 ± 24%
9.0 (2 x 4.5)	77.6 ± 32%	1.17 ± 46%	142 ± 35%	0.72 ± 63%	0.83 ± 23%	518 ± 38%	3.6 ± 38%	249 ± 36%

The systemic exposure of human subjects to oxybate increased disproportionately with dose. Doubling the nightly dose from 4.5 g (2 x 2.25 g) to 9 g (2 x 4.5 g) resulted in a 3.8-fold increase in AUC_{inf}. C_{max} values were higher after the second half of the nightly dose (administered 4 hours after the first half of the nightly dose) (Figure 5.1).

Figure 5.1 **Mean Oxybate Concentration Versus Time After Divided Doses of 4.5 g and 9.0 g in Healthy Volunteers**



The apparent $T_{1/2}$ of oxybate was < 1 hour, resulting in very low plasma concentrations by 10 hours after the start of this dosing regimen. Renal excretion of unchanged oxybate was minimal (<10%).

5.1.1.5 Effect of Food on Pharmacokinetics of Sodium Oxybate (OMC-SXB-11)

This was a randomized 2-way crossover study that determined the effect of food on the bioavailability of Xyrem (sodium oxybate) oral solution in 36 adult female healthy volunteers. Each subject received two treatments with 4.5 g sodium oxybate, one given after a high fat meal and the other after an overnight fast. Urine levels of oxybate, for determination of the extent of renal excretion of unchanged oxybate, were also assessed in this study.

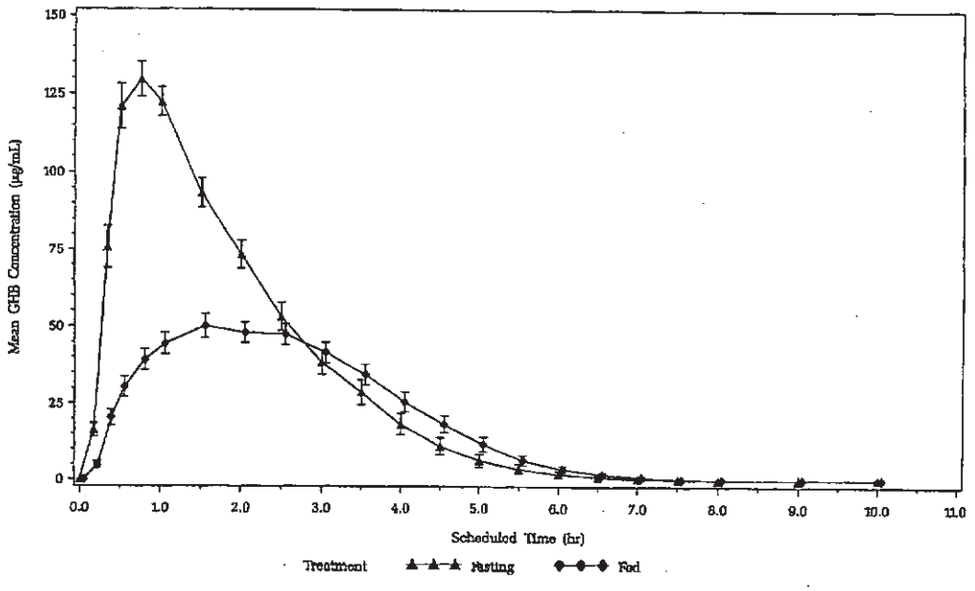
The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 34 subjects who completed the study.

Food State	C_{max} µg/mL	T_{max}^{**} hour	$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg
Fed	60.1* ± 33%	2.00*	0.68 ± 32%	188* ± 43%	6.2 ± 52%	384 ± 84%
Fasted	142 ± 24%	0.75	0.57 ± 53%	288 ± 38%	3.7 ± 38%	190 ± 51%

*Significantly different than fasted state ($P<0.05$)
**T_{max} value is median

A high fat meal significantly delayed Xyrem absorption following oral dosing (Figure 5.2). The systemic exposure of subjects to oxybate when Xyrem was administered after a high fat meal was not equivalent to the systemic exposure when Xyrem was administered after an overnight fast. On average, C_{max} decreased by 59% and AUC_{inf} decreased by 37% in the fed compared to fasted state. The 90% confidence interval for the fed:fasted ratio of C_{max} was 0.37-0.46 and of AUC_{inf} was 0.57-0.69. Absorption of Xyrem appeared to be slower when Xyrem was administered after a high fat meal than after an overnight fast, resulting in a later T_{max} of 2 hours compared to 0.75 hour. The apparent half-life of oxybate was <1 hour for both dosing conditions. Urinary excretion of unchanged oxybate was a minor elimination pathway (<10% of the dose).

Figure 5.2 Mean Plasma Concentration Versus Time of Oxybate After an Overnight Fast and After a High Fat Meal



5.1.1.6 Hypnotic Drug Interaction: Sodium Oxybate and Zolpidem (OMC-SXB-12)

This randomized 3-way crossover study determined the interaction between sodium oxybate and zolpidem tartrate (Ambien®) in 10 male and 5 female healthy adult volunteers. Each subject received each of the following treatments: a single dose of sodium oxybate (3 g) alone; a single dose of sodium oxybate (3 g) in combination with zolpidem (5 mg); and a single dose of zolpidem (5 mg) alone.

The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 15 subjects.

Treatment Regimen	Analyte	C_{max} µg/mL	T_{max}* hour	$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg
sodium oxybate alone	oxybate	83.8 ± 29%	0.50	0.74 ± 30%	136 ± 32%	4.3 ± 30%	260 ± 28%
sodium oxybate + zolpidem	oxybate	93.5 ± 30%	0.75	0.73 ± 25%	143 ± 34%	4.4 ± 52%	281 ± 82%
	zolpidem	107 $x10^{-3}$ ± 44%	0.75	3.35 ± 56%	420 $x10^{-3}$ ± 51%	2.6 ± 50%	643 ± 35%
zolpidem alone	zolpidem	96.3 $x10^{-3}$ ± 37%	0.50	3.34 ± 48%	424 $x10^{-3}$ ± 54%	2.8 ± 50%	640 ± 26%

*Median reported for T_{max}

The systemic exposure of healthy adult volunteers to oxybate when Xyrem was administered with zolpidem was equivalent to the systemic exposure when Xyrem was administered alone. On average, C_{max} of oxybate increased by 6% and AUC_{inf} by 3% in the presence of zolpidem. Conversely, the mean zolpidem C_{max} decreased by 8% and AUC_{inf} decreased by 2% in the presence of Xyrem. Overall, however, co-administration of Xyrem and zolpidem presents no pharmacokinetic changes for either drug that are clinically significant.

5.1.1.7 Antidepressant Drug Interaction: Sodium Oxybate and Protriptyline (OMC-SXB-14)

This randomized 3-way crossover study determined the interaction between sodium oxybate and protriptyline hydrochloride (Vivactil®) in 5 male and 7 female healthy adult volunteers. Each subject received each of the following treatments: sodium oxybate in a divided dose of 4.5 g (2 x 2.25 g) alone; sodium oxybate (2 x 2.25 g) in combination with protriptyline (10 mg); and a single dose of protriptyline (10 mg) alone.

The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 13 patients.

Treatment regimen	Analyte	C_{max}[a,b] µg/mL	T_{max}[a] hour	$T_{1/2}$ hour	AUC_{inf}[b] µg·hr/mL	CL/F[b] mL/min·kg	V_z/F[b] mL/kg
sodium oxybate alone	oxybate	64.6 ± 24%	0.50[c]	0.57 ± 33%	178 ± 41%	5.7 ± 44%	248 ± 18%
sodium oxybate + protriptyline	oxybate	58.3 ± 39%	0.75[c]	0.57 ± 32%	183 ± 43%	5.9 ± 56%	263 ± 37%
	protrip-tyline	4.7 $x10^{-3}$ ± 30%	8.0[c]	72.1 ± 53%	452 $x10^{-3}$ ± 67%	0.41 $x10^{3}$ ± 68%	32.0 $x10^{3}$ ± 36%
protriptyline alone	protrip-tyline	5.0 $x10^{-3}$ ± 26%	8.0[c]	68.2 ± 57%	463 $x10^{-3}$ ± 67%	0.40 $x10^{3}$ ± 75%	30.6 $x10^{3}$ ± 57%

[a]Shown are the C_{max} and T_{max} from the second of the divided doses of sodium oxybate; parameters from the first divided dose were no different when sodium oxybate was given alone or in combination with protriptyline; the mean (CV) C_{max} was 55.1 (26%) vs 55.5 (34%) µg/mL, respectively and median T_{max} was 0.75 vs 0.63 hours, respectively.
[b]Units for protriptyline have been converted from reported units for Cmax (ng/mL), AUC_{inf} (ng·hr/mL), CL/F (L/min·kg), and V_z/F (L/kg).
[c]median

On average, the oxybate C_{max} decreased by 2% and 16% after the first and second portion of the dose, respectively, and the combined AUC_{inf} decreased by 3%, following co-administration with protriptyline. Conversely, mean protriptyline C_{max} increased by 7% and AUC_{inf} increased by 3% following co-administration. Overall, however, co-administration of Xyrem and protriptyline presents no pharmacokinetic changes for either drug that are clinically significant.

5.1.1.8 Stimulant Drug Interaction: Sodium Oxybate and Modafinil (OMC-SXB-17)

This randomized 3-way crossover study determined the interaction between sodium oxybate and modafinil (Provigil®) in 7 male and 6 female healthy adult volunteers. Each subject received each of the following treatments: a single dose of sodium oxybate (4.5 g) alone; a single dose of sodium oxybate (4.5 g) in combination with modafinil (200 mg); and a single dose of modafinil (200 mg) alone.

The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 12 subjects.

Treatment regimen	Analyte	C_{max} µg/mL	T_{max} hour	$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg
sodium oxybate alone	oxybate	146 ± 21%	0.50[a]	0.76 ± 24%	302 ± 39%	3.1 ± 29%	190 ± 16%
sodium oxybate + modafinil	oxybate	135 ± 26%	0.50[a]	0.76 ± 28%	294 ± 56%	3.4 ± 38%	205 ± 20%
	modafinil	5.5 ± 31%	2.0[a]	12.3 ± 19%	71.8 ± 26%	0.66 ± 21%	690 ± 20%
modafinil alone	modafinil	5.2 ± 27%	1.0[a]	12.0 ± 15%	74.2 ± 27%	0.64 ± 20%	657 ± 21%

[a]median

On average, the oxybate C_{max} decreased by 8% and AUC_{inf} decreased by 7%. Conversely, mean modafinil C_{max} decreased by 6% and AUC_{inf} increased by 4%. It was concluded that Xyrem and modafinil when administered together presented no pharmacokinetic changes for either drug that are clinically significant.

5.1.1.9 Potential for Drug Interaction Through Inhibition of Cytochrome P450 Isozymes (Covance Study No. 6627-129)

The potential for drug interactions by an inhibitory effect of sodium oxybate on human hepatic microsomal cytochrome P450 (CYP) isozymes was assessed in this study. Characterized, pooled, human liver microsomal fractions from 10 individuals were used in these studies and the activity of the following CYP isozymes were determined:

- ethoresoflurin O-deethylase (CYP1A2)
- tolbutamide methyl hydroxylase (CYP2C9)
- S-mephenytoin 4'-hydroxylase (CYP2C19)
- dextromethophan O demethylase (CYP2D6)
- *p*-nitrophenol hydroxylase (CYP2E1)
- erythromycin N-demethylase (CYP3A).

Each assay was performed with a fixed substrate concentration and in the presence and absence of 3, 10, 30, 100, and 300 µM oxybate, with the aim of calculating the concentration of oxybate that inhibited activity by 50% (IC_{50}). However, no inhibitory activity of oxybate was observed in any of the assays at any of the concentrations tested; the IC_{50} was greater than 300 µM in all of the assays. Oxybate, therefore, does not inhibit activities of human CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A. Metabolic interactions with drugs metabolized through these pathways are, therefore, also not anticipated.

5.1.2 PHARMACOKINETICS OF SODIUM OXYBATE

A description of the pharmacokinetic characteristics of sodium oxybate is presented below. Information from the 8 clinical pharmacokinetic studies sponsored by Orphan Medical as well as information from 6 published studies (not sponsored by Orphan Medical) are included. Three published studies were conducted using oxybate oral solution[3]; two were dose-proportionality studies in healthy volunteers (Palatini 1993) and in alcohol-dependent patients (Ferrara 1992) and the other a single-dose study in patients with liver disease (Ferrara 1996). Three studies were conducted using an intravenous route of administration in patients needing sedation or undergoing surgery (Vree 1975, Vree 1978) and in pregnant women undergoing caesarian section (van den Bogert 1978); this study also reported use in a 2-day old neonate (van den Bogert 1978).

A summary of pharmacokinetic parameters derived from each of the studies sponsored by Orphan Medical as well as from published sources is presented in Table 5.1. This table shows the study population (ie, healthy volunteers or patients); dose, route, and duration of dosing with oxybate; mean pharmacokinetic parameters reported in each study; and study reference. A brief narrative description of the pharmacokinetic characteristics (absorption, distribution, metabolism, elimination) of sodium oxybate in healthy volunteers and narcoleptic and other patient populations follows Table 5.1.

[3]Oxybate dissolved in a black cherry syrup

Table 5.1 Pharmacokinetic Parameters for Oxybate in Healthy Volunteers and Patient Populations After Oral or Intravenous Administration

Study population	N	Oxybate administration			C_{max} µg/mL	T_{max} hour	$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg	Reference
		Route	Dose	Duration							
Healthy volunteers	8	Oral	12.5 mg/kg (0.87 g)[a]	Single	23	0.42[b]	0.45	15.1	14	NR	Palatini 1993
			25 mg/kg (1.75 g)[a]	Single	23[c]	0.5[b]	0.37	21.2[c]	9[c]	NR	
			50 mg/kg (3.5 g)[a]	Single	23[c]	0.75[b]	0.38	26.1[c]	7[c]	NR	
Healthy volunteers	15	Oral	3 g	Single	83.8	0.50[b]	0.74	136	4.3	260	OMC-SXB-12
Healthy volunteers	12	Oral	4.5 g	Single	146	0.50[b]	0.76	302	3.1	190	OMC-SXB-17
Healthy volunteers male	18	Oral	4.5 g	Single	88.3	1.25	0.65	241	3.8	202	OMC-SXB-8
female	18	Oral	4.5 g	Single	83.0	1.14	0.61	233	4.2	218	OMC-SXB-8
Healthy volunteers fed	36	Oral	4.5 g	Single	60.1	2.00[b]	0.68	188	6.2	384	OMC-SXB-11
fasted	36	Oral	4.5 g	Single	142	0.75[b]	0.57	288	3.7	190	OMC-SXB-11
Healthy volunteers	12	Oral	4.5 g (2x2.25 g)	Single	64.6[d]	0.50[b,d]	0.57	178	5.7	248	OMC-SXB-14
Healthy volunteers	12	Oral	4.5 g (2x2.25 g)	Single	60.1[d]	0.64[d]	0.59	138	6.6	325	OMC-SXB-9
			9.0 (2x4.5)	Single	142[d]	0.72[d]	0.83	518	3.6	249	

[a]Dose calculated for a 70-kg subject presented for comparative purposes
[b]median
[c]normalized to 12.5 mg/kg
[d]Values for second half of divided dose presented
NR = not reported

Table 5.1 Pharmacokinetic Parameters for Oxybate in Healthy Volunteers and Patient Populations After Oral or Intravenous Administration, continued

Study population	N	Oxybate administration			C_{max} µg/mL	T_{max} hour	$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg	Reference
		Route	Dose	Duration							
Narcoleptic patients	13	Oral	4.5 g	Single	90.0	0.75[b]	0.67	226	4.0	226	OMC-SXB-10
			4.5 g	8 weeks	104	0.50[b]	0.67	254	3.5	197	OMC-SXB-10
Narcoleptic patients	6	Oral	6 g (2x3 g)	single	91.2	0.59	0.88	295	4.2	307	OMC-GHB-4
Liver disease: Child's Class A patients	8	Oral	25 mg/kg (1.75 g)[a]	single	68	0.75[b]	0.53	85.4	4.5	198	Ferrara 1996
Child's Class C patients	8	Oral	25 mg/kg (1.75 g)[a]	single	47	0.75[b]	0.93	94.1	4.1	285	Ferrara 1996
Alohol-dependent patients	10	Oral	25 mg/kg (1.75 g)[a]	single	54	0.5[b]	0.45	52	9.6	NR	Ferrara 1992
				13 doses	55	0.5[b]	0.43	52	9.2	NR	
			50 mg/kg (3.5 g)[a]	single	45[c]	0.75[b]	0.58	90.3[c]	5.3[c]	NR	
Surgical patients	3	IV	50 mg/kg (3.5 g)[a]	single	NR	NR	~0.5	ND	ND	ND	Vree 1975
Surgical patients or sedation	6	IV	30-100 mg/kg (2.1-7 g)[a] (bolus)	single bolus and infusion	NR	NR	~0.67	ND	ND	ND	Vree 1978
Caesarian section patients	14	IV	26.7-50 mg/kg (1.9-3.5 g)[a]	single infusion	NR	NR	ND	ND	ND	ND	van den Bogert 1978

[a]dose calculated for a 70-kg subject presented for comparative purposes
[b]median
[c]normalized to 25 mg/kg
[d]values for second half of divided dose presented
NR = not reported
ND = not determined

5.1.2.1 Absorption

Xyrem (sodium oxybate) oral solution is rapidly absorbed following oral administration. The mean time to achieve peak plasma oxybate concentration (T_{max}) ranged from 0.5 to 1.25 hours across the 8 studies and was similar in narcoleptic and other patient populations (Table 5.1). The absorption characteristics of sodium oxybate were similar in males and females (OMC-SXB-8) and were not changed by chronic dosing (OMC-SXB-10).

The absorption characteristics of oxybate were influenced by food, which significantly ($P<0.05$) delayed the absorption of oxybate (OMC-SXB-11) (Figure 5.2). The average T_{max} in a fed state was 2.0 hours, representing an increase of over 100% when compared to a fasted state. The C_{max} was decreased by almost 60%, and the AUC_{inf} by 37%, following a high fat meal (OMC-SXB-11).

The absorption characteristics of oxybate were also dose-dependent. In Study OMC-SXB-9, peak plasma concentrations of oxybate were observed somewhat later at the higher dose, with T_{max} being approximately 0.9 hours after 2.25 g sodium oxybate and 1.2 hours after 4.5 g (Figure 5.1). Others have also reported the absorption of oxybate from the gastrointestinal tract to be dose-dependent. Palatini (1993) showed T_{max} increased as the GHB dose was increased from 12.5 mg/kg to 50 mg/kg (0.875 g to 3.5 g for a 70 kg subject) (Table 5.1). These observations were indicative of capacity limited absorption, which has also been reported in animal studies.

5.1.2.2 Distribution

The average apparent volume of distribution of oxybate divided by absolute bioavailability (V_z/F) ranged between 190 and 384 mL/kg across the studies sponsored by Orphan Medical (Table 5.1). In the only other study reporting this parameter, similar values were found in cirrhotic patients without and with ascites (198 and 285 mL/kg, respectively) (Palatini 1996). Vree (1978) reported the absolute bioavailability (F) of oral oxybate was approximately 27% and using this value, the volume of distribution ranges from 51 mL/kg to 104 mL/kg.[4]

The inter-subject variability of the apparent volume of distribution term for oxybate is indicated by the coefficient of variation, which ranged between 16% and 84% across the different studies. This wide range of inter-subject variation could be due to 2 factors. First, oxybate follows dose (or concentration) dependent pharmacokinetics. Second, the dose (and hence plasma concentration) at which non-linear pharmacokinetics of oxybate is observed varies among subjects, which, in comparison to a drug that follows linear kinetics, results in a wider range of AUC values for the same dose. The apparent volume of distribution term V_z/F is inversely related to AUC_{inf}, which increases more than proportionately once the oxybate dose is increased above 3 g. As a consequence, the inter-subject variation in the volume of distribution term is expected to increase exponentially once the threshold of non-linear pharmacokinetics is reached.

[4]Calculated by multiplying values for V_z/F (190 and 384 mL/kg) by F (0.27)

Oxybate readily crosses the placenta and is distributed to the fetus after intravenous injection in pregnant women undergoing cesarian section (van den Bogert 1978). Although fetal plasma oxybate concentration reached equilibrium with maternal concentration after approximately 30 minutes, it was rapidly eliminated from the neonate and doses of 35-45 mg/kg maternal weight were considered safe for this procedure (van den Bogert 1978). Rapid clearance of oxybate was also observed in a 2-day old male given 30 mg/kg oxybate (IV bolus) and the pharmacokinetic profile in this individual was similar to that observed in a 15-year old male given the same dose (van den Bogert 1978).

Plasma protein binding was not evaluated in the studies sponsored by Orphan Medical. Palatini (1993) reported that the free fraction of oxybate in plasma was consistent at 0.99 over a range of plasma concentrations between 3 and 300 µg/mL (pre-dialysis) and concluded that oxybate essentially does not bind to any plasma component.

5.1.2.3 Metabolism

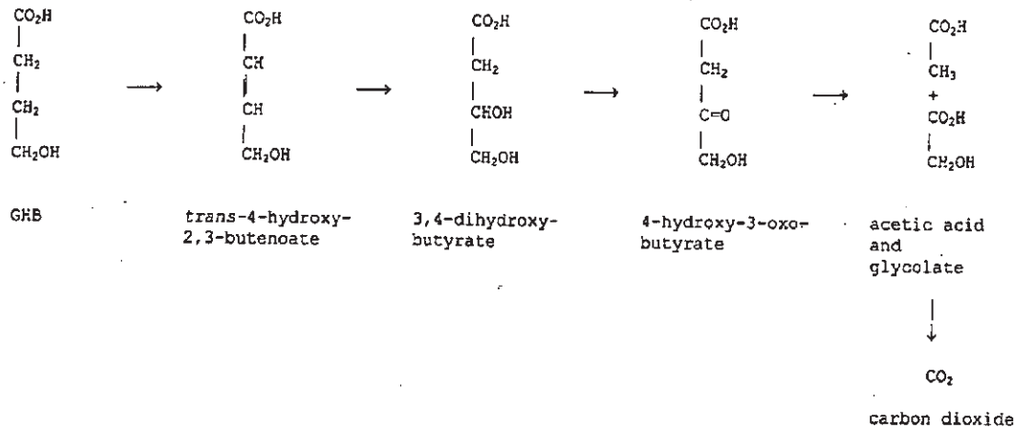
On average, less than 5% of an oral oxybate dose is eliminated unchanged in human urine (OMC-SXB-8, OMC-SXB-9, and OMC-SXB-11). Hence, metabolism is the major elimination pathway for oxybate.

Orphan Medical Inc. did not sponsor a mass balance and metabolic fate study in humans. The metabolism of exogenous and endogenous oxybate is well understood based on published investigations and the end product of the metabolism of oxybate, a simple 4-carbon molecule, is carbon dioxide regardless of biotransformation pathway. In addition, a ^{14}C-labeled mass balance and metabolic fate study in human volunteers is unethical because of the very real possibility of the radiolabel (*ie*, ^{14}C derived from ^{14}C-oxybate) being incorporated in structural protein via the amino acid pool.

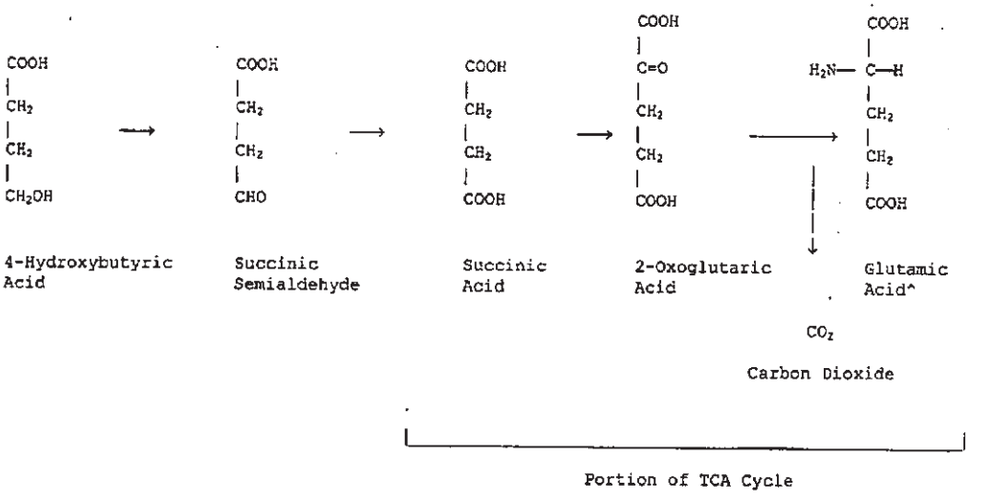
A review of the scientific literature shows that GHB may be metabolized via two distinct biotransformation pathways (Figure 5.3), one involving a β-oxidation pathway (Figure 5.3, upper panel) and the other involving the entry of an intermediate metabolite, succinic acid, into the tricarboxylic acid cycle (Figure 5.3, lower panel). The end product of both pathways is carbon dioxide.

The ß-oxidation pathway was proposed by Walkenstein and colleagues (Walkenstein 1964) based on the results of a ^{14}C mass balance and metabolism study in rats administered [1-^{14}C]GHB and [4-^{14}C]GHB (40 mg IP; specific activity 0.4 Ci/mg). Radiorespirometry indicated a rapid conversion of both ^{14}C-labeled molecules to ^{14}C-carbon dioxide, with approximately two-thirds of the dose excreted as carbon dioxide within 6 hours and an additional 10-20% over the next 18 hours. An intermediate metabolite, 3,4-dihydroxybutyrate, was identified. The proposed pathway involves biotransformation via β-oxidation to *trans*-4-hydroxy-2,3-butenoate, which became 3,4-dihyroxybutyrate, before proceeding to carbon dioxide (Figure 5.3, upper panel) (Walkenstein 1964).

Figure 5.3 Biotransformation Pathways for Oxybate (GHB)



Pathway 1: β-Oxidation of GHB as the Preliminary Step and Final Degradation to CO_2 from acetic acid and glycolaldehyde. Adapted from Walkenstein (1964) and Lee (1977).



Pathway 2: Formation of Semialdehyde Followed by Subsequent Degradation to CO_2 via the Tricarboxylic Acid Cycle. Adapted from Mohler (1976).

Oxybate and several metabolites of the ß-oxidation pathway (3,4-dihydroxybutyrate, 4-hydroxy-3-oxobutyrate, and glycolate) were identified in the urine of 2 male and 2 female volunteers who received a 1-g dose of oxybate in an aqueous solution (Lee 1977), validating the biotransformation pathway proposed by Walkenstein (1964). Further evidence in support of the ß-oxidation pathway came from a case report of a new inborn error of metabolism, γ-hydroxybutyric aciduria (Jakobs 1984, Jakobs 1990) with clinically manifestations including hypotonia, ataxia, and mental retardation.

Patients who were deficient in the enzyme that catalyzes the oxidation of oxybate to succinic semialdehyde (Figure 5.3, lower panel) developed abnormal accumulation of oxybate. It is of interest to note that Jacobs found the intermediate metabolites of the β-oxidation pathway, 3,4-dihyroxybutyrate and 3-keto-4-hydroxybutyrate (4-hydroxy-3-oxobutyrate), in the urine of such patients.

The second and principal biotransformation pathway (Figure 5.3, lower panel) involves the entry of an intermediate metabolite, succinic acid, into the tricarboxylic acid cycle. Studies in support of this pathway were reported by several researchers (Doherty 1975, Mohler 1976, Kaufman 1979, Kaufman 1983, Kaufman 1987, Kaufman 1988, Gibson 1989) who investigated the biosynthesis and catabolism of oxybate, which is a normal constituent in the brain, heart, kidney, liver, spleen, brown fat, and systemic circulation. Because of the striking effects of oxybate on behavior, most investigators initially limited their research efforts to studies on the central nervous system where oxybate is formed from GABA. The degradation of oxybate in the same tissue should be viewed as a mechanism to regulate its level, because its biosynthesis and catabolism pathways are closely linked.

Indirect evidence for the second biotransformation pathway was first provided by Doherty (1975) who injected [1-^{14}C]oxybate into the brain of rats and found that ^{14}C was incorporated into various amino acids in brain homogenates. Based on these results, it was postulated that brain tissue was capable of metabolizing oxybate to succinic acid via the formation of succinic semialdehyde as a first step. Similar results were observed in mice after intravenous injection of [^{14}C]oxybate (Mohler 1976). As well as demonstrating that oxybate readily crossed the blood-brain barrier, Mohler (1976) also demonstrated that radiolabeled oxybate disappeared from brain tissue quickly with a half-life of approximately 5 minutes and proposed the metabolic pathway for oxybate in brain tissue depicted in Figure 5.3 (lower panel).

Kaufman (1979, 1983, 1987, 1988a) subsequently isolated and characterized the 2 enzymes responsible for the interconversion between oxybate and succinic semialdehyde and subsequent conversion of succinic semialdehyde to succinic acid. An $NADP^+$-linked enzyme, termed GHB dehydrogenase, isolated from the cytosol of hamster liver and brain and purified 300-fold, catalyzes the interconversion between oxybate and succinic semialdehyde (Kaufman 1979, Kaufman 1987). GHB dehydrogenase is distinctly different from lactic dehydrogenase or alcohol dehydrogenase (Kaufman 1979). A second enzyme, hydroxyacid-oxoacid transhydrogenase is located in the mitochondria and is not dependent upon NAD^+ or $NADP^+$ (Kaufman 1988a, 1988b). This enzyme also catalyzes the conversion of oxybate to succinic semialdehyde in the presence of α-ketoglutarate. Succinic semialdehyde dehydrogenase is the enzyme system that catalyzes the biotransformation of succinic semialdehyde to succinic acid (Kaufman 1987). Finally, Gibson (1989) investigated the metabolism of oxybate in other isolated tissues, including the heart and kidney from rats. While the brain, liver, and kidney had the capability to metabolize oxybate, isolated heart tissue was lacking in this respect.

In summary, there is strong evidence for the metabolism of oxybate via 2 separate and distinct biotransformation pathways as depicted in Figure 5.3. The end product of both pathways is carbon dioxide. The succinic semialdehyde pathway plays an important role in the regulation of the endogenous GHB levels in the brain, liver, and kidney, while the β-oxidation pathway is invoked in patients with γ-hydroxybutyric aciduria. The β-oxidation pathway probably is also responsible for the first pass-metabolism of exogenous oral oxybate that results in an absolute bioavailability of <30% (Vree 1978).

5.1.2.4 Elimination

Clinically, plasma clearance (CL/F) is the most important pharmacokinetic parameter because it determines the patient's exposure to oxybate as represented by $AUC_{inf.}$ For the 8 human pharmacokinetic studies sponsored by Orphan Medical, the CL/F term was calculated by taking the ratio between the dose administered and $AUC_{inf.}$[5]

For agents whose pharmacokinetics are dose independent, plasma clearance generally remains consistent across a wide range of doses. Because the pharmacokinetics of oxybate are dose dependent, plasma clearance decreased as the oral dose of sodium oxybate increased. At the lower end of the therapeutic dose range (4.5 g as 2 x 2.25 g doses given 4 hours apart), the mean oral plasma clearance for oxybate was 6.6 mL/min·kg (OMC-SXB-9). Doubling the dose to the maximum recommended dose (9 g as 2 x 4.5 g doses given 4 hours apart) decreased the mean oral plasma clearance to 3.6 mL/min·kg, representing a nearly 50% decrease compared to the 4.5 g dose. Others have made similar observations. Ferrara (1992) reported an approximate 33% decrease in plasma clearance as oral oxybate dose increased from 25 to 50 mg/kg, while Palatini (1993) showed a 50% decrease (from 14 mL/min·kg to 7 mL/min·kg) as the oral oxybate dose increased from 12.5 mg/kg to 50 mg/kg.

Theoretically, the terminal parts of the elimination curves for different doses of any agent that follows non-linear kinetics are parallel. Practically, the apparent elimination half-life for agents with non-linear pharmacokinetics is dependent on dose. This behavior often is due to limitations imposed by the LOQ of the assay and the wider spacing of the plasma samples, especially around the end of the blood-sampling period. The apparent elimination half-life of oxybate following a 9 g dose (2 x 4.5 g administered 4 hours apart) averaged 0.83 hour and was approximately 40% longer than the mean apparent elimination half-life following a 4.5 g dose (2 x 2.25 g) in the same subjects (OMC-SXB-9). Although a 40% increase might be considered substantial, it is not clinically relevant due to rapid elimination. There were only 2 published studies in which oxybate elimination half-life was evaluated at 2 or more dose levels. Although a similar prolongation in apparent elimination half-life was observed in one study (Ferrara 1992), the second study (Palatini 1993) did not show any difference because its sampling

[5]Note: steady-state area under the curve (AUC_{ss}) is not reported for Xyrem. Because of its short $T_{1/2}$ (<1 hour), steady state plasma oxybate concentration is never achieved based on nocturnal dosing of Xyrem, with the nightly dose divided into 2 equal portions, administered 2.5 to 4 hours apart.

schedule successfully documented the terminal parts of the elimination curves, which were parallel for all 3 doses used in the study.

5.1.2.5 Other Pharmacokinetic Considerations

5.1.2.5.1 Non-linear Pharmacokinetics

Oxybate shows non-linear pharmacokinetics. This was observed in Study OMC-SXB-9, which showed that the highest recommended therapeutic dose of Xyrem (9 g given as 2 x 4.5 g) resulted in an AUC_{inf} that was 3.75 times of the AUC_{inf} elicited by the recommended starting therapeutic dose (4.5 g given as 2 x 2.25 g). Non-linear kinetics were also reported by Ferrara (1992) who determined the mean dose-normalized AUC_{inf} was 46% higher in alcohol dependent patients after a single oral oxybate dose of 50 mg/kg than after 25 mg/kg.

5.1.2.5.2 Chronic Pharmacokinetics

Chronic dosing at therapeutic levels did not alter the pharmacokinetics of Xyrem in a clinically significant manner (OMC-SXB-10). Although treatment with Xyrem for 8 weeks resulted in statistically significant 13% increase in systemic exposure to oxybate based on AUC_{inf} and a 16% increase in peak concentration, these modest increases are not considered to be clinically significant. It was also concluded that chronic Xyrem treatment did not result in auto-induction (self-induction of metabolism).

5.1.2.5.3 Drug Interactions

In clinical studies, there was no evidence for clinically significant interactions between Xyrem and Ambien®, Vivactil®, and Provigil®, which represent three classes of drugs (hypnotics, antidepressants, and stimulants, respectively) commonly used in the treatment of narcoleptic symptoms (OMC-SXB-12, OMC-SXB-14, OMC-SXB-17). There was no indication that oxybate inhibits CYP isoenzymes (Covance Study No. 6627-129).

5.1.2.6 Pharmacokinetics in Special Populations

5.1.2.6.1 Sex-related Differences

There are no significant differences in the single dose pharmacokinetics of Xyrem between male and female healthy volunteers (OMC-SXB-8). Values for log-transformed AUC_{inf}, log transformed C_{max}, CL/F (per kg), $T_{1/2}$, percentage of dose excreted unchanged in urine, apparent renal clearance ($P>0.05$; unpaired t-test), and T_{max} ($P>0.05$; Wilcoxon rank sum test) were no different in male and female healthy volunteers.

5.1.2.6.2 Hepatic Dysfunction

The single dose pharmacokinetics of oxybate were investigated in 16 patients with biopsy-proven liver cirrhosis, 8 without ascites (Child's class A) and 8 with ascites

(Child's class C) (Ferrara 1996) (Table 5.1). Compared to healthy adult volunteers given the same dose in a previous study, the mean apparent oral clearance was markedly reduced in cirrhotic patients without and with ascites (by 51% and 55%, respectively). The apparent elimination half-life was also significantly longer in cirrhotic patients without ascites when compared to healthy subjects (32 vs 22 minutes). These results indicate that from a systemic exposure perspective, it is prudent to start Xyrem therapy in patients with liver dysfunction at the lower end of the therapeutic dosage range and dose escalate in small increments when medically indicated.

5.1.2.6.3 Alcohol-Dependent Patients

Ferrara (1992) investigated the pharmacokinetics of oxybate in 10 alcohol-dependent subjects after single and repeated oral doses (25 mg/kg every 12 hours for 7 days). Oxybate was rapidly absorbed and eliminated with T_{max} of 20-45 minutes and mean $T_{1/2}$ of 27 minutes. The multiple-dose regimen resulted in neither accumulation nor in time-dependent changes of its pharmacokinetics. Administration of a 50 mg/kg dose to 5 of the 10 subjects resulted in significant increases in dose-normalized AUC, $T_{1/2}$ and mean residence time. Oxybate administered at 12-hour intervals did not cause any serious side effects.

5.1.2.6.4 Pediatric Patients

Orphan Medical has not sponsored any pharmacokinetic studies with Xyrem in pediatric patients and is not requesting an approval for use in pediatric patients in this application.

5.1.2.6.5 Patients with Renal Dysfunction

On average, less than 5% of a Xyrem dose was excreted by kidney as unchanged oxybate (OMC-SXB-8, OMC-SXB-9 and OMC-SXB-11). Since the kidney does not play a significant role in the excretion of oxybate, to date no pharmacokinetic study in patients with renal dysfunction has been deemed medically necessary.

5.1.3 OVERALL CONCLUSIONS

Oxybate is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations generally occurring within 1 hour from dosing. Food can delay the absorption of oxybate and Xyrem should be ingested on an empty stomach to obtain maximum systemic exposure. It has low oral bioavailability (<30%), most likely due to first-pass metabolism. It does not bind to plasma proteins and readily crosses the placenta and the blood-brain barrier. Its apparent volume of distribution divided by fraction absorbed into the systemic circulation is 202-384 mL/kg.

Oxybate shows non-linear pharmacokinetics. The elimination of oxybate from the human body is dose-dependent and systemic exposure to oxybate increases disproportionately with the dose of Xyrem administered. The elimination half-life also increases as the dose is increased but does not result in any risk of excessive drug accumulation when given on a divided nocturnal administration schedule. Plasma

oxybate should be non-detectable or at negligible levels 8 hours after the ingestion of the highest recommended daily Xyrem (9.0 g). Oxybate is almost exclusively cleared by biotransformation, eventually being degraded to carbon dioxide via 2 distinct biotransformation pathways. Renal excretion plays an insignificant role in the elimination of oxybate and only 1 to 7% of a dose is recovered as unchanged drug in urine following oral administration.

In vitro studies with pooled human liver microsomes show that oxybate does not significantly inhibit or enhance the activities of human CYP isozymes nor are significant pharmacokinetic interactions observed between Xyrem and zolpidem (Ambien), protriptyline (Vivactil), or modafinil (Provigil) in healthy volunteers.

The kinetics of Xyrem are similar in males and females and are comparable between narcoleptic patients and healthy human subjects as well as alcohol dependent patients. Accumulation of oxybate has not been observed with chronic therapeutic dosing, presumably because of its short half-life. However, severe cirrhosis can cause significant modifications of oxybate disposition kinetics. As a safety precaution, the initial Xyrem dose in narcoleptic patients with significant liver dysfunction should not be higher than 4.5 g per day and the dosage regimen for Xyrem may need to be reduced in such patients.

SECTION 6
ABUSE LIABILITY AND OVERDOSAGE

6.0 ABUSE LIABILITY AND OVERDOSAGE

6.1 Abuse Liability

6.1.1 INTRODUCTION

GHB is abused by those who take substances for perceived non-medical benefits (Dyer 1991, Chin 1998, Friedman 1996) and by those who intentionally adulterate foods and beverages with the intent of committing criminal acts (Galloway 2000). Illicit GHB is abused primarily to produce purported euphoric and/or hallucinogenic states and as an alleged growth hormone releasing/muscle building agent.

6.1.2 GHB MISUSE AND ABUSE

Enactment of Federal Law 106-172 in February 2000 classified GHB as a Schedule I drug when used for purposes other than specified in FDA approved clinical trials. The consequent crack down on Internet and other illegal sources of GHB combined with mandatory harsher penalties that Schedule I mandates have caused a decrease in illicit GHB availability. Despite this, new incidents of GHB misuse and abuse are still being reported in the United States, Europe and Australia (World Health Organization 2000, Substance Abuse and Mental Health Services Administration (SAMSHA) 2000c). For one, while GHB availability has diminished, it may still be obtained through some illicit sources or by home manufacture using recipes available on the Internet using precursor compounds (GBL and sodium hydroxide). However, anecdotal case reports and epidemiological data indicate that, although there has been a decrease in the abuse of GHB itself, illicit use of the GHB precursor compounds, gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) has dramatically increased (Ingels 2000, Winickoff 2000, Zvosec 2001, SAMHSA 2000b).

GHB continues to be misused as a "steroid replacement" and a sleep aid. In addition, there has been increased attention to the use of GHB as a "club drug" and as a drug used at "rave" parties (SAMHSA 2000b, Graeme 2000, Weir 2000). Government and public attention remains focused on GHB's association with "date rape". Reports of surreptitious GHB administration for purposes of sexual assault continue (LeBeau 2000, Schwartz 2000). The true incidence of GHB intoxication in cases of assault are difficult to determine due to lack of reliable and readily accessible testing but GHB has frequently been arbitrarily associated with any assault in which the victim was highly intoxicated and/or experienced amnesia. A study performed to determine the presence of various drugs in urine following sexual assault found ethanol to be the most prevalent "date-rape" associated drug, being present in almost 40% of the assault cases tested (ElSohly 1999). GHB was present in 4.1% of the cases, as compared to 8.2% for benzodiazepines, 8.2% for cocaine and 18.5% for marijuana, and was frequently present concurrent with one or more additional drugs. While the rapid metabolism of GHB may have underestimated the presence of GHB in these cases, this report suggests that GHB's involvement in drug-facilitated assault may be less common than is generally assumed. In addition, the cited study tested only for the presence of GHB without any

consideration to the role of the drug(s) in the assault or if they were administered unknowingly.

Few controlled studies in humans concerning aspects of GHB abuse potential have been published. In one controlled study of eight patients and in two anecdotal reports, the subjective effects of GHB have been compared to those of benzodiazepines, opiates, and alcohol (Friedman 1996, Galloway 1997, Rosen 1997). However, three of the eight subjects in the controlled study also reported GHB (30 mg/kg) to most closely resemble placebo, as it was unlike the other drugs (Rosen 1997).

Anecdotal reports continue to recount GHB administration resulting in positive subjective ratings (i.e., "feel good") with several accounts of GHB having a calming effect (Chin 1992, Galloway 2000).

Unlike some other drugs of abuse, GHB does not appear to produce strong physical or psychological dependence when administered under a therapeutic regimen (Moncini 2000, Beghe 2000). There continue to be instances of "GHB withdrawal" phenomena in case reports. An abstinence syndrome suggestive of physical dependence has been reported in patients following cessation of chronic high doses GHB (Galloway 2000, Hutto 2000, Miglani 2000, Price 2000, Dyer 2001). In all these cases, the patients had been consuming very frequently administered (i.e., every 3 hours or less), high-dose GHB for weeks to years. Withdrawal signs included insomnia, anxiety, mild diaphoresis and tremors. Some of the patients have also reported hallucinations (Craig 2000, Miglani 2000, Hutto 2000). The general health of these patients was normal with only one exhibiting hypertension and tachycardia (Craig 2000) and a second exhibiting moderate tachycardia (Hutto 2000). Signs associated with abstinence were alleviated by sedative drug administration (i.e., lorazepam, diazepam or chloral hydrate) with concurrent haloperidol administration in occasional cases. All patients' conditions resolved in 15 days or less. Review of the clinical trials underway in Europe for the treatment of opiate and alcohol addiction point to the therapeutic safety of GHB in a population at high risk for substance abuse. In a review of the various clinical trials, Beghé (2000) found that 3 to 10% of patients involved in various outpatient studies (N=732) assessing GHB treatment for ethanol dependence showed a tendency towards craving and dose escalation with only 1 account of a withdrawal syndrome requiring medical intervention following extreme dose escalation (Addolorato 1999a). When evaluated in a non-abusing patient population under therapeutic dosing conditions, there have been no reports of dose escalation, craving or withdrawal subsequent to cessation of treatment. This has been demonstrated in published reports (Broughton 1979, 1980, Scharf 1985, Mamelak 1986) as well as Orphan Medical clinical trials (OMC-GHB-3, OMC-SXB-6, OMC-SXB-7, OMC-SXB-21, Scharf trial). No evidence of dependence has been documented in any of the Orphan Medical narcolepsy clinical trials (OMC-GHB-2, OMC-GHB-3, OMC-SXB-6, OMC-SXB-7, OMC-SXB-21, Scharf Trial).

6.1.3 EXTENT OF THE PROBLEM OF GHB ABUSE

There are relatively few mentions of GHB in the Drug Abuse Warning Network (DAWN) reports (1992 to 2000) as compared to other sedative/hypnotics that are abused

(diazepam > 10,000 each year)(SAMHSA 2000b), but were significant enough to warrant Congressional scheduling of GHB in 2000. Although trending upwards, GHB abuse is still not listed separately in any U.S. database. The latest figures indicate no mentions of GHB in the 1999 Emergency Department Data from DAWN (SAMHSA 2000a) as drugs associated with fewer than 10 deaths per year are typically excluded. Data regarding GHB use was only made available in a special review because of the current focus by NIDA and other government agencies on the abuse of "club drugs". In March of 2000 the Drug Enforcement Administration reported documentation of over 5700 overdoses and law enforcement encounters with GHB-related substances (Federal Register, March 13, 2000, 13235-13238). However, the true incidence of GHB mentions are clouded by the co-mingling of GHB cases with those due to abuse of the two precursor compounds, gamma butyrolactone (GBL) and 1,4-butanediol (1,4-BD). Unfortunately, all mentions of GHB are grouped with those for its precursor chemicals, GBL and 1,4-BD under the heading of "GHB-like drugs". There are extensive data that these three compounds are not identical in quantitative and qualitative pharmacological characteristics.

GHB, GBL and 1,4-BD are all endogenous compounds. It is well documented that both GBL and 1,4-BD can be rapidly metabolized to GHB (oxybate) in the body following ingestion. GBL and 1,4-BD are significantly more lipid soluble than GHB. Thus, following oral ingestion both GBL and 1,4-BD are absorbed more rapidly than GHB and produce higher peak blood levels. As a result GBL and 1,4-BD are significantly more toxic compounds than GHB. Direct evidence of this important difference is shown by comparison of lethal doses in laboratory animals (LD50s). For example, the LD50 (mg/kg) in mice following the intraperitoneal administration of the three drugs is: GHB =3550, GBL =880, 1,4-BD =2180. Likewise, in rats orally, the LD50s are: GHB =9990, GBL =1800, 1,4-BD =1780. These data clearly indicate that GBL and 1,4-BD are 2 to 5 times more toxic than GHB in these species.

The true extent of abuse is also impaired by limited availability of analytical methods to verify the actual illicit substance consumed, the dose ingested or the levels of drug or metabolites in body fluids. For example, since illicit GHB has made been a Schedule I drug (March 13, 2000) and GBL became a listed chemical, much of what is being used illicitly as GHB is actually 1,4-BD. However, emergency room physicians must currently treat presumed GHB overdose or withdrawal patients symptomatically because drug identity, dose and drug plasma levels are unavailable. Furthermore, since GHB is an endogenous substance found in many tissues and body fluids and which actually increases postmortem, bioanalytical methods must be able to clearly differentiate between endogenous GHB and exogenous GHB or GHB analogues.

While mentions of these compounds increased significantly from 1994 to 1999, the actual increase in numbers is relatively small when compared to mentions for sedative hypnotics with known abuse potential. GHB accounted for less than 0.3% of all drug related emergency department (ED) visits. It must also be stated that drug "mentions" in the DAWN system do not imply that the substance was responsible for the ED admission nor whether the drug alone was involved in a case. Of the ED mentions of GHB in 1999, 71% were in combination with one or more drugs, with ethanol being present in over 50% of all GHB mentions. In addition to drugs of abuse which are

identified in the DAWN system, other commonly used drugs which always receive mentions include aspirin, ibuprofen, and fluoxetine (SAMHSA 1999, 2000a).

Additional information concerning GHB and precursor chemical abuse comes from reports by the NIDA Community Epidemiology Work Group (CEWG), a nationwide network of epidemiologists and drug abuse researchers that meet regularly to discuss emerging substance abuse problems. Evidence of localized GHB abuse began to be reported as early as 1995, identifying it as a new "club drug" (CEWG 1996). In each subsequent annual report of the CEWG, increasing attention has been paid to the problem of GHB abuse and more recently the abuse of its precursor chemicals, GBL and 1,4-BD (CEWG 2000b). The June 1999 full report (CEWG 1999), December 1999 advance report (CEWG 2000a) and June 2000 advance report (CEWG 2000b) all describe increasing nationwide abuse of GHB or its precursors in dance clubs and at raves as well as reporting some mortalities associated with this practice. However mention of GHB and its precursors was absent from the December 2000 advance report (CEWG 2001). Whether this reflects an improvement or stabilization in the levels of GHB-like drug abuse is unclear.

Other sources of information on the level of abuse of various drugs as yet provide little data on GHB. As of 2000, questions about GHB have been included in the nationwide "Monitoring the Future" survey of high school students conducted annually. However, the information will not be available until April 2001. Nor is there information available about rates of GHB abuse in reports of the National Household Survey on Drug Abuse as of the most recently reported results which contain the 1998 survey results (SAMHSA, 1999). Although survey respondents may have included GHB under one of the "other" drug categories, since the use of GHB is not queried specifically, it is impossible to know if the prevalence of abuse is below the threshold of about 0.1% of the population which can be detected in the Household Survey.

Deaths attributable to the abuse of GHB have been reported. There is considerable variability, however, in the numbers reported that appears to be dependent on the source. The annual Toxic Exposure Surveillance System review performed by the American Association of Poison Control Centers listed 10 deaths (< 20 total for 1995 through 1999) attributable to GHB or GHB-precursors in 1999 (Litovitz 2000). In two of these cases, GHB was not the primary drug involved. Of the eight cases which were attributed to GHB or GHB-precursor toxicity, only three were accompanied by GHB blood level determinations. The special report from DAWN (2000c) on "club drugs" lists medical examiner reports of GHB or GHB-precursor involvement in a total of 12 deaths from 1994 to 1998. No specific information was provided regarding method of diagnosis of GHB involvement. In contrast to the low level of mortality in these reports, the U.S. Drug Enforcement Administration (DEA 2000) reported that their staff have identified 65 GHB-related deaths since 1990 through aggressive case-finding when deaths have been brought to the attention of agency officials. As yet, no information about GHB tissue levels or method of drug analysis has been provided for these cases.

6.1.4 PRECLINICAL STUDIES RELEVANT TO ASSESSMENT OF ABUSE POTENTIAL OF GHB

Table 6.1 summarizes preclinical studies relevant to the assessment of the abuse potential of GHB.

6.1.4.1 Drug Discrimination

Drug discrimination studies in animals are considered to be predictive of subjective drug effects in humans (Schuster 1988). In addition, when the discriminative stimulus effects of drugs are compared to each other, classifications of drugs based on the results can be predictive of commonalities in cellular sites of action. In rats trained to discriminate IP GHB (200 mg/kg) from saline, none of the variety of different classes of drugs tested fully substituted for GHB (Winter 1981). Notably, GBL produced only partial substitution for GHB, indicating differences in the discriminative stimulus effects of the two compounds. Morphine, lysergic acid diethylamine (LSD), chlodiazepoxide, muscimol, baclofen, and 3-aminopropane sulfonic acid also produced, at best, partial substitution; *d*-amphetamine, apomorphine, and ethanol produced a very low partial substitution; barbital, phencyclidine and the phencyclidine-like compound N-allylnormetazocine, failed to support GHB-lever responding at any dose tested. The discriminative stimulus effects of GHB were not blocked by naloxone, bicucculine, pizotyline, phentolamine, or butaclamol (Winter 1981).

In rats trained to discriminate oral GHB (700 mg/kg or 300 mg/kg) from water, the GHB antagonist NCS-382 antagonized the discriminative stimulus of GHB at either training dose (Colombo 1995a), indicating a possible involvement in the GHB receptor mediating the discriminative stimulus effects of GHB. The $GABA_B$ antagonist, CGP 35348, on the other hand, had differential effects depending on the training dose of GHB. It completely blocked the discriminative stimulus effects of GHB in rats trained to discriminate 700 mg/kg but only partially blocked the effects in rats trained to discriminate 300 mg/kg (Colombo 1995b). Neither the phencyclidine-like drug dizocilpine nor the cannabinoid WIN 55,212-2 substituted for GHB at either training dose (Colombo 1995b). In rats trained to discriminate 300 mg/kg GHB, only one dose of ethanol (1 g/kg) fully substituted for GHB; higher and lower doses of ethanol produced primarily saline-lever responding (Colombo 1995c). Likewise, GHB substituted for ethanol at only one dose (300 mg/kg) and only in rats trained to discriminate a low dose (1.0 g/kg) of ethanol from water; GHB did not substitute in rats trained to discriminate a higher dose of ethanol (2.0 g/kg) (Colombo 1995c). In rats trained to discriminate intragastric GHB (700 mg/kg or 300 mg/kg) from water, baclofen fully substituted in both groups but was more potent in producing GHB-like effects in the high dose group (Lobina 1999).

Metcalf (1999) sought to continue the investigation of the interrelationship between the subjective effects of GHB and ethanol through the use of drug discrimination procedures. In the Metcalf study, rats were trained to discriminate either intragastric (IG) GHB (300 mg/kg) from saline, IG ethanol (1000 mg/kg) from saline, or IG combination of 150 mg/kg GHB and 500 mg/kg ethanol from saline. Subsequent testing for cross generalization found that GHB, at best, partially substituted for ethanol in the ethanol-

trained rats. Similarly, ethanol only partially substituted for GHB in the GHB-trained group. These results did not replicate Colombo's findings of cross generalization across a narrow dose range and were more similar to those obtained by Winter (1981). The results to date in rats suggest that GHB administration produces unique discriminative stimulus effects with some characteristics most similar to those of ethanol and some GABAmimetic drugs, particularly $GABA_B$ drugs, such as baclofen, which are not abused. In addition there is some evidence that different cross substitution patterns can occur at different doses of GHB.

Testing of GHB in both heroin- and phencyclidine-trained rats also failed to demonstrate any substitution with GHB (Beardsley 1996). The results to date suggest that GHB administration produces unique discriminative stimulus effects with some characteristics similar to those of ethanol, morphine and some GABAmimetic drugs, and that the characteristics of these effects are not equivalent across different doses of GHB. Additional studies of the discriminative stimulus effects of GHB have been done as part of the College on Problems of Drug Dependence abuse liability testing program. These results are discussed in section 6.1.4.4.

6.1.4.2 Tolerance and Dependence

Data are available from two additional preclinical studies which do not speak directly to the abuse potential of GHB but do support its clinical use for treating ethanol and opiate withdrawal in humans. Gessa and colleagues (2000) demonstrated the ability of GHB to alleviate a constellation of withdrawal signs in ethanol-dependent rats, supporting previous studies suggestive of a possible cross tolerance/dependence between GHB and ethanol (Fadda 1989, Colombo 1995d). Typically, true cross-tolerance/dependence is seen in drugs with common neural sites of action. Ethanol and GHB have not been shown to have overlapping sites of cellular action. Ethanol has activity as a $GABA_A$ receptor agonist (Ticku 1989) and as an NMDA antagonist (Gonzales 1990). GHB has no activity at the $GABA_A$ receptor and only very low affinity for the NMDA receptor ion channel (Gessa 1993). These studies suggests that the apparent cross-dependence between GHB and alcohol may be reflective of GHB's ability to selectively attenuate some of the signs and symptoms of alcohol withdrawal (Agabio 1998), much as clonidine does for opioid withdrawal (Rosen 1996). In a similar study in morphine-dependent rhesus monkeys, lower, but not higher, doses of GHB were able to significantly attenuate morphine withdrawal signs (Aceto 2000). Again, there are no indications that GHB has any direct activity at opiate receptors which could explain this effect (Feigenbaum 1996b). It is believed instead that this effect is due to GHB-stimulated modulation of endogenous opioid release (Gobaille 1994).

6.1.4.3 Drug Self-Administration and Related Studies

The behavioral effects of GHB have also been examined in animal models said to be predictive of the reinforcing properties of the drug. Conditioned place preference (CPP) relies on pairing of drug administration with a specific environment, and subsequently testing for preference for that environment over one paired with the nondrug condition. In a study by Martellotta and colleagues (1997), GHB was shown to induce CPP. Under

similar testing conditions, other sedative hypnotics, such as diazepam, have also been shown to induce CPP. Typically, drugs with known strong reinforcing effects, such as cocaine and opiates, will produce CPP after only 2 to 3 drug exposures. In the study with GHB, a minimum of 6 drug exposures were required to produce CPP, suggesting a weaker effect compared to highly abused drugs like cocaine.

The pharmacokinetic profile of GHB in rats shows a very rapid metabolism and elimination of GHB with virtually no GHB remaining three hours after i.v. administration (Lettieri 1979). This should make GHB comparable to the shorter acting barbiturates and benzodiazepines that are the most reliably self-administered. A series of studies has been done in which rats were shown to drink GHB solutions. This occurred more readily in rats selectively bred to self-administer alcohol (Colombo 1995a, Colombo 1998b). In this series of studies, rats were given forced access to GHB for a period of a couple weeks and then given a two-bottle choice between a single concentration of GHB and water. On about one-half the days, animals drank more of the GHB solution than they did water. On the other one-half of the days, they drank more water than GHB. Such results would also be expected if there were no preference for the solutions, or a side preference (the bottles were switched from side to side). Because of uncertainties about the interpretation of these drinking studies, it is difficult to unambiguously conclude that they provide evidence for GHB self-administration. There has been a report of i.v. self-administration of GHB in mice, but only in abstract form (Martellotta 1996).

A study of GHB self-administration has been carried out in rhesus monkeys using a substitution procedure widely used for abuse potential assessment (Beardsley 1996). In this study, monkeys experienced in PCP self-administration were tested with a wide range of doses of GHB. The results were negative. In only 1 of 18 tests was the rate of GHB self-infusion greater than for vehicle, and even in this case the rate of responding was very much lower than were obtained with PCP. It is clear that behaviorally-relevant doses of GHB were tested since some observable sedation was seen in the monkeys. A CPDD study of GHB self-administration in barbiturate experienced monkeys is reviewed in section 6.1.4.4 below.

GHB has also been examined for its ability to attenuate self-administration of other drugs of abuse. Non-hypnotic doses of GHB and/or GBL have been observed to reduce ethanol intake in rats and humans as well as decrease cocaine self-administration in rats (Fadda 1983, Biggio 1992, Gallimberti 1992, Addolorato 1996, Martellotta 1998). In humans, this effect was associated with a decrease in craving (Biggio 1992, Gallimberti 1992). There are various possible explanations for these apparently therapeutic effects of GHB. One reason is that GHB may be mimicking the effect of the abused drug. For example, because of the similarities of the behavioral effects of ethanol and GHB, ethanol consumption may be diminished due to a substitution effect. Alternatively, GHB may truly alter the reinforcing efficacy of some drugs of abuse, either by direct receptor interaction or by indirect CNS effects. This is certainly a possibility for the effects on both alcohol and cocaine self-administration given GHB's ability to diminish dopamine neurotransmission (see section 2.1.1.3). A third possibility is that the decrease in drug self-administration is a nonspecific effect of GHB. In the operant studies (Biggio 1992,

Martellotta 1998), no control tests were conducted to determine if GHB could have decreased responding for any reinforcer (e.g. food) because of its depressant effects.

6.1.4.4 College on Problems of Drug Dependence Testing Program

As a service to industry and the government, the College on Problems of Drug Dependence (CPDD) sponsors an animal testing program for assessing drug abuse potential. GHB has been extensively tested under this program. Most of the tests were performed under the Stimulant/Depressant Program, but one study was done under the Opiate Testing Program. GHB was submitted to the testing facilities as CPDD 0044 or NIH 10947. The CPDD testing program includes a battery of validated animal tests designed to provide information relevant to regulatory decisions regarding drug abuse potential. The general approach used by the CPDD testing program reflects the recommendations of many expert groups who have provided guidelines for abuse liability assessment, including the World Health Organization Expert Committee on Drug Dependence (World Health Organization 1978) and the Committee on Problems of Drug Dependence (CPDD) (Committee on Problems of Drug Dependence 1977, Brady 1984, May 1989). The reports of the results of testing GHB by the CPDD Drug Evaluation Program can be found in their annual reports to the College (Jacobson 1997, Jacobson 1998, Jacobson, In Press). In addition, most of the data were assembled for a scientific journal publication (Woolverton 1999).

Drug Discrimination

The discriminative stimulus effects of GHB were compared to those of *d*-amphetamine and pentobarbital in rhesus monkeys using standard 2-lever operant conditioning procedure utilizing food reinforcement. For these studies, monkeys were trained using gavage via a nasogastric tube. GHB tests were conducted using the same route up to doses as high as 170 mg/kg. In *d*-amphetamine-trained monkeys (N=4), GHB produced a maximum mean of 50% drug lever responding. This partial substitution for *d*-amphetamine was not dose-related nor were any response rate decreasing effects obtained. GHB completely failed to substitute for pentobarbital (N=3). There was no pentobarbital-lever responding in any subject at any dose. There was a small increase in rates of responding, suggesting that a behaviorally-effective dose range was tested.

In a separate laboratory, the discriminative stimulus effects of GHB were compared to those of triazolam and flumazenil. Rhesus monkeys were used for both studies. A 2-lever operant conditioning procedure was used with behavior maintained by mild electric shock avoidance. For the triazolam comparison, monkeys (N=3) were trained to discriminate s.c. injections of triazolam and saline. GHB tests also utilized the s.c. route. Only one of the three monkeys showed any evidence for triazolam-like effects of GHB. In that one monkey, 81% and 40% triazolam-lever responding was obtained at doses of 3.2 and 10 mg/kg respectively. A higher dose of GHB did not substitute for triazolam. Some response rate decreasing effects were obtained, suggesting that a behaviorally-active dose range of GHB was tested. The rationale for the flumazenil discrimination study is as follows. These monkeys (N=2) were given daily oral doses of diazepam resulting in diazepam dependence. Thus, flumazenil injections would precipitate a mild

withdrawal that was discriminated from saline injections. GHB did not substitute for flumazenil. These results can help rule out the possibility that GHB is a GABA antagonist.

Drug Self-Administration

A self-administration study was performed with GBL using a standard substitution procedure in rhesus monkeys. These procedures are very commonly used for abuse potential assessment. The monkeys (N=3) were trained to lever-press under a fixed-ratio 10 schedule to obtain intravenous infusions of methohexital during two daily 2-hour sessions. In addition, sessions were frequently conducted in which only saline deliveries were available. Animals typically obtained about 5-10 times more infusions of methohexital than saline. Various doses of GHB were tested once or twice in single sessions in each subject. The number of infusions of GHB that were self-administered was approximately the same as the number of infusions of saline and considerably less than the number of infusions of methohexital. In all tests except two, the number of GHB infusions was not significantly different from the mean number of saline infusions. In two tests, rates of GHB self-administration exceeded those for saline. This occurred in two different monkeys at two different doses, and even in these cases the infusion rates were quite low and did not approach those seen with methohexital in these monkeys. It is also possible that these 2 out of 14 tests with marginally higher rates than on saline tests simply reflect normal variation in day to day response rates under saline availability and thus would be considered false positives. The authors of the study concluded that GHB was, at most, only a weak positive reinforcer.

Interactions with Morphine

A study was done to investigate whether GHB would alter the analgesic effects of morphine or the expression of morphine tolerance (Jacobson, In Press). These studies were done using a mouse tail flick procedure. In the first study, various doses of GHB were tested in combination with doses of morphine that produced about 25% maximal analgesia when given alone. GHB did not produce appreciable analgesia at any dose, but it dose-dependently enhanced morphine analgesia. In mice made tolerant to morphine analgesia, GHB in combination with morphine restored some of morphine's analgesic effects. These studies are not directly related to abuse potential assessment, but do speak to the safety of GHB in combination with opiates and also could suggest additional therapeutic uses.

The CPDD testing program evaluated the abuse potential of GHB using drug discrimination and drug self-administration procedures in rhesus monkeys. These tests show a lack of pharmacological equivalence between GHB and pentobarbital, triazolam and d-amphetamine, supporting the view that GHB has a unique profile of psychoactive effects. Little evidence was obtained for self-administration of GHB, although there was a suggestion of weak reinforcing effects in some subjects. The scientists associated with the testing program concluded that the profile of effects obtained "suggests that GHB has, at most, low potential for abuse" (Woolverton 1999).

6.1.4.5 Conclusions

Based on preclinical studies alone, there is not compelling evidence that GHB represents a significant drug abuse hazard. In the first place, GHB is a natural constituent of the human body. Although high doses of exogenously administered GHB can reasonably be expected to produce effects that would not occur under normal physiological conditions, the difference from normal is likely to be one of degree not a qualitative difference. The idea that a person could be severely dependent on some aspects of one's own physiology is difficult to conceptualize. Secondly, GHB is not pharmacologically equivalent to any existing controlled substances. Although it shares some effects with abused depressant drugs, clear differences from these drugs can also be shown. GHB appears to have a unique cellular site of action in the brain, its own receptor, that is not a receptor for any other drugs except various GHB analogs, an antagonist and several benzamide neuroleptics. GHB does not interact with known sites of action of any abused drug, including any known modulatory sites on the $GABA_A$ receptor. The preclinical pharmacological profile of GHB also differs from classical depressant drugs. Although it can produce depressant effects, it also has excitatory effects at high doses and can be a convulsant. There is some speculation that the sedation seen in some animals with GHB may actually reflect a type of absence seizure.

Self-administration studies of GHB fail to show evidence for strong reinforcing effects. Two studies were performed in rhesus monkeys using a substitution procedure that has been extensively validated for use in abuse potential prediction. One of these was done as part of the CPDD testing program. GHB had, at most, weak reinforcing effects in these studies. Rodent studies with GHB have been inconclusive. There is one study showing a conditioned place preference with GHB, but this procedure has only rarely been used in abuse potential assessment. Both oral and i.v. self-administration has been shown in rodents, but results were variable and difficult to interpret conclusively as reflecting centrally-mediated reinforcing effects.

Repeated administration of GHB can result in tolerance development, although there is some evidence that it is more difficult to produce tolerance with GHB than with ethanol. Many drugs produce tolerance, so this fact alone has little relationship to abuse potential. There are studies showing cross-tolerance with ethanol. The significance of this for abuse is unclear, although it could support a conclusion that GHB and alcohol share some common mechanisms of action. On the other hand, cross tolerance of GHB with baclofen and muscimol have also been reported. There have been no reports of physical dependence development with repeated GHB administration in animals. It could be predicted that it would be difficult to produce primary physical dependence with GHB because its short duration of action would require many multiple daily administrations to maintain elevated levels in the body. There are a few studies showing that GHB can attenuate withdrawal signs in animals made dependent on ethanol. This may be due to a true cross-dependence with ethanol or to a physiological attenuation of specific withdrawal signs. Taken together, preclinical studies of tolerance and dependence could not be used to support a finding that GHB has a high physical dependence potential.

6.1.5 TABULAR SUMMARIES OF PRECLINICAL STUDIES RELEVANT TO ABUSE POTENTIAL ASSESSMENT

Table 6.1. Studies Pertaining to Abuse Liability Assessment of GHB in Animals

ANIMAL						GHB ADMINISTRATION			RESULTS	REFERENCE
Species	Strain	No.	Sex	Age	Weight (g)	Route	Dose (mg/kg)	Frequency/ Duration		
Mouse	CD-1	NA	M	NA	25-28	IV	0.01-0.05 per inject-ion	Determined by mouse	GHB was self-administered at higher rates than vehicle; antagonized by NCS 382	Martellotta 1998 (reviewed in Fattore 2000)
Rat	Sardinian ethanol preferring (SP)	6	NA	NA	NA	PO	300	Twice a day for 5 days	GHB suppressed ethanol consumption	Fadda 1989 (Biggio 1992)
Rat	Wistar	20	M	4 months	400-500	PO	1% (w/v)	Sole fluid for 14 days, then frequency determined by rat	After a 14-day period in which GHB is sole fluid available, GHB and water are self-administered at about the same frequency	Colombo 1995c
Rat	SP & SnP	9-12/group	M	3-4 months	Mean: 400-500	PO	1% (w/v)	Sole fluid for 14 days, then frequency determined by rat	After a 14-day period in which GHB is sole fluid available, GHB was self-administered with higher frequency in SP (alcohol-preferring) rats.	Colombo 1998c
Rat	Long-Evans	NA	M	NA	300-350	IG	175-350	daily	GHB attenuated cocaine self-administration	Martellotta 1996 (reviewed in Fattore 2000)
Rat	Long Evans	5-6/group	M	12 weeks at start of training	80% of free feeding weights	PO	300	daily	GHB could be trained as a discriminative stimulus. One dose of ethanol (1.0 g/kg) substituted for GHB, higher and lower doses did not. In ethanol trained rats, GHB substituted for ethanol at one dose (300 mg/kg) in rats trained to discriminate 1.0 g/kg ethanol, but not 2.0 g/kg ethanol.	Colombo 1995a
Rat	NA	NA	NA	NA	NA	IG	300 or 700	daily	GHB could be trained as a discriminative stimulus at either dose; dizocilpine and WIN 55 212-2 did not substitute for GHB at either training dose. Baclofen blocked the discriminative stimulus of the high, but not the low training dose.	Lobina 1999 (Colombo 1998a [abstract])

Table 6.1. Studies Pertaining to Abuse Liability Assessment of GHB in Animals (continued)

ANIMAL						GHB ADMINISTRATION			RESULTS	REFERENCE
Species	Strain	No.	Sex	Age	Weight (g)	Route	Dose (mg/kg)	Frequency/ Duration		
Rat	Long Evans	10/group	M	Adult	90% of free feeding weights	IG	300	daily	GHB could be trained as a discriminative stimulus. Ethanol produced partial substitution for GHB. In rats ethanol trained to discriminate 1.0 g/kg ethanol, GHB produced partial substitution.	Metcalf 1999
Rat	Sprague-Dawley	8-10/group	M	Adult	180-200	IG	87.5-350	daily	GHB induced conditioned place preference	Martellotta 1997 (reviewed in Fattore 2000)
Rat	Sprague-Dawley	NA	M	3 months at start	250-300	IG	400-1000	daily	Tolerance developed to the motor-impairing effects of GHB and ethanol.	Colombo 1995d
Rat	Sprague-Dawley	16/group	M	NA	200-220	IP	250-1000	Acute	GHB decreased signs of ethanol withdrawal in ethanol-dependent rats	Fadda 1989
Rat	Wistar	7	NA	NA	NA	IP	1000	Acute	GHB alleviated signs of withdrawal in ethanol-dependent rats.	Gessa 2000
Rat	CFN	14	F	8 weeks at start of training	NA	IP	200	daily	GHB could be trained as a discriminative stimulus; other drugs did not fully substitute for GHB, including morphine, LSD, chlodiazepoxide, competitive GABA agonists, d-amphetamine, ethanol, barbital, PCP, PCP-like compounds.	Winter 1981
Rat	Sprague-Dawley	4	M	Adult	85% of free feeding weights	IP	10-300	1 dose every 2-4 days	GHB did not substitute for PCP in rats trained to discriminate PCP from saline	Beardsley 1996
Rat	Sprague-Dawley	5	M	Adult	85% of free feeding weights	IP	10-300	1 dose every 2-4 days	GHB did not substitute for heroin in rats trained to discriminate heroin from saline	Beardsley 1996
Monkey	Rhesus *Macaca mulatta*	7	NA	adult	6.4-12.2 kg	IG	1-170	Acute	GHB did not engender pentobarbital-lever responding in 3/3 monkeys trained to discriminate pentobarbital from saline. GHB engendered a maximum of 50% amphetamine-lever responding in ¾ monkeys trained to discriminate amphetamine from saline.	Woolverton 1999 (Jacobson 1997)

Table 6.1. Studies Pertaining to Abuse Liability Assessment of GHB in Animals (continued)

ANIMAL						GHB ADMINISTRATION			RESULTS	REFERENCE
Species	Strain	No.	Sex	Age	Weight (g)	Route	Dose (mg/kg)	Frequency/ Duration		
Monkey	Rhesus	4	1F/3M	Adult	6.4-11.4 kg	IV	3-7.5 per infusion	Determined by monkey 4-day test	GHB did not maintain responding in monkeys that self-administer PCP	Beardsley 1996
Monkey	Rhesus *Macaca mulatta*	4	NA	NA	8-12 kg	IV	1-10/ infusion	Acute	GHB maintained responding only marginally above that for saline in monkeys that self-administer methohexital	Woolverton 1999 (Jacobson 1997)
Monkey	Rhesus *Macaca mulatta*	5	NA	3 adult 2 juv-enile	3-9 kg	SC	1-178	Acute	GHB does not have flumazenil or triazolam-like discriminative stimulus effects and does not antagonize the discriminative stimulus effects of these benzodiazepines	Woolverton 1999 (Jacobson 1998)
Monkey	Rhesus *Macaca mulatta*	3+	M/F	adult	2.5-7.5	SC	7.5-240	Acute	Lower doses of GHB (7.5, 30) alleviated signs of withdrawal in morphine-dependent monkeys.	Aceto 2000

6.2 Overdosage

The purported rationales for abuse of GHB include its use by body builders as a steroid replacement, as a diet aid, to treat insomnia, and as a euphoria-inducing agent and aphrodisiac (Galloway 2000). More recently, some individuals have turned to GHB in order to combat depression. The latter most likely reflects the influence of the Internet where GHB has been promulgated to be a "natural" antidepressant (http://heelspurs.com/cure.html, http://www.dog.net.uk/claude/ghb-1.html).

In evaluating the anecdotal reports of GHB overdose, identification of the ingested GHB dose and its relationship to the users clinical condition continues to be complicated by three important factors: (1) The drug is usually obtained via clandestine manufacture, including being homemade, making the actual dose ingested unknown; (2) Toxicity due to precursor chemicals is often erroneously included in the case reports as due to GHB based on clinical interpretation; (3) Reports frequently involve coadministration of other drugs of abuse, especially alcohol.

As GHB use has decreased, the incidence of illicit use of its precursor chemicals appears to be increasing. This illicit use of GHB interchangeably with its precursor chemicals, GBL and 1,4-BD, may contribute to variable dosing and consequently to acute toxicity (Ingels 2000, Winickoff 2000, Zvosec 2001). Although these precursor chemicals are metabolically converted in the body to GHB, there are major differences in their kinetic time courses and distribution that can alter pharmacodynamic effects. For one thing, neither GBL nor 1,4-BD show appreciable binding at the GHB-receptor, which has been shown to be primarily responsible for many of GHB's clinical and behavioral effects (Feigenbaum 1996a, Snead 2000). GBL is more rapidly absorbed and is lipid soluble in comparison to oxybate, which is water soluble (Lettieri 1978, Arena 1980). This difference alone will produce significant kinetic and distributional differences. In addition, GBL failed to fully substitute for GHB in preclinical discrimination studies (Winter 1981) and has been noted to have stronger GABAergic characteristics than GHB (Feigenbaum 1996a) suggesting qualitative as well as quantitative differences may exist between the two compounds. As well as having a low level of direct activity as an alcohol (Poldrugo 1984), 1,4-BD is converted to GHB *in vivo* by sequential alcohol dehydrogenase and aldehyde dehydrogenase metabolism (Maitre 1997). Competitive inhibition of alcohol dehydrogenase conversion of 1,4-butanediol to GHB by ethanol has been demonstrated (Poldrugo 1984, 1986). Concurrent ethanol and GHB administration has also been shown to alter the time course of ethanol and 1,4-BD metabolism through competition for the same enzyme in rats (Poldrugo 1985). The clinical impact of these interactions in acute users of 1,4-butanediol/ethanol combinations has yet to be fully investigated but initial studies suggest a prolonged intoxication and/or enhanced toxicity (Shannon 2000).

These pharmacological differences between GHB and its precursor chemicals almost certainly contribute to inexact dosing and subsequent risk of acute toxicity. Sporadic accounts of GHB-related acute toxicity requiring medical attention continue to be reported (O'Connell 2000, Ingels 2000, Yates 2000). Over half of the toxicity cases have been associated with co-ingestion of another drug (Centers for Disease Control 1997,

Chin 1998, Galloway 2000). In the majority of the cases reported, GHB was the presumed cause of the adverse reactions based on the description of the incident, time of onset, etc. (Galloway 1997, Chin 1998, Ingels 2000). Because laboratory tests for GHB are not generally available to clinicians, only rarely have actual blood/urine levels of GHB measured (Dyer 1994, Li 1998b). In some cases, the presence of GHB was noted but actual levels were not provided (O'Connell 2000). This continues to make evaluation of the true risk associated with GHB use difficult, especially when considering that the majority of GHB toxicity cases resulting in hospitalization involved the co-ingestion of alcohol or another drug. More and more frequently, acute toxicities are associated with the consumption of one of the precursor chemicals and not GHB itself (Ingels 2000, Winickoff 2000, Zvosec 2001).

The recommended course of treatment continues to be general symptomatic and supportive care with primary attention to airway protection (Galloway 2000, Graeme 2000) particularly in consideration of the risk of gastric aspiration. As yet, no reversing agent for GHB is available. There is some evidence that physostigmine may be efficacious in rapidly reversing the sedation induced by GHB (Henderson 1976, Yates 2000). This recommendation remains controversial as many concerns have been raised regarding potential toxicity issues with physostigmine use (Mullins 2000), including bradycardia or asystole (Pentel 1980) and seizure induction (Newton 1975). At present, the principles of management remain supportive care with particular attention to maintenance of the airway and blood oxygen levels. Additional attention should be directed toward the institution of laboratory analysis of GHB levels in hospitals in order to more rationally interpret dose response, clinical presentation and patient outcome. Overall, based on the current and previous accounts of overdose cases, prognosis is good for patients receiving medical attention (Li 1998b, Chin 1998, Galloway 2000, O'Connell 2000, Ingels 2000). Mortality was usually associated with unattended individuals who were found already deceased rather than associated with death in the emergency department (Winickoff 2000, Graeme 2000).

SECTION 7
SCHEDULING

7.0 SCHEDULING

7.1 Introduction

The Controlled Substances Act (CSA), Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, is the legal foundation of the government's fight against the abuse of drugs and other substances. The CSA primarily impacts the DEA but the FDA has been charged with the scientific component of this act. The FDA has developed an approach evaluating specific criteria relating to abuse/dependence that forms the basis for recommendations to the DEA on behalf of the Secretary of Health and Human Services (HHS).

The CSA places all substances that are regulated under existing federal law into one of five schedules. This placement is based upon the substance's medicinal use, potential for causing physical harm, and potential for abuse or addiction.

- **Schedule I** is reserved for drugs which have any potential for abuse, that have no recognized medical use or there is a lack of accepted safety under medical supervision. Until FDA approval, any drug scheduled must be placed in Schedule I regardless of whether following FDA approval it is a Schedule II or V entity.
- **Schedule II** is reserved for drugs which have a high potential for abuse, has a currently accepted medical use in treatment in the US or a currently accepted medical use with severe restrictions and potential abuse of the drug may lead to severe psychological or physical dependence.
- **Schedule III** is for drugs, which have a potential for abuse less than the drugs in schedules I and II, have a currently accepted medical use in treatment in the US and abuse of the drug may lead to moderate or low physical dependence or high psychological dependence.
- **Schedule IV** is for drugs, which have a low potential for abuse relative to the drugs in schedule III, have a currently accepted medical use in treatment in the US, and abuse of the drug may lead to limited physical dependence or psychological dependence relative to the drugs in schedule III.
- **Schedule V** is for a drug which has a low potential for abuse relative to the drugs in schedule IV, has a currently accepted medical use in treatment in the US and the abuse of the drug may lead to limited physical dependence or psychological dependence relative to the drugs in schedule IV. This is the classification used for medications with the least potential for physical harm.

When a petition to change the scheduling of a drug is received by DEA, the agency begins its assessment of the drug. DEA may also begin an assessment of a drug at any time based upon information received from law enforcement laboratories, state and local law enforcement and regulatory agencies, or other sources of information.

Once necessary data has been collected, the DEA Administrator requests from HHS a scientific and medical evaluation and a recommendation as to whether the drug should be controlled or removed from control. This request is sent to the Assistant Secretary of the HHS. The HHS solicits information from the Commissioner of the FDA, evaluations

and recommendations from the National Institute on Drug Abuse (NIDA), and on occasion, from the scientific and medical community at large. The Assistant Secretary compiles the information and transmits back to the DEA a medical and scientific evaluation regarding the drug, a recommendation as to whether the drug should be controlled, and in what schedule it should be placed.

This formal evaluation and rule-making process may take a year or more to complete. However, should the Attorney General deem a drug an imminent hazard to public health, that office's emergency powers may be used to add the drug to the Schedule I list of banned substances.

While the scheduling of a drug through the formal rule-making process is most common, the US Congress has legislatively scheduled several drugs when it felt necessary. Some of the drugs legislatively scheduled by Congress are:

Anabolic Steroids	C3 (1990)
Methaqualone	C1 (1984)
Pipradol	C1 (1978)

7.2 The Scheduling of GHB

The scheduling of GHB was first considered in the mid-1990s after data from local law enforcement, Drug Abuse Warning Network (DAWN) and Poison Control Centers showed it to be an increasing drug of abuse. It was also beginning to appear as a drug utilized to facilitate sexual assault. The form used was manufactured GHB or "homemade" GHB. The expansion of the Internet spawned numerous e-commerce sites selling kits, with which to make GHB, for as little as $35.

The Attorney General determined she was unable to use her emergency authority to schedule GHB as a schedule I agent because an active IND for a pharmaceutical formulation of GHB existed which constituted "valid medical use".

Consequently, DEA took steps to begin the administrative scheduling of GHB. In September 1997, DEA forwarded its request to HHS and requested a scientific and medical evaluation and a scheduling recommendation. The FDA's Office of Health Affairs and NIDA undertook that assignment.

In July 1998, the Crime Subcommittee of the House Judiciary Committee, chaired by Rep. Bill McCollum, held a hearing at the request of Rep. Sheila Jackson Lee to consider her proposal to schedule GHB as a Schedule I drug. The Hillory J. Farias Date Rape Prevention Act was initiated by Rep. Jackson Lee following the apparent GHB-related death of Hillory Farias, a LaPorte, Texas high school senior. Most committee members expressed a desire to somehow distinguish the illicit forms of GHB from the pharmaceutical formulation being studied for the treatment of cataplexy.

Rep. Jackson Lee's proposal was re-introduced in January 1999. That month, 15-year-old Samantha Reid died at a Michigan emergency room after drinking a soda spiked with

either clandestinely manufactured GHB or GBL. As a result of that incident, Michigan Congressmen Fred Upton and Bart Stupak sponsored separate bills to schedule GHB. The House Subcommittee on Oversight and Investigation considered those bills at a March 1999 public hearing.

FDA informed members that it was still conducting its scientific and medical evaluation with NIDA, which would result in their scheduling recommendation for GHB.

> "FDA would agree that there is a critical need to protect the public health from the dangers posed by drugs and substances of abuse," the Agency's spokesperson testified. "At the same time, we have to recognize that many drugs that have the potential for abuse may also be medically beneficial, and a large segment of the population might benefit from the optimization of drug development. These interests sometimes create tension in this scheduling process. In FDA's dual role as the evaluator of products that promote public health and the evaluator of substances that present a danger to the public, we will use the best available scientific data to make the speediest and best decisions".

In May 1999, the Attorney General formally asked Congress to use its legislative authority to schedule GHB. Within days of that request, HHS provided DEA with the medical and scientific analysis of GHB and its recommendation regarding the scheduling of GHB. The analysis gave particular notice to the new forms of GHB being abused by rave partygoers as a euphoric when mixed with alcohol, by body builders as a muscle-enhancer and by sexual predators to facilitate sexual assault.

During the approximately 20 months that FDA and NIDA conducted their medical and scientific evaluation, the sources of GHB abuse changed rapidly. Aggressive moves by FDA, DEA and state authorities had shut down numerous GHB Internet sites. But clandestine manufacturers and home-brewers of GHB discovered they didn't have to compound GHB. Instead, they marketed and used certain legal and inexpensive industrial chemicals for their GHB effect. Put simply, they relied on a person's body to naturally convert ingested industrial solutions into GHB.

GBL was apparently the first industrial solvent ingested for its GHB effect. Abuse of GBL as a GHB analogue accelerated in 1998. In January 1999, FDA asked dietary supplement companies to recall all products containing GBL. At that time, GBL products had been associated with reports of at least 55 adverse health effects, including one death. GBL became a list I chemical in 1999 and dietary supplement makers and drug dealers were fast to market a new GHB analogue using another easily available and inexpensive industrial solvent 1,4 BD. Like GBL, 1,4 BD converts to GHB following ingestion. In May 1999, FDA warned consumers to stop using dietary supplement products containing 1,4 BD.

7.3 The HHS - FDA - NIDA Recommendation

In May 1999, the Secretary for Health and Surgeon General at HHS recommended that GHB be scheduled based on its different forms, taking into consideration both the

legitimate medical use and the illicit use. It recommended that illicit forms of GHB be placed in Schedule I. HHS also recommended that authorized formulations of GHB be listed in Schedule III.

The HHS recommendation was made as a result of an eight-factor analysis, which was conducted as stipulated by the Controlled Substances Act. When evaluating the control of any drug, the following factors are considered:

(1) Its actual or relative potential for abuse.
(2) Scientific evidence of its pharmacological effect, if known.
(3) The state of current scientific knowledge regarding the drug or other substance.
(4) Its history or current pattern of abuse.
(5) The scope, duration, and significance of abuse.
(6) What, if any, risk there is to the public health.
(7) Its psychic or physiological dependence liability.
(8) Whether the substance is an immediate precursor of a substance already controlled under this title.

After evaluating the eight factors, the HHS must make a scheduling recommendation based on the substance's relative potential for abuse, its accepted medical use and its capacity for producing physical and psychological dependence.

Under the Controlled Substances Act, substances in Schedule I have a high potential for abuse and no accepted medical use. Substances in Schedule II have a high potential for abuse but do have an accepted medical use. Substances in Schedules III-V have an accepted medical use and a relatively lower potential for abuse.

HHS concluded that illicit forms of GHB - clandestinely manufactured GHB, homebrewed GHB and industrial chemicals used as GHB - have a high potential for abuse. It concluded that illicit forms of GHB have no accepted medical use and, in fact, are unsafe for use under medical supervision. Accordingly, HHS advised that illicit forms of GHB be controlled as Schedule I drugs.

Mindful of the growing list of legal industrial chemicals being ingested for their GHB effect, as well as the ease of home brewing GHB, HHS concluded that authorized investigational formulations of GHB (Xyrem) were unlikely to be sources of abuse. Rather the abuse potential for Xyrem was consistent with substances typically controlled under Schedule IV. Authorized investigational formulations, however did not meet the "accepted medical use" criteria set forth in Schedule IV due to the lack of FDA marketing authorization. Authorized investigational formulations fit more closely with the standard of Schedule II drug having a "currently accepted medical use with severe restrictions".

Under these circumstances, HHS recommended placing FDA authorized formulations of GHB in Schedule III - a level of control higher than Schedule IV in order to take into account the lack of accepted medical use of the investigational product, and a level of

control lower than Schedule II to account for the products low dependence liability and abuse potential.

7.4 Public Law 106-172

HHS's Schedule I/III recommendation for GHB was the foundation for proposals embraced by a broad coalition of Republicans and Democrats in Congress in late 1999 and early 2000. The Senate unanimously adopted its proposal to require the Attorney General to use her emergency powers and immediately list GHB in Schedule I. The measure also listed FDA-approved GHB in Schedule III, if or when FDA approved such products. The House adopted the same bill by a vote of 339 to 2.

The Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000 was signed into law on Feb. 18, 2000. Called Public Law 106-172, the measure also penalized the illicit use of any form of GHB (including the FDA-approved formulation) with severe Schedule I penalties; controlled the legitimate sale of GBL the industrial solvent and potential GHB analogue; and criminalized the use of a controlled substance analogue to facilitate a sexual assault.

7.5 WHO Recommendation

In September of 2000 a panel of experts was convened by the World Health Organization (WHO) to review the abuse potential of GHB and to make a recommendation for what schedule GHB should be placed. The recommendation of this expert working group was for placement into schedule IV. This recommendation was published in the US Federal Register in the spring of 2001. Following verbal communication from the Controlled Substances Staff at FDA, there were no comments submitted, either in favor or opposed to this recommendation. Therefore the recommendation will most likely stand and be signed into law by the WHO president. Since a WHO schedule IV is not much different than a US schedule III, no changes are anticipated to US laws as a result of this recommendation. A copy of the WHO recommendation is included with this section.

7.6 Conclusion

The recommendation of HHS, along with the weight of scientific and medical evidence continues to support a placement of Xyrem, if approved by FDA, into Schedule III. Moreover, given the ease with which GHB can be compounded, the availability of inexpensive industrial chemicals that are used as GHB analogues and the specialty distribution system designed to prevent diversion (which is presented in Section 8), the abuse potential of Xyrem is low. Orphan Medical continues to sponsor and assist with state legislation which addresses GHB analogs and inappropriate use of GHB, with both clinical and preclinical studies designed to further investigate the abuse potential of GHB, and distribution systems which minimize diversion while making Xyrem available for patients with narcolepsy.

ATTACHMENT 1

David Satcher, MD, PhD (DHHS) Letter (May 19, 1999),

Gamma Hydroxybutyrate: Eight Factor Analysis (September 1997),

and

James Milford (DEA) Letter (September 16, 1997)

BEST AVAILABLE COPY

DEPARTMENT OF HEALTH AND HUMAN SERVICES — Office of the Secretary

MAY 19 1999

Assistant Secretary for Health
Office of Public Health and Science
Washington D.C. 20201

Mr. Donnie R. Marshall
Deputy Administrator
Drug Enforcement Administration
Washington, D.C. 20537

Dear Mr. Marshall:

In response to your request dated September 16, 1997, and pursuant to the Controlled Substances Act (CSA), 21 U.S.C. §811 (b), (c), and (f), the Department of Health and Human Services (HHS) recommends that gamma-hydroxybutyric acid (GHB) should be subject to control under Schedule I of the CSA, except that GHB substances and products that are the subject of investigational new drug (IND) applications authorized by the Food and Drug Administration (FDA) should be subject to control under Schedule III.

GHB is a central nervous system depressant. As discussed in the attached analysis, GHB has a high potential for abuse relative to substances controlled in Schedules III, IV, and V. GHB has no accepted medical use, and when manufactured clandestinely, it is unsafe for use under medical supervision. Accordingly, and except as provided below, HHS recommends that GHB be controlled in Schedule I of the CSA.

Formulations of GHB currently are being studied under FDA-authorized INDs. At least one sponsor's formulation has been granted orphan drug status under Section 526 of the Food, Drug, and Cosmetic Act, and is available under a treatment use protocol under 21 CFR §312.34. None of the reports of actual abuse of GHB that support the Schedule I recommendation have involved GHB that was diverted from an authorized study. Moreover, given the ease with which GHB can be synthesized from readily available materials, it is unlikely that authorized studies will become a source for abuse. Rather, the abuse potential of GHB, when used under an authorized research protocol, is consistent with substances typically controlled under Schedule IV. Information on the dependence-producing effects of GHB is limited, but available data suggest that its potential for physical and psychological dependence is also consistent with control under Schedule IV.

Authorized formulations of GHB, however, do not meet the "accepted medical use" criteria set forth in Schedule IV. An authorized formulation of GHB is far enough along in the development process to meet the standard under Schedule II of a drug or substance having a "currently accepted medical use with severe restrictions." Under these circumstances, HHS recommends placing authorized formulations of GHB in Schedule III.

You will find enclosed a document prepared by FDA's Drug Abuse Evaluation Staff that is the basis for the combined Schedule I/Schedule III recommendation.

Should you have any questions regarding this recommendation, please contact Stuart L. Nightingale, M.D., FDA's Associate Commissioner for Health Affairs, at (301) 443-6143.

Sincerely yours,

David Satcher, M.D., Ph.D.
Assistant Secretary for Health
and Surgeon General

Enclosure

Gamma hydroxybutyrate:

Eight Factor Analysis

On September 16, 1997, the Deputy Administrator of the Drug Enforcement Administration (DEA) requested that the Department of Health and Human Services (DHHS) develop a scientific and medical evaluation and recommendation to schedule gamma-hydroxybutyric acid (GHB) under the Controlled Substances Act (CSA). GHB is under active development as a therapeutic agent in the United States. The Food and Drug Administration (FDA) recently authorized a sponsor's investigational new drug application for the treatment use of a GHB drug product for cataplexy associated with narcolepsy, to provide early availability of the drug product for patients suffering from this condition (see 21 CFR 312.34), and to facilitate the collection of data in support of a new drug application (NDA). This sponsor has also obtained "orphan" designation of its product from FDA in accordance with section 526 of the Federal Food, Drug, and Cosmetic Act. An orphan drug is a drug that is intended to treat a rare disease or condition that affects fewer than 200,000 people in the United States. To obtain an orphan drug designation, a sponsor must present sufficient information about the drug, or the disease or condition for which it is intended, to establish a medically plausible basis for expecting the drug to be effective in the prevention, diagnosis, or treatment of that disease or condition. The purpose of the Orphan Drug Act is to provide incentives for the development of products which, without incentives, are of little interest to the pharmaceutical industry. There have been no reports of diversion from clinical trials or authorized studies.

At the same time, however, GHB compounds are being manufactured in clandestine laboratories for recreational use, the scale of which is undetermined. Because of this clandestine manufacture of GHB, and its associated abuse, numerous States have controlled GHB under State laws in Schedules II, IV, or I. Some deaths and numerous hospital emergency room cases have been documented from the clandestine substance.

In accordance with 21 U.S.C. 811(b), the DEA gathered information relevant to scheduling GHB in the CSA. Pursuant to 21 U.S.C. 811(b), the Secretary is required to consider in a scientific and medical evaluation eight factors determinative of control under the CSA. Following consideration of the eight factors, if it is appropriate, the Secretary must make the findings to recommend scheduling a substance in the CSA. The findings relate to a substance's abuse potential, legitimate medical use, and its safety or dependence liability.

Administrative responsibilities for evaluating a substance for control under the CSA are performed by the FDA, with the concurrence of the National Institute on Drug Abuse (NIDA), as described in the Memorandum of Understanding (MOU) of March 8, 1985 (50 FR 9518-20).

In this document, FDA is recommending the control of GHB and all mixtures, compounds, and preparations thereof in Schedule I of the CSA, except that GHB drug substances and products being studied under FDA authorized INDs are recommended for control in Schedule III.

1. ITS ACTUAL OR RELATIVE POTENTIAL FOR ABUSE.

GHB, as one might expect of a sedative-hypnotic drug, produces dose- and concentration-dependent CNS depressant effects in humans and a variety of laboratory animals including mice,

rats, rabbit, cat, dog and monkey.[1] Its abuse potential was evaluated in preclinical tests, such as drug discrimination and self-administration[2] in which GHB produced sedative-like stimulus effects. The CNS depressant effects might be expected to correlate with use in a polydrug abuse setting, such as to counteract the effects of stimulants. The dose-response curve for the sedative and hypnotic effects of GHB is steep.[3] That is, the onset of effect is rapid, making it an effective hypnotic, but also an effective drug of abuse in some settings.

Discriminative Stimulus Properties. Several studies have characterized GHB's discriminative stimulus effects (i.e., the ability of a subject to distinguish the drug from a control).[4] Results from these studies have shown that GHB can function as a discriminative stimulus in rats and that the GHB stimulus cue is complex, sharing some properties with some CNS depressants and, to a lesser extent, with some GABA-mimetic substances and morphine.

The ability of GHB to function as a discriminative stimulus was first reported by Winter (1981).[1] Controls included an array of controlled and non-controlled substances.

> Experiment. Using a two-lever operant procedure under a fixed-ratio (FR 10) schedule of reinforcement, rats (n=14) were trained to discriminate 200 mg/kg (intraperitoneally) of GHB sodium salt from saline. After criterion was established, morphine (1.0 and 3.0 mg/kg), LSD (0.03, 0.1, and 0.3 mg/kg), phencyclidine (PCP) (2.0 and 4.0 mg/kg), SKF 10,047 (6.0 and 10.0 mg/kg), ethanol (630.0, 945.0, 1260.0 mg/kg), barbital (80.0 and 160.0 mg/kg), chlordiazepoxide (3.0, 10.0, 20.0, and 30.0 mg/kg), d-amphetamine (0.8, 1.5, and 3.0 mg/kg), apomorphine (0.3, and 1.0 mg/kg) and the GABA-mimetics muscimol (0.3, 1.0, 2.0, 3.0 mg/kg), gamma-butyrolactone (GBL) (10.0, 30.0, 100.0, and 200.0 mg/kg), baclofen (1.0, 3.0, 6.0, and 10.0 mg/kg), and 3-aminopropane sulfonic acid (100.0, 150.0, and 300.0 mg/kg) were substituted for GHB. GHB functioned as a discriminative stimulus in all rats trained to discriminate 200 mg/kg of GHB. The mean number of sessions required to establish criterion were 43 (S = 5; range 1-67 sessions). Substitution tests revealed that the discriminative stimulus cue of GHB was more depressant-like.

During substitution tests, PCP (CII), ethanol, barbital, d-amphetamine (CII) and apomorphine failed to generalize to GHB. Morphine (CII) and 3-aminopropane partially generalized to the GHB cue. The GABA-mimetics muscimol (not controlled), and baclofen (not controlled) generalized to GHB in a dose-dependent manner. Chlordiazepoxide (CIV) also dose-dependently generalized to GHB. These findings confirmed that the discriminative stimulus cue of GHB was largely depressant-like.

Dose Response. The drug discriminative properties of GHB have been shown to be dose-responsive

> Experiment. By a T-maze, food-reinforced drug discrimination procedure, GHB functioned as a discriminative stimulus in rats.[5] The ability of GHB to function as a discriminative stimulus was evaluated in rats trained to discriminate 300 mg/kg (n=4; 30-minutes pretreatment, i.g.) or 700 mg/kg (n=6; 30-minutes pretreatment; i.g.) from water

in a two-arm T-maze procedure under a FR10 schedule of reinforcement. After criterion (a: the first trial was correct; b: at least 9 correct trials out of 10) was established, substitution tests were conducted with GHB at a range of doses (0, 50, 100, 300, 500, 700, and 1000 mg/kg; i.g.). To assess the ability of the GHB antagonist NCS-382, to block the discriminative stimulus of GHB, doses of NCS-382 (0, 12.5, 25.0, and 50.0 mg/kg; 10-minutes pretreatment) were tested in both 300 mg/kg and 700 mg/kg GHB-trained rats. Both 300 and 700 mg/kg GHB functioned as a discriminative stimulus in rats; time to acquired GHB discrimination was 48.0 @ 5.1 (35-58) and 42.8 @ 2.7 (35-54) days for the 300 and 700 mg/kg group, respectively. GHB dose dependently substituted for the stimulus cue of both training doses of GHB. Complete substitution occurred at doses of GHB equal to and greater than the training dose in the 300 mg/kg GHB group. In the 700 mg/kg GHB group, doses equal to or greater than 500 mg/kg of GHB completely generalized to 700 mg/kg of GHB. During the antagonist test, NCS-382 (25 and 50 mg/kg) attenuated the GHB-discriminative stimulus effects. Pretreatment with 25 mg/kg of NCS-382, 91.2% and 16.7% GHB-appropriate responding was observed in the 300 and 700 mg/kg training groups, respectively. NCS-382 (50 mg/kg) resulted in 7.5 and 9.2 mg/kg percent GHB-appropriate responding in 300 and 700 mg/kg GHB groups, respectively.

Alcohol. GHB and alcohol exhibit common discriminative stimulus effects within a narrow dose range.

Experiment The discriminative stimulus properties of GHB were evaluated in rats trained to discriminate ethanol (1.0 or 2.0 g/kg; p.o.) or GHB (300.0 mg/kg; p.o.) from water in the T-maze procedure (Colombo, et al., 1995c). Once criterion (i.e., 5 consecutive training sessions) was established, doses of ethanol (0.0, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 g/kg) and GHB (0.0, 50.0, 100.0, 300.0, 500.0, 700.0, and 1500.0 mg/kg) were substituted for both ethanol- and GHB-trained rats GHB and ethanol demonstrated common discriminative stimulus effects; however, the symmetrical generalization occurred within narrow dose windows Ethanol dose dependently substituted for the training doses of both 1.0 and 2.0 g/kg of ethanol. When GHB was substituted in the ethanol-trained rats, GHB only generalized to the ethanol cue elicited by the 1.0 m/kg training group. An inverted "U-shaped function" was observed following the substitution of GHB doses. GHB (300 mg/kg) elicited 82.0% ethanol-appropriate responding. Doses lower than 300 mg/kg of GHB did not generalize to the ethanol cue. As reported earlier (Colombo et al , 1995a), doses of GHB generalized to GHB in a dose dependent manner. Substitution of doses of ethanol in GHB-trained rats also elicited an inverted "U-shaped" function curve Ethanol (1.0 g/kg) elicited 90.9% GHB-appropriate responding; whereas 1.5 g/kg of ethanol elicited 72 0% of drug-appropriate responding.

GHB and alcohol have synergistic hypnotic effects. In rats, GHB produces a loss in righting reflex (sleep time) which was significantly potentiated by ethanol, specifically a 4- to 5- fold increase in sleep time in rats administered GHB (0.41 nmole) in combination with 6 51 nmole ethanol.[6]

Cocaine, PCP, and heroin. GHB failed to effect the discriminative stimulus control of cocaine, PCP and heroin in rats at any GHB dose tested.

Experiment. (Beardsley *et al.*, 1996). The discriminative stimulus effects of GHB were also assessed in rats trained to discriminate cocaine (10.0 mg/kg, i.p.), PCP (2.0 mg/kg, i.p.) or heroin (0.3 mg/kg, s.c.) from vehicle (saline for PCP and cocaine; water for heroin), in a two-lever operant procedure under a FR schedule [FR 10 for (cocaine and heroin trained rats; FR 32 for PCP-trained rats] of reinforcement. After criterion, substitution tests were conducted. (Criterion was as follows: PCP-trained rats: at least 80% of the total responses were made on the correct lever during four consecutive training sessions, and the first 32 consecutive responses were completed on the correct lever during each of these sessions; cocaine- and heroin-trained rats: the first completed fixed ratio occurred on the lever designates correct at least eight of the consecutive training sessions, and at least 80% of the total responses were made on the correct lever during those eight sessions). On substitution test sessions, heroin (0.1-2.0 mg/kg), cocaine (1.0-30.0 mg/kg), and PCP (0.5-6.0 mg/kg) were tested in their respective training groups. Doses of GHB (10.0-300.0 mg/kg) were substituted for PCP- and heroin-trained groups. In the cocaine-trained rats, the ability of doses of GHB (10.0-300.0 mg/kg) to antagonize cocaine discriminative stimulus effects was evaluated. When GHB (10.0-300.0 mg/kg) was substituted for PCP or heroin, the subjects responded exclusively on the vehicle lever. In the antagonist test, GHB failed to affect the discriminative stimulus control exerted by 10.0 mg/kg of cocaine; that is, the mean percent cocaine-appropriate responding was never reduced to below 79% cocaine-appropriate responding at any of the GHB doses tested.

Reinforcing Effects. The reinforcing effects of GHB were evaluated in two primate species (rhesus monkey and baboon) and rodents (rats). GHB has not been shown to be reinforcing in primates trained to self-administer PCP (CII), cocaine (CII) and methohexital (CIV). Preference for GHB over placebo (water) was demonstrated in rodents. These findings are described in the following relevant experiments:

Experiment1: (Beardsley *et al.*, 1996) Reinforcing effects of GHB were evaluated in rhesus monkeys experienced in self-administration of PCP under a FR 10 schedule of reinforcement for two monkeys and for two other monkeys, the FR requirement was gradually increased to FR 200 for one monkey and to FR 50 for the other. Four adult rhesus monkeys (3 males; 1 female) were trained to self-administer PCP (10.0 or 5.6 :g/kg/injection) under a FR 10 schedule of reinforcement. Upon completion of training, the maintenance dose of PCP was established at 10.0 :g/kg/injection for all four monkeys. The monkeys had access to PCP during daily one-hour sessions. After stable responding was obtained (i.e., less than 20% variation in the number of PCP infusions per session for at least 3 consecutive sessions with PCP), vehicle and GHB (300 - 7500 :g/kg/injection) were substituted for PCP injections for four consecutive days. Following each behavioral session, monkeys were observed immediately afterwards for several hours for signs of overt toxicity and/or drug-induced behavioral changes. Substitution of doses of PCP

produced an inverted "U-shaped" dose-response function with at least thr e doses in all monkeys maintaining responding above saline levels where the range did n ot overlap. In comparison to PCP, GHB failed to maintain rates of responding indicative of reinforcing efficacy in all primates. GHB, at a dose of 3000.0 :g/kg/infusion, occasion ally produced ptosis and lethargy suggestive of sedative-like effects.

Experiment 2: (France *et al.*, 1997) GHB was tested in three rhesus mon keys trained to self-administer 0.1 mg/kg/infusion of methohexital. Four doses (amount not specified) of GHB were substituted for methohexital. Each of the 3 monkeys rec eived the two largest GHB doses (0.1 and 1.0 mg/kg/injection). GHB maintained v ery little self-administration behavior in the primates. Furthermore, the researchers : tated that the number of injections did not exceed the number of saline injectic ns and were considerably less than the number of infusions for methohexital.

Experiment 3: (Ator, 1995) The reinforcing effects of intravenous GHB w ere evaluated in baboons trained to self-administer 0.32 mg/kg/infusion cocaine HCl u nder a FR 160 schedule of drug delivery. GHB (3.2 - 100.0 mg/kg/injection) was exa mined in two baboons and initiated in a third, though not completed. Throughout the st udy, each dose of GHB and vehicle was substituted for cocaine for 15 consecutive days, f ollowed by re-establishment of cocaine baseline for three consecutive days. GHB di d not reliably maintain self-administration at any of the doses tested under the specific co nditions of the study. Higher doses of GHB could not be evaluated due to limitations of d rug solubility. When 100:g/kg/injection GHB was substituted for methohexital, sedation was observed after the behavioral session.

Experiment 4: Oral self-administration of GHB was evaluated. During th e initial phase of the study, the rats experienced a two-week forced-choice period. Duri g this period, GHB sodium salt (1% w/v in water) was the only available drinking fluid. Subsequently, the rats were changed to a free-choice period; the rats had a choice b etween GHB solution (1% w/v) and tap water. During the no-choice phase, the in take of GHB remained fairly stable (800-1200 mg/kg/day). The preference for G HB was also established during the free-choice period of the study. However, during his period all rats displayed alternate periods of high daily intake of GHB with tem porarily self-imposed cessation of GHB intake. Large variability among the rats was o bserved in the length of the GHB- and tap water-preference periods; the range was be ween 1 to 12 days. On GHB-preference days, GHB consumption averaged 666.3 @ 1 .2 mg/kg/day; and there appeared to be a pattern in the self-administration of GHB. ats tended to consume GHB solution in distinct binges which occurred over 3 to 5 ho urs during the dark phase of the light cycle, during which the rats consumed pharmacolo ically relevant doses (100 to 300 mg/kg) of GHB. This 3-5 hour interval between GH B binges was constant with the pharmacokinetics of oral GHB in rats[7] suggesting a self-controlled adjustment of GHB dose by the rats over the 24-hour light cycle.

Clinical Studies of Abuse Potential. There have been no reliable clinical st dies of abuse potential of GHB.

GHB's pharmacology as a sedative/hypnotic and its potentiation with alcohol make it a candidate drug for recreational abuse and use to physically and mentally incapacitate individuals without their knowledge. GHB in low doses produces amnesia and hypotonia. Higher doses produce effects ranging from sedation to profound CNS depression. The onset of effects is seen 15 minutes after administration, lasting up to 3 hours.[8] The rapid onset of sedation, coupled with the amnestic features of this agent, particularly when added to alcohol to conceal its presence and potentiate its effects, would be expected to be a very effective agent in the commission of a crime such as sexual assault. Other sedative hypnotics coupled with alcohol, notably chloral hydrate (CIV) and flunitrazepam (CIV) have in the past demonstrated this same pattern of abuse. However, what increases the likelihood of GHB's use in this manner is the extraordinary availability of chemical precursors and ease of clandestine synthesis by non-chemists.

2. SCIENTIFIC EVIDENCE OF ITS PHARMACOLOGICAL EFFECTS, IF KNOWN.

GHB is a naturally occurring compound found in small quantities in many mammalian tissues.[9] Its administration produces a wide range of pharmacological effects, but its physiologic role has not been clearly defined.[10] GHB can induce nonREM and REM sleep, anesthesia, and hypothermia. It has been studied in cats as a model for petit mal epilepsy. It markedly increases brain dopamine levels. It is also found in many peripheral tissues, in concentrations sometimes higher than in the brain. GHB may act through different neurotransmitter systems including the dopamine and opioid systems. GHB raises dynorphin levels and its metabolic and some pharmacological, but not behavioral, effects can be blocked by naloxone.

Neurochemistry of GHB

GHB is a psychoactive drug that produces its effect when administered intravenously or orally and is fundamentally different from established neurotransmitters that do not normally pass through the blood-brain barrier. Nonetheless, GHB is found unevenly distributed in mammalian brain[11] and patterns of regional distribution are species dependent.[12] Although the physiological role of GHB has not yet been fully defined, there are purported brain receptor sites as well as brain mechanisms for synthesis, release and uptake of GHB.[13]

Endogenous brain GHB is synthesized via transamination and reduction of GABA in neurons. An apparently specific enzyme for GHB biosynthesis from GABA via succinic semialdehyde has been described in both rat and human brain, and is released from reloaded brain slices under depolarizing conditions.[14]

Radioligand studies have identified specific binding sites for GHB in both rat and human CNS.[15] Characterization of GHB binding in rat and human brain synaptosomal membranes showed that binding was saturable, pH dependent, and linear with protein concentration.[16] The density of [^{3}H]GHB binding was highest in the hippocampus and lowest in the cerebellum. Competition and saturation experiments demonstrated the existence of high and low affinity binding sites.

The GHB binding sites in both rat and human synaptosomal membranes appear to be coupled to a chloride anion channel.[17] All ions that are active at the chloride ion channel inhibited the binding of [^{3}H]GHB in a dose-dependent manner. Compounds that were impermeable to the chloride ion channel, i.e., sulfate, acetate, and fluoride, did not inhibit [^{3}H]GHB binding. GABA and its structural analogues (agonists and antagonists), opiate antagonists, and anticonvulsants did not inhibit [^{3}H]GHB binding.[18] Recently, GHB receptors from adult rat brain were solubilized, unmasking a significant amount of membrane-bound receptors, and suggesting the presence of endogenous inhibitors or ligands.[19]

Several recent studies have attempted to find the underlying neurotransmitter system responsible for GHB's effects. GHB appears to act through dopamine and opioid systems, but has no effect on NMDA or GABA systems.[20] GHB causes a rapid and significant increase in brain dopamine when administered to animals in doses that produce behavioral depression.[21]

The effects of GHB on the dopaminergic system have been evaluated in both *in vivo* and *in vitro* assays. Results from these studies indicated that GHB effects on dopamine release is biphasic. Using both striatal slices and microdialysis of caudate-putamen, GHB inhibited the release of dopamine for approximately 5 to 10 minutes which resulted in the accumulation of dopamine within these tissues.[22] Subsequently, as a result of a negative feedback mechanism, an increase in dopamine release occurred. GHB, at doses that produce behavioral depression, causes a rapid and significant increase in brain dopamine levels in animals[23] limited to extrapyramidal regions.[24] Alpha-methyl-p-tyrosine and apomorphine (dopamine agonist) block GHB-induced increase in brain dopamine.

GBL, the synthetic precursor and metabolic prodrug of GHB, also appears to modulate extrapyramdial dopaminergic activity.[25]. Within the pars compacta of the substantia nigra, both GBL and GHB suppressed firing of dopaminergic neurons.[26] In a study conducted by Diana *et al.* (1991), it was demonstrated that the effects on dopaminergic neurons are dose- and route-dependent. Following administration of GHB (50 to 400 mg/kg i.v.), a dose-related stimulation (10-56%) of the firing rate of dopaminergic neurons in the pars compacta of the substantia nigra was produced. In contrast, higher doses of GHB (1000 and 1500 mg/kg) almost completely inhibited the firing rate of the pars compacta's dopaminergic neurons. Administration of GHB (750 mg/kg i p) to unanesthetized rats initially produced a brief stimulation (23% of firing rate followed by a modest reduction in the firing rate (29%)

GHB is not a direct or indirect opiate or opioid antagonist It does not bind to mu, delta or kappa opioid receptors[27] However, several investigators have suggested that GHB may act as an indirect agonist, stimulating the release of endogenous opioid peptides.[27] Following administration of an anesthetic dose of GHB to rats, the brain level of dynorphin was augmented. However, there were numerous differences between the behavioral effects of GHB and dynorphin, indicating that GHB's effects are not likely to occur via enhancement of dynorphin. In one study, opioid-like substances in striatal dialysates were detected after intrastriatal microinfusions of GHB (0 25 nM) in preclinical studies.[29]

GHB's effect on brain serotonin is much less pronounced than its dopaminergic effects. GHB can either increase the turnover rate of brain serotonin or elevate its levels in specific brain regions.[30] This effect appears to be age-related--following the administration of a high dose of GHB, GHB increased the rate of synthesis and degradation of serotonin in adolescent rats and not in neonatal rats.[31].

GHB may modulate the activity of the cholinergic neurons. Following administration of GHB to rats, a selective increase in acetylcholine levels was detected in the midbrain and critical regions. GHB effect on acetylcholine is thought to be an indirect effect arising from the interaction between dopaminergic and cholinergic systems.[32]

Pharmacodynamics—CNS Effects.

Animal studies have evaluated GHB as an anxiolytic. An early study on isolated-induced stress found that 50 mg/kg GHB produced a significant decrease in the appearance of defensive behavior in previously isolated mice, a characteristic stress response.[33] Higher doses (200 mg/kg) reduced the manifestations of passive-defensive behavior, but also produced sedative effects. This study suggested that a low dose of GHB inhibited the appearance of alarm and anxiety, but did not produce general sedative actions. These findings were similar to those observed after administration of benzodiazepines.

GHB produced a loss in righting reflex (sleep time) in rats, which was significantly potentiated by ethanol.[34] There was a 4- to 5-fold increase in sleep time in rats administered GHB (0.41 mmole) in combination with 6.51 mmole ethanol. These authors found synergism when GHB and ethanol are combined, suggesting a common mechanism of action.

In humans GHB doses of 10 mg/kg produce amnesia and hypotonia. Oral or intravenous doses of 20-30 mg/kg promote the normal sequences of REM and nonREM sleep when given to normal subjects. Oral doses in this range produce high voltage slow wave activity and occasionally spindle sleep.[35] Higher doses produce effects ranging from sedation to profound CNS depression. The onset of effects is seen 15 minutes after administration, lasting up to 3 hours.[36]

GHB produces dose- and concentration-dependent changes in level of consciousness. Oral or intravenous doses of GHB greater than 50 mg/kg produce anesthesia in children and adults.[37] In children, GHB 70 mg/kg, administered intravenously produces rapid onset (within 5 minutes of infusion) of sleep.[38] In adults, drowsiness, unconsciousness, and profound coma, accompanied by hypertonia, and muscle rigidity, were observed within 30 minutes after oral administration of 50 mg/kg GHB.[39] As GHB levels decrease, these patterns recur in reverse order. GHB is rapidly metabolized and the central effects of a 60-70 mg/kg dose last about 2 hours.

Effects of GHB on Cardiovascular and Respiratory Control and Thermal Regulation.

In animal studies, respiratory depression has been shown to occur at high doses of GHB.[40] An intraperitoneal dose of 750 mg/kg GHB in adult rats produced a 40% decrease in the minute

ventilation, although the same dose given subcutaneously resulted in apnea and cyanosis in rat pups.[41]

In humans doses in the range of 65-70 mg/kg do not appear to result in respiratory depression. In children, GHB (70 mg/kg) administered intravenously produced changes in respiration, with no apparent clinical consequences, that is, there was no evidence of respiratory depression.[42] When GHB 65 mg/kg, administered intravenously was used as an anesthetic agent of labor and delivery, normal spontaneous ventilation was maintained with little change in rate or volume.[43] Cardiac output falls, however, as evidenced by a slight decrease in stroke volume and heart rate.

There have been reports of GHB used at high doses (in the setting of recreational use and coadministration with other substances) resulting in toxicity and overdose, which indicate effects on heart rate, blood pressure and respiration.

Effects of GHB on Growth Hormone.

GHB has been found to stimulate release of human growth hormone (HGH) from the anterior pituitary gland in humans. GHB 2.5 grams administered intraveniously in six healthy male volunteers caused a rise in plasma levels of HGH at 30, 45, 60 and 90 minutes after injection.[44] In addition, plasma prolactin levels increased at 45 and 60 minutes after GHB.

The effects of GHB on HGH have been confirmed by several recent clinical studies.[45] Intravenous injection of 1.5 grams of GHB to human volunteers caused a significant increase in plasma levels of HGH without significantly altering levels of other hormones such as prolactin, TSH, LH, ACTH or cortisol.[46] The HGH plasma levels were significantly elevated at 45 and 60 minutes following injection. Oral administration of 1.5 grams of GHB produced a significant rise in plasma HGH levels at 15 to 30 minutes which peaked at 46 to 60 minutes and declined precipitously by 90 minutes post-administration.[47]

3. THE STATE OF CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR OTHER SUBSTANCE.

Chemistry

The sodium salt of GHB is also known as sodium oxybate; sodium oxybutyrate; 4-hydroxybutyrate; 4-hydroxybutanoic acid monosodium salt; 4-hydroxybutyric acid sodium salt; gamma hydrate; NSC-84223; and Wy-3478. The chemical abstract number for GHB is [502-85-2]. Trade names include Anetamin, Gamma-OH, Somsanit and Somaromax PM, and Xyrem™. GHB as the sodium salt is a white hygroscopic powder with a melting point of 115-146°.[48] It is soluble in water and forms crystals from alcohol. GHB (sodium salt) has a formula weight of 126.09 and its molecular formula is $C_4H_7NaO_2$.

GHB is prepared by reaction of sodium hydroxide and gamma-butyrolactone (GBL); high yields and purity of product are obtained. These two main ingredients are readily available and may be

obtained from chemical and cleaning supply businesses, and through the INTERNET. GHB is easily synthesized by base catalyzed hydrolysis of GBL. This is a simple chemical procedure that can be accomplished by individuals who lack knowledge of chemistry.

The immediate precursor, GBL, is a hygroscopic oily liquid with a boiling point of 204-205 °C at 760 mm Hg. It is also known by the following chemical names: dihydro-2(3H)-furanone, 1,2-butanolide, 1,4-butanolide, butyric acid lactone, 3-hydroxybutyric acid lactone, 4-hydroxybutanoic acid lactone. GBL has a molecular weight of 86.09 and formula $C_4H_6O_2$. GBL has wide industrial applications, including use as an intermediate in the synthesis of polyvinylpyrrolidone, D, L-methionine, piperidine, phenylbutyric acid, thiobutyric acids; as a solvent for polyacrylonitrile, cellulose acetate, methyl methacrylate polymers, polystyrene, and in paint removers and textile aids.

Preclinical safety, pharmacokinetics and efficacy

The pharmacokinetics of GHB appear to be extremely complex. The absorption and elimination processes appear to be capacity-limited. In preclinical studies, GHB pharmacokinetics were studied as a function of dose and route of administration.[49] Oral absorption of GHB (200-1600 mg/kg) is fairly extensive; bioavailability of GHB increased from 200 to 400 mg/kg but declined as the dose increased. Blood levels after oral dosing were found to be considerably lower than those after intravenous administration.[50]

GHB has a half-life of about one hour in the rat, but the half-life is longer in the cat due to its slower clearance.[51] The elimination half-life of GHB in rats is biphasic after oral dosing with an α half-life of 1.02 hours and a β half-life of 2.68 hours.[52] Similarly, a half-life of 1 to 2 hours was reported for dogs, but this was based on a one-compartment model.[53] A non-linear elimination has been demonstrated in the dog, cat and human.[54]

In rats, cats, and dogs, a relative consistency was found between brain/plasma ratios, confirming penetration across the blood-brain barrier.[55] However, peak plasma levels were relatively low and not dose-dependent; sedative effects and hypnosis were seen only at the highest oral doses.[56] In cats, administration of an anesthetic dose of GHB 3.5 mMol/kg resulted in a GHB level of 0.7 mM in the brain and twice that level in the blood.[57] There is wide variability among animals in the plasma and brain concentrations of GHB when animals recovered from the hypnotic effects of GHB 400 mg/kg, intracardiac or 800 mg/kg, intravenous.[58] In dogs, GHB is taken up into the brain, showing an approximately 2:1 ratio between blood:brain levels, followed by a rapid outflow of GHB from the brain to the cerebrospinal fluid.[59] Thus, GHB passes readily from the bloodstream to the brain and rises to levels of over 100-times its normal endogenous levels, but does not appear to be actively taken up or retained by the brain. This non-linear elimination of GHB was interpreted as due to saturation of one or more of its as yet unknown metabolic pathways.[60]

GHB is metabolized to carbon dioxide, which is eliminated in expired air. The exact site and pathway is unknown.[61] Radioisotope studies in animals have demonstrated rapid absorption and metabolism following administration. Almost immediately, $^{14}CO_2$ appeared in respired air, after

administration of 1-^{14}C-labelled GHB. Highest levels of drug were found in most tissues within 15 minutes of dosing. Ninety percent of the injected 1-^{14}C-labelled GHB was excreted in the respired air, 10-20% in urine, and virtually none in feces.

In animal studies, respiratory depression has been demonstrated at high doses of GHB.[62] An intraperitoneal GHB dose of 750 mg/kg produced a 40% decrease in the minute ventilation in the adult rat, although the same dose given subcutaneously resulted in apnea and cyanosis in rat pups.[63]

There is some evidence that GHB may provide tissue protection during conditions of hypoxia by conserving cerebral energy utilization.[64]

Dose-dependent hypothermic effects have been found after administration of GHB in a number of laboratory animal species, including mouse, rat, dog, and monkey.[65] In rats, heat loss was found to be due to a decrease in metabolic heat production and an increase in cutaneous circulation. The decrease in body temperature produced by GHB can be blocked by the opioid antagonist naloxone[66] as well as the dopamine receptor antagonist haloperidol.[67]

In mice and cats, oral administration of GHB increases general CNS depression with increasing dosage. The first effect noticed is cessation of spontaneous motor activity, followed by loss of body tone (muscle relaxation). In mice and cats, doses can be administered that produce depression for long periods (up to 5 hours) after which animals have recovered with no obvious ill effects (e.g., nausea or ataxia). GHB potentiates barbiturate sleeping times in mice. It possesses general anticonvulsant activity as indicated by its efficacy in preventing or reducing convulsions induced by electroshock, metrazol or semicarbazide. Antagonism of depression was induced by GHB

Deaths from GHB in animals result with very high doses. GHB has an LD_{50} of 5300 mg/kg (in mice, p.o.) and 3705 mg/kg (in rats p.o.), 4225 mg/kg (mice, i.p.), 2020 mg/kg (rats, i.p.), and 1855 mg/kg (mice i.v.). It should be noted that the recommended dose in humans that has been shown to be effective in treatment of cataplexy associated with narcolepsy is 9 grams/day (or approximately 0 .13 gm/kg p.o.) in divided doses.

Human Pharmacokinetics and pharmacodynamics.

In humans the absorption from the gastrointestinal tract is rapid and onset of effects occurs within 15 minutes.[68] Oral doses in man of 75 to 100 mg/kg gave peak blood levels of 0.97 and 1.15 nMol/L (90 and 120 mg/L) at 1 5 and 2 0 hours.[69] Oral doses of 12.5 to 50 mg/kg in eight healthy male volunteers resulted in peak plasma concentrations of 20-23 µg/ml after 25-45.[70] Distribution of GHB into tissues follows a two-compartment model. Initial blood levels declined rapidly following a longer period of metabolic degradation. The plasma $t_{1/2}$ after either 12 5, 25 or 50 mg/kg was 22 minutes (range 20-23 minutes). Ascending doses from 12 5 to 50 mg/kg resulted in an increase in t_{max} and $t_{1/2}$ and a decrease in c_{max}.[71] Another study also found that

GHB rapidly metabolized central effects of a 60-70-mg/kg dose lasting about : hours. These doses produced initial plasma levels of 200-300 :g/ml.[72]

GHB in humans induces somnolence leading to arousable sleep at 40-50 mg/k , and, at 60-70 mg/kg, coma for 1-2 hours. As noted above, this amount of GHB approximates t that some have considered to be an appropriate therapeutic dose. In addition, the LD_{50} has been estimated at 5-15 times that which induces coma. This distinguishes GHB from prototyp schedule IV substances, like the widely used benzodiazepines for which the difference betwe n an acceptable therapeutic dose and a dose which would lead to serious harm (true coma or fata) is significant. GHB and alcohol have synergistic hypnotic effects.[73]

Symptoms of acute toxicity with GHB include GI upset, CNS and respirat ry depression, confusion, inebriation, stupor, uncontrolled movements, myoclonus and seizures. There are also reports of GHB overdose and toxicity documenting GHB's effects on heart rate, blood pressure and respiration. This information was not collected from clinical trial experience but rather from anecdotal reports of overdose following illicit use, which frequently includes poly drug use.

Medical Use

Currently, several investigational new drug applications (INDs) are active at the DA, including a treatment IND for cataplexy associated with narcolepsy, which is an orphan in lication. GHB is available for medical use in a number of foreign countries. It is primarily f rmulated as an intravenous solution intended for use as an adjunct to anesthesia. In Europe, it i manufactured by the German based companies Cemep and Kohler who supply it for use as a ge eral anesthetic under the proprietary names Gamma-OH and Sanansit, respectively. GHB is sold as an intravenous formulation under the name Gamma-OH in the Netherlands, Fr nce, Morocco, Hungary, French West Africa, and Tunisia In France, the Netherlands, Moroc co, and French West Africa, GHB is available in vials containing 200 mg/ml. In Italy it is sold s a solution of 24.5 grams in 140 ml under the name Alcover

There are also several combination products containing GHB in Taiwan, New Zealand and the Dominican Republic. In Taiwan, GHB is sold as a combination product in t blet form with caffeine, chlorpheniramine, ethenzamide and thiamine under the name Anig -cold. In the Dominican Republic, GHB is available in a combination product (liquid) c ntaining citrus aurantium, cyanocobalamin, cyara scolymus, nicotinamide, pantothenic ac d, pyridoxine, riboflavin and thiamine. In New Zealand, it is sold under the name Nyal Me icated GHB in solution.

GHB is listed in the United States Pharmacopoeia Drug Information for th **Health Care Professional (USP/DI 1995)** as a treatment for narcolepsy and the auxiliar symptoms of cataplexy, sleep, paralysis, hypnagogic hallucinations, and automatic behavior. General dosing information is provided but needs to be individualized for each patient. Doses r nging from 1.5 to 2 25 grams orally at bedtime have been utilized. One or two additional dos s of 1 0 to 1.5 grams may be given at 3- or 4- hour intervals As much as 9 grams per night in 3 divided doses has been administered without harmful effect. Elderly and debilitated patients sh ould receive an

initial dose of 1.5 grams to avoid development of sedation, dizziness, and/or ataxia. In the event of overdosage, vital signs and body temperature should be carefully monitored. Patients are required to stay in bed for approximately 8 hours or until the effects of the drug wear off.

GHB is currently being commercially developed for the treatment of cataplexy associated with narcolepsy. The FDA has granted a sponsor orphan status for its GHB product for the treatment of narcolepsy. In addition, the FDA has determined that there is sufficient data to grant expanded access under medical supervision through an approved Treatment IND for the use of the sponsor's GHB product in the treatment of cataplexy associated with narcolepsy.

4. ITS HISTORY AND CURRENT PATTERN OF ABUSE.

In the late 1980's, GHB became available through health food stores or by mail order. GHB was sold in California Bay Area retail stores and distributed by San Francisco-based companies. Marketed as a sleep and diet aid, GBH was initially used by bodybuilders for its alleged role as a growth hormone releaser, as a diet aid, to counter the effects of stimulants, and to effect sleep after workouts.

Luby *et al.* (1992) traced the source of GHB that was sold in South Carolina bars to local gymnasiums catering to bodybuilders, all of whom (in this study) were white, average age of 30, and primarily male. In their report, 71% described themselves as regular users; 18% mixed GHB with alcohol.

Bodybuilders have accounted for a significant number of emergency room cases and cases of dependence. Two of the confirmed deaths associated with GHB have involved bodybuilders. Also, GHB is often encountered in product seizures of anabolic steroids. During the time GHB was legally available, medical, law enforcement and poison control center reports appeared indicating that those who began using the drug as a sleep or diet aid continued to use it for its euphoric effects [74]

In 1990, FDA issued a health alert and prohibited the sale of GHB.[75] Although substance abuse in the bodybuilding community continues, the pattern of GHB use and distribution has changed. Dyer *et al.* (1994) concluded that although GHB has a history of abuse by bodybuilders, in recent years it has been used for its euphoric effects predominantly by young people at dance parties. Since the early 1990's, GHB has been sold at nightclubs, rave parties, and bars. Kits for making GHB by the general public are sold through magazines and the Internet. GHB has been made in small quantities using the kits on college campuses, and in larger scale clandestine laboratories.

GHB is taken orally as a liquid or as a powder that is mixed in a liquid (water, juice, or alcohol). GHB abuse at nightclubs and rave parties is intended for the purpose of getting high, producing a more profound effect from alcohol, countering the effects of stimulants, "regulating" the effects of hallucinogens, or alleviating withdrawal effects from alcohol. Users claim that GHB elicits effects common to alcohol and CNS depressants, marijuana, hallucinogens, and narcotics. GHB euphorigenic effects at low doses or in the early stages of intoxication have been compared to those produced by alcohol, barbiturates, marijuana, or MDMA. Thus, abusers report using GHB

to "get high", to get intoxicated, to relax, and as a sexual enhancer.

GHB has been abused alone as a substitute for alcohol, MDMA or other depressants, but in many cases, it is taken with other drugs. Users report that reasons for taking GHB with other psychoactive drugs include (1) production of a more profound sedative effect when taken with CNS depressants, including alcohol (primarily), barbiturates and benzodiazepines, (2) countering the effects of stimulants, (3) regulating effects of more powerful hallucinogens, or (4) alleviating the withdrawal symptoms of drugs. Some drug dealers market GHB as MDMA ("Ecstasy"), although files from federal agencies find that only a minority of abusers use GHB for its hallucinogenic effects (often compared to a mild "acid"). The Internet and underground literature include exchanges promoting GHB's aphrodisiac or sexually enhancing effects.

There appears to be an increase in the use of GHB among young individuals in social settings.[1] Recently, the drug has found its way into the rave and party communities where, typically taken in higher doses, it is sold as a "legal" high or a substitute for MDMA. As further evidence of GHB's penetration into the club scene, an August 1995 DEA investigation in Manhattan revealed that some rave clubs owners hire promoters whose job is to establish a club theme and to sell drugs. Analysis of the drugs sold in these clubs by runners included MDMA, cocaine, methamphetamine, and GHB.[6]

According to Mack (1993), a typical single dose of GHB needed to produce intoxication or euphoria is 1 to 3 grams taken orally. Powdered GHB is usually dissolved in a liquid such as alcoholic beverages or fruit-flavored drink prior to ingestion. In some locales, liquid GHB is distributed and dispensed from medicine droppers; for $5, users purchase several drops of GHB, apply it to the tongue and swallow it. GHB dissolved in liquid has been packaged in small vials or in water/sports bottles, and sold in gymnasiums.

There have been a number of high profile cases of GHB used in facilitating sexual assault (so-called "date rape") the reports of which have originated from the states of Florida, Texas, Maryland, Louisiana, California, Michigan, Wisconsin, and Massachusetts.

5. THE SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE.

The DEA considers the abuse and trafficking of GHB to be underreported. Because the substance is not controlled under the CSA, it is not a target or priority of the DEA. However, at the end of 1998, GHB had been encountered in 36 states on 550 occasions. The forms of GHB seized by the DEA included powder, liquid, capsule, and tablet. Up to 1 kilogram has been seized at a time. GHB has been found in a variety of containers, including water bottles, plastic bags, vials, gallon milk containers, buckets and drums

1 Additional information regarding the demographics of GHB users can be gleaned from the DAWN, Poison Center, and literature reports (DEA report, 1997) The changing pattern of GHB use and abuse is also discussed in the DEA's San Francisco Field Division report of January 23, 1996

All reports of actual abuse relate to clandestinely synthesized and formulated substances. DEA has determined that none of the abused GHB is from the pharmaceutical drug product being developed for medical use and that there has been no diversion from clinical trials and authorized studies.

Several states have controlled GHB under state laws, including Georgia (CI), Rhode Island (CI), Hawaii (CI), Illinois (CI), Nevada (CI), Wisconsin (CI), Michigan (CI), Delaware (CI), Idaho (CI), Oklahoma (CI), Nebraska (CI), Alabama (CI), Florida (CII), California (CII), Louisiana (CII), Indiana (CII), New Hampshire (CII), Tennessee (CIV), Alaska (CIV), and North Carolina (CIV). GHB possession and sale is penalized in three States (Texas, New Jersey and Massachusetts).

According to the DEA, abuse and trafficking of GHB manufactured in clandestine laboratories have been increasing since 1993. DEA has documented over 3,500 "encounters" of GHB. These encounters include overdose, abuse and trafficking encounters in 36 states, 72 deaths associated with GHB abuse, and 13 sexual assault cases involving 22 victims under the influence of GHB. The source of such data originates from the law enforcement arena, poison control centers and hospitals. According to the DEA, GHB that is involved in these abuse cases has been clandestinely manufactured, using simple methods and readily available commercial chemicals, gamma-butyrolactone (GBL) and sodium hydroxide. The methods for manufacture, including kits and information on the effects of GHB, are widely available on the Internet.

There is considerable information on the use, availability, and synthesis of GHB through the Internet and other sources. While FDA and other regulatory and law enforcement agencies have successfully disrupted some of the distribution through websites that claim to offer GHB or its precursors, illicit distributors may have altered their distribution schemes to avoid enforcement actions. At one time, however, a 500g bottle of the GHB precursor GBL was offered at one website for $99.99 with the second bottle at half price. Other websites have offered GHB manufacturing kits with enough material to produce one quart of a solution containing 202 g of the potassium salt, which is equivalent to 180 g of GHB; for $200.

Local, regional and national trafficking of GHB have been identified. For example, in late 1995, the DEA investigated the activities of an MDMA trafficker, which resulted in the seizure of GHB. The sources of GHB were clandestine laboratories, laboratories functioning under the cover of producing "nutritional supplements," or occasionally, smuggled product from Europe. Product seizures ranged from 0.37 grams to 1 kg and 0.001 ml to 6688 ml in containers such as plastic bags, vials, water bottles, gallon milk containers and buckets. Individuals apprehended were distributing GHB through mail order catalogs, often offering MDMA or anabolic steroids as well as GHB.

GHB that is abused is manufactured in clandestine laboratories by procedures that are available on the Internet and underground chemistry "cookbooks." Simple "kitchen" stove top methods, requiring little knowledge of chemistry, are found on the Internet and in underground drug literature (such as the "Underground Steroid Handbook for Men and Women Update: 1992").

Precursor chemicals that are used are gamma-butyrolactone (GBL) and sodium hydroxide. One simple chemical step is all that is needed and heat is not required.

Most of the clandestine laboratory activity, according to the DEA, was reported from California, Georgia, Arizona, Texas, Florida, North Carolina, Rhode Island, New York, Washington, Michigan, and Illinois. A total of 84 clandestine laboratories have been documented by the DEA. Of these, 58 (69%) such clandestine laboratories have been encountered in the United States in 1997 and 1998 alone. In addition, DEA's STRIDE (System To Retrieve Information from Drug Evidence) database have documented 90 exhibits of GHB from 44 cases between 1994 and 1998. Sixty-one (68%) were obtained in 1997 and 1998.

Recent seizures of clandestine laboratories found both small and large (interstate) distribution patterns. Some individuals manufacture GHB in their homes for personal use and for personal contacts. Larger laboratories operate to supply GHB within a single geographical area or across state lines. Law enforcement investigational files indicate that clandestine laboratories have been found throughout the United States. The price of GHB on the black market varies and can be $50.00 to $80.00 for 100 grams (The Informant, February 1996). Reports of GHB overdose and toxicity in the United States are rising [77]

GHB has been identified as a drug of abuse in a number of countries, including Australia, the United Kingdom, Sweden, Spain and Italy (INTERPOL Reports, 2/19/96; 3/7/97) In these countries, GHB is abused for many of the same reasons as in the US. In Sweden, GHB was introduced as a medical anesthetic, but is used illicitly by bodybuilders and affluent individuals. The INTERPOL reports "GHB parties" occurring in Sweden. A recent report from Sweden documented ten emergency room cases involving bodybuilders taking GHB (Myrenfors, 1996). Australian Police reported nine GHB overdoses in 1996 on the eastern Gold Coast of Australia. This incident prompted changes in the federal and state laws in Queensland, New South Wales and the Australia Capital Territory (ACT). Queensland amended its Poison Regulations to include GHB and changes to the Drug Misuse Act in Queensland and Drugs of Dependence Act in the ACT are also being made. Also, the Australian Federal Therapeutic Goods Administration banned GHB as a prohibited import allowing the New South Wales Government to outlaw GHB and its derivatives. GHB is a new drug of abuse in the UK where it has been reported to be available in powder or granule form, and sometimes dissolved in water. GHB is abused in the UK, reportedly for its euphoric effects, as a substitute for MDMA and amphetamines at rave party, and as an aphrodisiac. Several cases of toxicity from GHB were recently reported in the London area with four patients presented in coma (Stell and Ryan, 1996). Thomas *et al.* (1997) reported a UK case of coma and respiratory depression in a 32-year-old man who had taken a tablet of temazepam and "half a bottle" of GHB.

FDA's Office of Criminal Investigation (OCI) conducts investigations involving large-scale interstate manufacturers and distributors. To date, OCI has investigated 124 cases. Of the 124 cases, 35 resulted in convictions. The number of cases investigated had increased recently from 18 cases in 1996 to 33 and 24 in 1997 and 1998, respectively. Between January and March 1999, 17 cases have been under investigation

6. WHAT, IF ANY, RISK THERE IS TO THE PUBLIC HEALTH

The public health risk of GHB results from the feasibility and simplicity of its chemical synthesis, the availability of its chemical precursors, its widespread illicit promotion, and the adverse consequences of its use outside of medical direction.

GHB abuse has resulted from widespread dissemination of information on the Internet related to its manufacture. GHB's easy synthesis and medically unsupervised intake are public health risks. The chemical synthesis is accomplished with two readily available chemicals both of which are legal to possess and the manufacturing recipe which does not require extensive chemistry background or experience to be successfully accomplished. The clandestinely manufactured substance does not meet the standards of an approved drug product, being variable and unpredictable in content. The clandestinely produced GHB is not used for an authorized medical purpose and, as such, lacks product labeling with directions for use, warnings and possible drug or alcohol interaction information. Currently, abuse of GHB appears to fall into two categories: (1) Self inflicted abuse, including recreational use for its effects as an intoxicant, euphoriant, or aphrodisiac and use by bodybuilders for its alleged effects as a growth hormone releasing agent or diet/sleep aid; and (2) Abuse (or misuse) of third parties for the purpose of committing a crime.

GHB is taken in combination with other drugs, primarily alcohol, but also stimulants, hallucinogens, marijuana and sedatives. Of the total GHB-related episodes reported in DAWN, most originated from San Francisco, Dallas, Los Angeles, San Diego and Atlanta. Data reported to DAWN by participating medical examiners show that there were seven deaths associated with GHB reported between 1992-1997, of which five occurred in 1997.

According to the DEA, the GHB that is abused is taken in a dose of one to five grams. GHB onset of effects and duration of action are described above under the **Pharmacokinetics** section. GHB potentiates the CNS depressant effects of alcohol and other CNS depressants. Adverse effects of GHB that are produced include the following: drowsiness, dizziness, confusion, inebriation, stupor, reduced muscle tone, reduced blood pressure, reduced heart rate, decreased respiration, seizures, and coma. DEA has documented 32 deaths related to GHB use since 1990.

Twenty-two (69%) were male and 10 (31%) were female. Deaths have been reported in the following states: Florida (9), California (8), Texas (4), Georgia (2), and one each in Illinois, Maryland, Michigan, Nebraska, North Carolina, Ohio, Missouri, and Virginia. Statistics of the deaths are documented in TABLE's 2 and 3, on the next page.

TABLE 2. GHB Deaths Reported in the United States (1990 to 1998)

YEAR	NUMBER OF DEATHS
1990	1
1993	1
1995	3
1996	12
1997	8
1998	7

Source: DEA

The GHB-associated deaths are further reported by age in the table below:

TABLE 3. GHB Deaths by Age

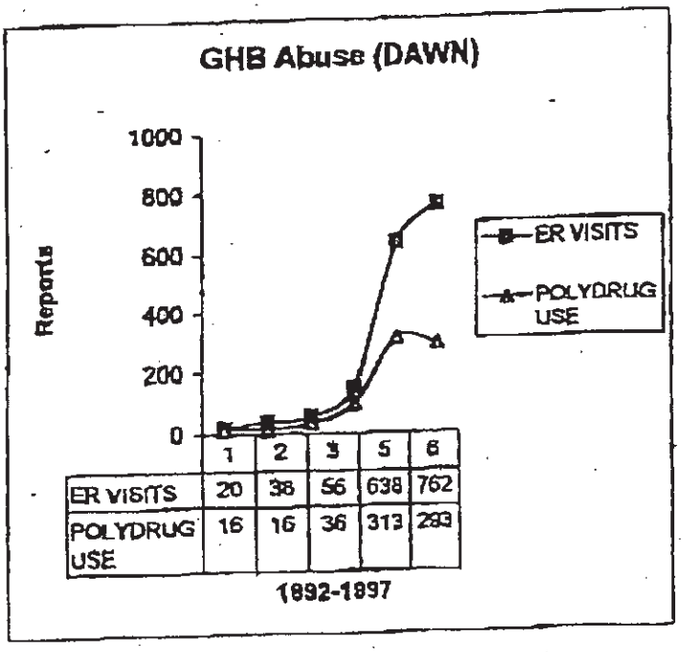
AGES OF DECEASED	NUMBER	PERCENT
10-19 years	3	9%
20-29 years	17	53%
30-39 years	7	22%
40-49 years	3	9%
50-59 years	1	3%
70-79 years	1	3%

Source: DEA

GHB emergency room episodes have been documented in the Drug Abuse Warning Network (DAWN). DAWN reported 1664 GHB-related emergency department episodes from 1991 to 1997. GHB-related emergency department episodes increased from 20 in 1992 to 762 in 1997 (TABLE 4, FIGURE 1) The source of the drug has been clandestinely manufactured GHB of unknown purity. Most of the reports involved Caucasian males, followed by "other" or "unknown" ethnicity. The majority of episodes involved individuals 18 to 25 years of age. The motivation for taking GHB was primarily for recreational use, followed by dependence and suicide. In 60% of the episodes, GHB was taken in combination with alcohol followed by stimulants, hallucinogens, marijuana and sedatives. Consistent with the DEA data, DAWN shows that GHB ED episodes primarily concerned abuse by young people. In addition, Poison Control Center databases show that there were over 600 GHB cases in 1996 and over 900 cases in 1997. None of these cases resulted from abuse of pharmaceutical or research material covered under FDA IND (Source: DEA and DAWN)

These findings suggest that recreational use of GHB has been increasing over the past 5 years, but that the number of deaths relative to that increase is infrequent. The frequency of ER visits related to GHB alone may be approaching that of polydrug use of GHB.

Figure 1



Data from Poison Control Centers (originating from California, Georgia, Florida, South Carolina, Minnesota, Arizona, Ohio, Texas and Virginia) accounted for 57 case reports of GHB intoxication from June through November 1990 (CDC, 1990) Initial symptoms of intoxication were reported to include vomiting, drowsiness, hypnagogic state, hypotonia, and vertigo. Loss of consciousness, irregular and depressed respiration, tremors, or myoclonus sometimes followed. Seizures, bradycardia, hypotension, and/or respiratory arrest have also been reported. Severity and duration of symptoms depended upon the dose of GHB and the presence of other CNS depressants. Although none of the 57 cases resulted in death, most patients required emergency room treatment; at least 11 were hospitalized and 9 required ventilator support or other intensive care As a result of these reports, on November 8, 1990, FDA moved to withdraw GHB from the dietary supplements market (CDC, 1990, 1996).

TABLE 4. Distribution of GHB-related emergency department episodes by selected demographic characteristics: 1992-1997.

	1992	1993	1994	1995	1996	1997
Total	20	38	56	149	638	962
Age						
6-17	-	-	-	-	14	17
18-25	-	13	16	86	427	575
26-34	-	-	16	48	163	201
35 +	-	-	-	-	30	58
Sex						
Male	-	-	29	98	506	730
Female	12	13	12	51	125	228
Unknown	-	-	-	-	-	-
Race/Ethnicity						
White	18	25	47	105	336	570
Black	-	-	-	-	6	8
Hispanic	-	-	-	12	15	26
Other/Unknown	-	-	-	15	281	368
Motive for Taking Drug[1]						
Dependence	-	-	-	15	25	29
Suicide	-	-	-	-	13	18
Recreational Use	14	31	25	85	421	536
Other Psychic Effects	-	-	-	-	17	1
Unknown	-	-	22	41	160	16
Reason for Visit[1]						
Unexpected Reaction	-	-	-	49	172	229
Overdose	11	34	38	94	312	476
Withdrawal	-	-	-	-	-	
Chronic Effects	-	-	-	-	-	
Seeking Detoxification	-	-	-	-	-	17
Other/Unknown	-	-	-	-	138	27
Drug Concomitance						
Single Drug	-	10	-	28	261	90
Multiple Drugs	16	16	36	98	313	93
Unknown	4	12	20	23	64	78

"-" Estimated quantity <10 or = zero.

[1] Motive and Reason refers to entire drug episode, not particular drugs mentioned.

Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network (3-9-99)

Reports of GHB overdose and toxicity in the U.S. appear to be increasing.[78] In 1990, a preliminary study of GHB poisonings, based on data from Poison Control Centers, revealed that at least 57 cases of illness were attributed to GHB exposure in nine states (CDC, 1990). However, GHB-related intoxication is on the rise. In 1996, Poison Control Centers in New York and Texas documented 43 cases of acute poisonings associated with GHB in one year (CDC, 1996). The symptoms of acute GHB toxicity included vomiting, drowsiness, vertigo, and loss of consciousness, respiratory depression, tremors, myoclonus, coma, and seizure activity. Most patients required emergency room care and four fatalities were reported. The demographics of the New York abusers indicated 18 males and 12 females with an average age of 24; there were 8 adverse events reported in teenagers. Eleven of the 30 were admitted to critical care and required intubation or assisted respiration; seizures were reported in two cases.

In Fayette County, Georgia, there were 37 cases of GHB poisoning from 1991 through 1993. Most cases involved white males 17-22 years of age who were body builders. The San Francisco Bay Area Regional Poison Control Center (Dyer *et al.*, 1994) reported 66 encounters with GHB from 1992 though April 1994. In most instances, GHB was reportedly taken alone (79%) but the combined substances featured alcohol (11%), MDMA (1.5%), methamphetamine (4.5%), and opiates (1.5%) and nitrous oxide (1.5%)

In response to fifteen overdose cases that occurred in the last week of December 1995 through the first week of January 1996, the Oklahoma Poison Control Center issued a press release warning about GHB. These cases involved young adults aged 19-27 who had overdosed on GHB and received emergency medical treatment. There were no deaths, but in one incident, a 19-year-old female went into cardiac arrest within 15 minutes of ingesting GHB. All had obtained GHB from a local bar and consumed the GHB with alcohol Individuals have also developed complications from exposure to two of the manufacturing components of GHB, sodium hydroxide and gamma-butyrolactone.

Ross (1995) reported two GHB overdoses occurring in Atlanta. One case involved a 22-year-old male who had been taking 1-2 tablespoons of GHB twice daily for 5 years. The patient confirmed ingesting alcohol with GHB. Since this episode, the patient was treated three additional times for GHB overdose in the emergency department. During all of these episodes the patient required assisted ventilation. A second case involved a 28-year-old female bodybuilder who reported taking 1.5 teaspoons of GHB to help her relax after an intense bodybuilding session. James (1996) described several patients with seizures/decreased levels of consciousness, including one death, a 20-year-old woman who drank GHB in combination with alcohol.

After doses greater than 50 mg/kg orally, somnolence was reported in as little as 15 minutes, unconsciousness and profound coma within 30-40 minutes following ingestion[79] exacerbated when taken with alcohol GHB is relatively short acting After treatment in hospital emergency Symptoms were departments all individuals awoke within 2 to 4 hours of GHB ingestion.[80]

Reports of abuse of illicit GHB use indicate that the drug can be used to endanger the health and safety of others. For example, there have been reports of GHB users driving motor vehicles or caring for young children while impaired.[81] The DEA reported five cases of persons being found behind the wheel of a car while intoxicated with GHB.

Also significant are the reports of how GHB has been used to physically- and mentally-incapacitate women to facilitate sexual assault and "date-rape." The DEA has documented at least seventeen such cases originating from Florida, Texas, Louisiana, and Maryland. These cases have been substantiated by urinalysis and law enforcement investigations.

7. Its Psychic or Physiologic Dependence Liability

Dependence upon GHB has not been formally evaluated in preclinical or clinical studies. Galloway *et al* (1997) published case reports of eight individuals abusing GHB for its sedative, euphorigenic, and anabolic effects. Individuals (6 of 8) abused GHB for its psychoactive effects and obtained drug by illicit purchase. Upon discontinuation of GHB, mild withdrawal symptoms, which included insomnia, muscle cramps, tremor and anxiety, were described. Frederick *et al.* (1995) also described one individual who abused GHB for 1.5 years and described tolerance to GHB's euphoric and sedative effects. In this individual, abrupt cessation resulted in symptoms of insomnia, anxiety, tremor, and sweating. These anecdotal reports originating from the Haight-Ashbury Free Clinic (San Francisco) have all involved clandestinely manufactured GHB.

Although these and other anecdotal reports describe mild withdrawal symptoms following abrupt discontinuation of excessive use of GHB, these reports cannot be relied upon as evidence of significant physical dependence. These symptoms were largely described in the setting of polydrug and alcohol abuse, and therefore in the setting of withdrawal from other substances taken concomitantly. Clinical trial experience has failed to confirm a physical dependence profile.

There are no well-developed clinical data from which to conclude that there is psychological dependence on GHB. Psychological dependence may only be intimated by anecdotal reports of escalation of GHB dose, increased frequency of use, and continued use despite adverse consequences.

8. Whether the substance is an immediate precursor of a substance already controlled under this article.

GHB is not an immediate precursor of any controlled substance

RECOMMENDATION

After consideration of the eight factors discussed above, FDA recommends that GHB and all mixtures, compounds and preparations of GHB should be placed in schedule I of the CSA, except that any mixture, compound or preparation of GHB that is the subject of an FDA authorized investigational new drug application pursuant to 21 CFR part 312 should be placed in schedule III.

Part I

Except as discussed in Part II below, GHB meets the criteria for placing a substance in schedule I of the CSA under 21 U.S.C. 812(b)(1).

A. Abuse Potential

GHB can penetrate the blood brain barrier and is active in the central nervous system. It is a sedative-hypnotic agent that produces dose- and concentration-dependent CNS effects in humans. Its onset of sedative action occurs within 15 minutes of oral ingestion and it lasts up to 3 hours. GHB in low doses has been associated with amnesia and hypotonia. Depending on the dose ingested, its effects may range from mild sedation to profound coma and, if respiratory function is not supported, death. It is water soluble and therefore miscible in alcoholic beverages. Its CNS effects are further enhanced by alcohol.

Self-administration and drug discriminative effects studies in animals indicate that GHB's reinforcing and stimulus generalization effects were similar to those of alcohol and substances in schedule IV such as the benzodiazepines rather than schedule I or II opiates and hallucinogens. Its abuse potential is theoretically similar to that of other substances in lower schedules of control.

However, the rapid onset of sedation coupled with the amnestic features of this agent, particularly when added to alcohol to conceal its presence and potentiate its effects, appear to make GHB an effective agent to physically and mentally incapacitate victims in the commission a crime. In addition, pharmacodynamic data indicate that GHB has a narrow therapeutic index, with the difference between the dose of GHB necessary for a desired hypnotic effect and that which produces unconsciousness being relatively small—and even smaller in the presence of alcohol. In comparison, some of the benzodiazepines in Schedule IV have a much wider therapeutic index. Epidemiological data show significant increases in emergency room and medical examiner reports related to GHB, and law enforcement data confirm GHB's use in third party abuse settings.

GHB has one additional characteristic which increases its abuse liability—it can be easily manufactured in a clandestine setting, resulting in a potentially unlimited supply. There is widespread dissemination of information on the INTERNET and other sources regarding its manufacture using a simple, one-step synthesis from readily available and inexpensive chemical

precursors. No specialized training or equipment is needed. In addition, the widesp read availability of illicit preparations of unknown strength and purity raise further pub c health concerns that distinguish GHB's abuse liability from that of other sedative/hypnoti agents.

For these reasons, and except as provided in Part II of this Recommendation, FD believes that GHB has a "high potential for abuse" relative to substances controlled in schedule III, IV and V.

B. Medical Use

FDA has not approved a new drug application (NDA) for a GHB product, nor can GHB be marketed lawfully for medical use in the United States without an NDA. For this reason FDA believes that GHB has "no currently accepted medical use in the United States" at this time.

C. Safety

Clandestinely produced GHB is a substance of unknown, unregulated, and highly variable quality, strength, and purity. It has not been studied in any reliable manner and there is no accepted safety profile for this substance. Even if used under medical supervision, the safety of such a substance could not be predicted. Therefore, the FDA believes that there is a "lack of accepted safety for use of the drug or other substance under medical supervision."

Part II

GHB substances and products that are the subject of FDA authorized investigational new drug applications, pursuant to 21 CFR part 312, do not meet the criteria for placement in schedule I. Instead, such products and substances should be subject to control under schedule III of the CSA, 21 U.S.C. 812 (b)(3)

A. Abuse Potential

GHB products are currently being studied under FDA authorized investigational new drug applications. None of the reports of actual abuse of GHB that support the scheduling recommendation in Part I has involved GHB that was diverted from an authorized study. Moreover, given the ease with which GHB can be synthesized from readily available materials, it is considerably less likely that these authorized studies will become a source for unlawful use or abuse of GHB. In essence, the widespread availability of clandestinely produced GHB decreases the abuse liability and potential for abuse of the products being studied in authorized research programs and well-supervised clinics. For this reason, a GHB product or substance that is the subject of an authorized protocol and is being studied under a carefully designed research

protocol has a "low potential for abuse relative to drugs or other substances in schedule III" (see 21 U.S.C. 812 (b)(4)(A).

B. Medical Use

As discussed in Part I, GHB does not have a "currently accepted medical use in treatment in the United States" as that term has been interpreted in by the FDA and DEA.

A GHB product, however, has recently been granted a protocol under 21 CFR 312.34 to allow for expanded, treatment use of the product in patients who suffer from cataplexy associated with narcolepsy. In this instance, the study and development of a GHB product is sufficiently far along to suggest that authorized formulations of GHB may be considered as having a "currently accepted medical use with severe restrictions" under the CSA (see 21 U.S.C. 812 (b)(2)(B); see also 47 FR 281241, June 29, 1982).

C. Physical or Psychological Dependence

There is no well-developed evidence from clinical studies to suggest that GHB leads to psychological dependence. The few available anecdotal case reports suggest only mild withdrawal symptoms that may be indicative of low risk of physical dependence. Similarly, from these few anecdotal reports, instances of escalation of GHB dose, increased frequency of use, and continued use despite adverse consequences are only suggestive of dependence production. There is no evidence, however to suggest that abuse of GHB leads to "severe" dependence (see 21 U.S.C. 812 (b)(2)(C)). When compared to substances in schedules II and III, GHB's physical and psychological dependence producing effects appear to be "limited" (see 21 U.S C. 812 (b)(4)(C)).

GHB has a high potential for abuse relative to substances controlled in schedules III, IV and V. GHB has no accepted medical use and, when manufactured clandestinely, is unsafe for use under medical supervision. Accordingly, and except as provided below, GHB should be controlled in Schedule I

Formulations of GHB currently are being studied under FDA-authorized INDs. At least one sponsor's formulation has been granted orphan drug status under section 526 of the Food, Drug, and Cosmetic Act, and is available under a treatment use protocol under 21 CFR § 312.34. None of the reports of actual abuse of GHB that support the Schedule I recommendation has involved GHB that was diverted from an authorized study. Given the ease with which GHB can be synthesized from readily available materials, it is unlikely that authorized studies will become a source of GHB for abuse. Rather, the abuse potential of GHB, when used under an authorized research protocol, is consistent with substances typically controlled under Schedule IV. Information on the dependence producing effects of GHB is limited, but available data suggest that its potential for physical and psychological dependence is also consistent with control under Schedule IV

Authorized formulations of GHB, however, do not meet the "accepted medical use" criteria set forth in Schedule IV. At best, an authorized formulation of GHB is far enough along in the development process to meet the standard under Schedule II of a drug or substance having a "currently accepted medical use with severe restrictions." Under these circumstances, FDA recommends placing authorized formulations of GHB in Schedule III, a level of control higher than Schedule IV to take into account the lack of an accepted medical use and a level of control lower than schedule II to take into account the abuse and dependence liability findings for authorized formulations of GHB.

Endnotes

[1] Winters and Wallach, 1969; Snead, 1977; Mamelak, 1989
[2] Winter, 1981; Beardsley et al., 1996; Colombo et al. 1995c
[3] Galloway et al., 1997
[4] Winter, 1981; Colombo, et al , 1995b,c, Beardsley, et al., 1996
[5] Colombo et al , 1995b
[6] Fance et al , 1997
[7] Lenieri and Fung, 1979
[8] (Jenney et al., 1962; Mamelak et al , 1977, 1986, Mamelak, 1989; Laborit, 1964)
[9] Bessman and Fishbein, 1963; Maitre, 1997
[10] Mamelak, 1989; Cash, 1994; review by Maitre, 1997
[11] Nelson et al., 1981; Vayer et al , 1988
[12] Doherty et al., 1978
[13] Vayer et al., 1987, Tunnicliff, 1992, Maitre, 1997.
[14] Doherty et al., 1978; Rumigny et al., 1980, Cash et al., 1979; Maitre et al., 1983; Maitre, 1997
[15] Benavides et al., 1982; Snead and Liu, 1984; Maitre, 1997
[16] Snead and Liu, 1984
[17] Snead and Nichols, 1987
[18] Snead and Liu, 1984; Maitre and Mandel, 1984; Mandel et al., 1986; Snead and Nichols, 1987
[19] Cash et al., 1996
[20] Diana et al., 1991; Mamelak, 1989, Banerjee and Snead, 1995, Feigenbaum and Howard, 1996
[21] Gessa et al., 1966; Gessa et al., 1968a,b; Roth et al , 1970
[22] Hechler et al , 1991
[23] Gessa et al., 1966, 1968a,b and Roth et al , 1970
[24] Gessa et al , 1966
[25] Gessa et al , 1966, Gessa et al , 1968a,b, Roth et al., 1970; Diana et al , 1991
[26] Roth et al., 1973; Diana et al., 1991
[27] (Feigenbaum and Simantov, 1996

[28] (Gobaille et al., 1994; Hechler et al., 1991; Larson et al., 1983).
[29] Hechler et al., 1991
[30] Spano and Przegalinski, 1973; Waldmeier and Fehr, 1978; Hedner and Lungborg, 1983
[31] Hedner and Lungborg, 1983
[32] Giarman and Schmidt, 1963; Stadler et al., 1974; Sethy et al., 1974; Snead, 1977
[33] (Kršiak et al., 1974).
[34] McCabe et al., 1971
[35] Mamelak et al., 1977
[36] (Jenney et al., 1962; Mamelak et al., 1977, 1986; Mamelak, 1989; Laborit, 1964)
[37] Metcalf et al, 1966; Humer et al., 1971; Mamelack, 1989
[38] Humer et al., 1971
[39] Metcalf et al, 1966
[40] Hedner et al., 1980
[41] Hedner et al., 1985
[42] (Hunter et al., 1971).
[43] Virtue et al., 1966
[44] Takahara et al., 1977
[45] (Gerra et al , 1994a,c, 1995)
[46] . Gerra et al., 1994a.
[47] Gerra et al , 1994c, 1995
[48] Blackledge and Miller, 1991
[49] Lettieri and Fung, 1979
[50] Guidotti and Ballotti, 1969
[51] Snead, 1977
[52] Hoes et al., 1980
[53] Shumate and Sneed, 1979, Van der Pol et al , 1975
[54] Roth and Giarman, 1966; Van der Pol et al., 1975; Lettieri and Fung, 1979, Palamini et al., 1993
[55] Roth and Giarman, 1966, Shumate and Snead, 1979
[56] Lettieri and Fung, 1979
[57] Roth and Giarman, 1966
[58] Lettieri and Fung, 1979).
[59] Shumate and Snead, 1979
[60] Palamini et al., 1993
[61] Doherty et al., 1975
[62] Hedner et al , 1980).
[63] Hedner et al., 1985).
[64] MacMillan, 1978, 1979
[65] Hutchins et al , 1972; Lin et al., 1979, Shumate et al., 1979; Snead, 1978
[66] Crosby et al , 1983
[67] Lin et al., 1979
[68] Vickers, 1969
[69] Hoes et al , 1980
[70] minutes (Palamini et al , 1993)

[71] Palamini et al., 1993
[72] Helrich et al., 1964
[73] Goodman and Gilman, The Pharmaceutical Basis of Therapeutics, 8Th Edition, 991, p356.
[74] Luby et al., 1992;CDC 1990, 1996; Gast and Frenia, 1994; Dyer, 1994; Ross 1995; James, 1996; Galloway et al., 1994, 1997
[75] CDC Report, JAMA, 265(4): 44-45, January 1991
[76] DEA report, 1997
[77] CDC 1990, 1996; Gast and Frenia, 1994; Dyer, 1994; Ross, 1995; James, 1996
[78] CDC 1990, 1996; Gast and Frenia, 1994; Dyer, 1994; Ross, 1995; James, 1996
[79] Metcalf et al., 1966).
[80] CDC, 1996; Galloway et al., 1994, 1996
[81] Stephens and Baselt, 1994; Galloway et al., 1994, 1997

Drug Enforcement Administration

Washington, D.C. 20537

SEP 16 1997

1997

Dr. John M. Eisenberg
Acting Assistant Secretary for Health
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Eisenberg:

In accordance with the provisions of Title 21, U.S.C., Section 811(b), of the Controlled Substances Act (CSA), the Drug Enforcement Administration (DEA) has gathered and reviewed the available data on gamma hydroxybutyrate (GHB). Your scientific and medical evaluation of the enclosed data and your scheduling recommendation for GHB are requested so that the DEA can make a final determination regarding the scheduling of this substance.

GHB is a substance that is currently not controlled under the Controlled Substances Act (CSA). To date, the data available to DEA shows that GHB is abused as a Central Nervous System (CNS) depressant, an intoxicant and euphoriant, a growth hormone releasing agent, and in criminal assaults. It is easily synthesized illicitly in clandestine laboratories with readily obtainable precursors by those inexperienced in chemistry. The drug is easily administered orally, taken in the form of the sodium salt usually dissolved in water or alcoholic drink.

Abuse of GHB is nationwide, increasing and associated with serious public health and safety risks. Since 1990, approximately 500 encounters with GHB have been documented by information gathered from federal, state and local law enforcement agencies, poison control centers, hospitals medical examiners, and the scientific literature. GHB has been encountered in at least 35 states. DEA is aware of 19 deaths associated with GHB use. GHB is sold either in solid or powder form or dissolved in liquid and abused by the oral route. It is trafficked locally, regionally and nationally.

DEA is only aware of limited research into the therapeutic use of GHB in the United States. DEA is not aware of any legitimately marketed products containing GHB in the United States. The Food and Drug Administration (FDA) considered GHB unsafe and banned its manufacture and distribution in dietary supplements. Since GHB is not controlled federally or under most

state laws, it is not the target of law enforcement investigations and its illicit manufacture, abuse and trafficking are severely under reported. Nevertheless, the data contained in the enclosed document show that there is an alarming level of GHB abuse, that it is widespread and increasing, that the GHB is illicitly produced in clandestine laboratories, and that this abuse is associated with many and serious adverse public health and safety risks. These data strongly indicate that GHB has a high potential for abuse and strongly support its placement in a restrictive schedule under the CSA. Final determination of the specific schedule must await the scientific and medical evaluation of the DHHS.

Appropriate members of the DEA staff are available to provide whatever assistance may be needed. In order to facilitate the exchange of information, the DEA staff is authorized to exchange relevant information directly with designated members of your staff. John H. King, Deputy Assistant Administrator, Office of Diversion Control, will act as liaison for this exchange of information. He can be reached at (202) 307-7165.

Sincerely,

James S. Milford

James S. Milford
Acting Deputy Administrator

Enclosure

ATTACHMENT 2

Public Law 106-172 (February 18, 2000)

Public Law 106–172
106th Congress

An Act

To amend the Controlled Substances Act to direct the emergency scheduling of gamma hydroxybutyric acid, to provide for a national awareness campaign, and for other purposes.

Feb. 18, 2000
[H.R. 2130]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000.
Law enforcement and crimes.
21 USC 801 note.
21 USC 812 note.

SECTION 1. SHORT TITLE.

This Act may be cited as the "Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000".

SEC. 2. FINDINGS.

Congress finds as follows:

(1) Gamma hydroxybutyric acid (also called G, Liquid X, Liquid Ecstasy, Grievous Bodily Harm, Georgia Home Boy, Scoop) has become a significant and growing problem in law enforcement. At least 20 States have scheduled such drug in their drug laws and law enforcement officials have been experiencing an increased presence of the drug in driving under the influence, sexual assault, and overdose cases especially at night clubs and parties.

(2) A behavioral depressant and a hypnotic, gamma hydroxybutyric acid ("GHB") is being used in conjunction with alcohol and other drugs with detrimental effects in an increasing number of cases. It is difficult to isolate the impact of such drug's ingestion since it is so typically taken with an ever-changing array of other drugs and especially alcohol which potentiates its impact.

(3) GHB takes the same path as alcohol, processes via alcohol dehydrogenase, and its symptoms at high levels of intake and as impact builds are comparable to alcohol ingestion /intoxication. Thus, aggression and violence can be expected in some individuals who use such drug.

(4) If taken for human consumption, common industrial chemicals such as gamma butyrolactone and 1.4-butanediol are swiftly converted by the body into GHB. Illicit use of these and other GHB analogues and precursor chemicals is a significant and growing law enforcement problem.

(5) A human pharmaceutical formulation of gamma hydroxybutyric acid is being developed as a treatment for cataplexy, a serious and debilitating disease. Cataplexy, which causes sudden and total loss of muscle control, affects about 65 percent of the estimated 180,000 Americans with narcolepsy, a sleep disorder. People with cataplexy often are unable to work, drive a car, hold their children or live a normal life.

(6) Abuse of illicit GHB is an imminent hazard to public safety that requires immediate regulatory action under the Controlled Substances Act (21 U.S.C. 801 et seq.).

SEC. 3. EMERGENCY SCHEDULING OF GAMMA HYDROXYBUTYRIC ACID AND LISTING OF GAMMA BUTYROLACTONE AS LIST I CHEMICAL.

21 USC 812 note.

(a) EMERGENCY SCHEDULING OF GHB.—

(1) IN GENERAL.—The Congress finds that the abuse of illicit gamma hydroxybutyric acid is an imminent hazard to the public safety. Accordingly, the Attorney General, notwithstanding sections 201(a), 201(b), 201(c), and 202 of the Controlled Substances Act, shall issue, not later than 60 days after the date of the enactment of this Act, a final order that schedules such drug (together with its salts, isomers, and salts of isomers) in the same schedule under section 202(c) of the Controlled Substances Act as would apply to a scheduling of a substance by the Attorney General under section 201(h)(1) of such Act (relating to imminent hazards to the public safety), except as follows:

Deadline.

(A) For purposes of any requirements that relate to the physical security of registered manufacturers and registered distributors, the final order shall treat such drug, when the drug is manufactured, distributed, or possessed in accordance with an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (whether the exemption involved is authorized before, on, or after the date of the enactment of this Act), as being in the same schedule as that recommended by the Secretary of Health and Human Services for the drug when the drug is the subject of an authorized investigational new drug application (relating to such section 505(i)). The recommendation referred to in the preceding sentence is contained in the first paragraph of the letter transmitted on May 19, 1999, by such Secretary (acting through the Assistant Secretary for Health) to the Attorney General (acting through the Deputy Administrator of the Drug Enforcement Administration), which letter was in response to the letter transmitted by the Attorney General (acting through such Deputy Administrator) on September 16, 1997. In publishing the final order in the Federal Register, the Attorney General shall publish a copy of the letter that was transmitted by the Secretary of Health and Human Services.

Federal Register, publication.

(B) In the case of gamma hydroxybutyric acid that is contained in a drug product for which an application is approved under section 505 of the Federal Food, Drug, and Cosmetic Act (whether the application involved is approved before, on, or after the date of the enactment of this Act), the final order shall schedule such drug in the same schedule as that recommended by the Secretary of Health and Human Services for authorized formulations of the drug. The recommendation referred to in the preceding sentence is contained in the last sentence of the fourth paragraph of the letter referred to in subparagraph (A) with respect to May 19, 1999.

(2) FAILURE TO ISSUE ORDER.—If the final order is not issued within the period specified in paragraph (1), gamma

hydroxybutyric acid (together with its salts, isomers, and salts of isomers) is deemed to be scheduled under section 202(c) of the Controlled Substances Act in accordance with the policies described in paragraph (1), as if the Attorney General had issued a final order in accordance with such paragraph.

(b) ADDITIONAL PENALTIES RELATING TO GHB.—

(1) CONTROLLED SUBSTANCES ACT.—

(A) IN GENERAL.—Section 401(b)(1)(C) of the Controlled Substances Act (21 U.S.C. 841(b)(1)(C)) is amended in the first sentence by inserting after "schedule I or II," the following: "gamma hydroxybutyric acid (including when scheduled as an approved drug product for purposes of section 3(a)(1)(B) of the Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000),".

(B) CONFORMING AMENDMENT.—Section 401(b)(1)(D) of the Controlled Substances Act (21 U.S.C. 841(b)(1)(D)) is amended by striking ", or 30" and inserting "(other than gamma hydroxybutyric acid), or 30".

(2) CONTROLLED SUBSTANCES IMPORT AND EXPORT ACT.—

(A) IN GENERAL.—Section 1010(b)(3) of the Controlled Substances Import and Export Act (21 U.S.C. 960(b)(3)) is amended in the first sentence by inserting after "I or II," the following: "gamma hydroxybutyric acid (including when scheduled as an approved drug product for purposes of section 3(a)(1)(B) of the Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000),".

(B) CONFORMING AMENDMENT.—Section 1010(b)(4) of the Controlled Substances Import and Export Act (21 U.S.C. 960(b)(4)) is amended by striking "flunitrazepam)" and inserting the following: "flunitrazepam and except a violation involving gamma hydroxybutyric acid)".

(c) GAMMA BUTYROLACTONE AS ADDITIONAL LIST I CHEMICAL.—Section 102(34) of the Controlled Substances Act (21 U.S.C. 802(34)) is amended—

(1) by redesignating subparagraph (X) as subparagraph (Y); and

(2) by inserting after subparagraph (W) the following subparagraph:

"(X) Gamma butyrolactone.".

SEC. 4. AUTHORITY FOR ADDITIONAL REPORTING REQUIREMENTS FOR GAMMA HYDROXYBUTYRIC PRODUCTS IN SCHEDULE III.

Section 307 of the Controlled Substances Act (21 U.S.C. 827) is amended by adding at the end the following:

"(h) In the case of a drug product containing gamma hydroxybutyric acid for which an application has been approved under section 505 of the Federal Food, Drug, and Cosmetic Act, the Attorney General may, in addition to any other requirements that apply under this section with respect to such a drug product, establish any of the following as reporting requirements: Records.

"(1) That every person who is registered as a manufacturer of bulk or dosage form, as a packager, repackager, labeler, relabeler, or distributor shall report acquisition and distribution transactions quarterly, not later than the 15th day of the month succeeding the quarter for which the report is submitted, and annually report end-of-year inventories. Deadline.

Deadline.

"(2) That all annual inventory reports shall be filed no later than January 15 of the year following that for which the report is submitted and include data on the stocks of the drug product, drug substance, bulk drug, and dosage forms on hand as of the close of business December 31, indicating whether materials reported are in storage or in process of manufacturing.

"(3) That every person who is registered as a manufacturer of bulk or dosage form shall report all manufacturing transactions both inventory increases, including purchases, transfers, and returns, and reductions from inventory, including sales, transfers, theft, destruction, and seizure, and shall provide data on material manufactured, manufactured from other material, use in manufacturing other material, and use in manufacturing dosage forms.

"(4) That all reports under this section must include the registered person's registration number as well as the registration numbers, names, and other identifying information of vendors, suppliers, and customers, sufficient to allow the Attorney General to track the receipt and distribution of the drug.

"(5) That each dispensing practitioner shall maintain for each prescription the name of the prescribing practitioner, the prescribing practitioner's Federal and State registration numbers, with the expiration dates of these registrations, verification that the prescribing practitioner possesses the appropriate registration to prescribe this controlled substance, the patient's name and address, the name of the patient's insurance provider and documentation by a medical practitioner licensed and registered to prescribe the drug of the patient's medical need for the drug. Such information shall be available for inspection and copying by the Attorney General.

Applicability.

"(6) That section 310(b)(3) (relating to mail order reporting) applies with respect to gamma hydroxybutyric acid to the same extent and in the same manner as such section applies with respect to the chemicals and drug products specified in subparagraph (A)(i) of such section.".

SEC. 5. CONTROLLED SUBSTANCES ANALOGUES.

(a) RULE OF CONSTRUCTION REGARDING CONTROLLED SUBSTANCE ANALOGUES.—Section 102(32) of the Controlled Substances Act (21 U.S.C. 802(32)) is amended—

(1) in subparagraph (A), by striking "subparagraph (B)" and inserting "subparagraph (C)";

(2) by redesignating subparagraph (B) as subparagraph (C); and

(3) by inserting after subparagraph (A) the following new subparagraph (B):

"(B) The designation of gamma butyrolactone or any other chemical as a listed chemical pursuant to paragraph (34) or (35) does not preclude a finding pursuant to subparagraph (A) of this paragraph that the chemical is a controlled substance analogue.".

(b) DISTRIBUTION WITH INTENT TO COMMIT CRIME OF VIOLENCE.—Section 401(b)(7)(A) of the Controlled Substances Act (21 U.S.C. 841(b)(7)(A)) is amended by inserting "or controlled substance analogue" after "distributing a controlled substance".

SEC. 6. DEVELOPMENT OF MODEL PROTOCOLS, TRAINING MATERIALS, FORENSIC FIELD TESTS, AND COORDINATION MECHANISM FOR INVESTIGATIONS AND PROSECUTIONS RELATING TO GAMMA HYDROXYBUTYRIC ACID, OTHER CONTROLLED SUBSTANCES, AND DESIGNER DRUGS.

21 USC 801 note.

(a) IN GENERAL.—The Attorney General, in consultation with the Administrator of the Drug Enforcement Administration and the Director of the Federal Bureau of Investigation, shall—

(1) develop—

(A) model protocols for the collection of toxicology specimens and the taking of victim statements in connection with investigations into and prosecutions related to possible violations of the Controlled Substances Act or other Federal or State laws that result in or contribute to rape, other crimes of violence, or other crimes involving abuse of gamma hydroxybutyric acid, other controlled substances, or so-called "designer drugs"; and

(B) model training materials for law enforcement personnel involved in such investigations; and

(2) make such protocols and training materials available to Federal, State, and local personnel responsible for such investigations.

(b) GRANT.—

(1) IN GENERAL.—The Attorney General shall make a grant, in such amount and to such public or private person or entity as the Attorney General considers appropriate, for the development of forensic field tests to assist law enforcement officials in detecting the presence of gamma hydroxybutyric acid and related substances.

(2) AUTHORIZATION OF APPROPRIATIONS.—There are authorized to be appropriated such sums as may be necessary to carry out this subsection.

(c) REPORT.—Not later than 180 days after the date of the enactment of this Act, the Attorney General shall submit to the Committees on the Judiciary of the Senate and House of Representatives a report on current mechanisms for coordinating Federal, State, and local investigations into and prosecutions related to possible violations of the Controlled Substances Act or other Federal or State laws that result in or contribute to rape, other crimes of violence, or other crimes involving the abuse of gamma hydroxybutyric acid, other controlled substances, or so-called "designer drugs". The report shall also include recommendations for the improvement of such mechanisms.

Deadline.

SEC. 7. ANNUAL REPORT REGARDING DATE-RAPE DRUGS; NATIONAL AWARENESS CAMPAIGN.

21 USC 801 note.

(a) ANNUAL REPORT.—The Secretary of Health and Human Services (in this section referred to as the "Secretary") shall periodically submit to Congress reports each of which provides an estimate of the number of incidents of the abuse of date-rape drugs (as defined in subsection (c)) that occurred during the most recent 1-year period for which data are available. The first such report shall be submitted not later than January 15, 2000, and subsequent reports shall be submitted annually thereafter.

Deadline.

(b) NATIONAL AWARENESS CAMPAIGN.—

(1) DEVELOPMENT OF PLAN; RECOMMENDATIONS OF ADVISORY COMMITTEE.—

(A) IN GENERAL.—The Secretary, in consultation with the Attorney General, shall develop a plan for carrying out a national campaign to educate individuals described in subparagraph (B) on the following:

(i) The dangers of date-rape drugs.

(ii) The applicability of the Controlled Substances Act to such drugs, including penalties under such Act.

(iii) Recognizing the symptoms that indicate an individual may be a victim of such drugs, including symptoms with respect to sexual assault.

(iv) Appropriately responding when an individual has such symptoms.

(B) INTENDED POPULATION.—The individuals referred to in subparagraph (A) are young adults, youths, law enforcement personnel, educators, school nurses, counselors of rape victims, and emergency room personnel in hospitals.

Deadline. Establishment.

(C) ADVISORY COMMITTEE.—Not later than 180 days after the date of the enactment of this Act, the Secretary shall establish an advisory committee to make recommendations to the Secretary regarding the plan under subparagraph (A). The committee shall be composed of individuals who collectively possess expertise on the effects of date-rape drugs and on detecting and controlling the drugs.

Deadline.

(2) IMPLEMENTATION OF PLAN.—Not later than 180 days after the date on which the advisory committee under paragraph (1) is established, the Secretary, in consultation with the Attorney General, shall commence carrying out the national campaign under such paragraph in accordance with the plan developed under such paragraph. The campaign may be carried out directly by the Secretary and through grants and contracts.

Deadline.

(3) EVALUATION BY GENERAL ACCOUNTING OFFICE.—Not later than 2 years after the date on which the national campaign under paragraph (1) is commenced, the Comptroller General of the United States shall submit to Congress an evaluation of the effects with respect to date-rape drugs of the national campaign.

(c) DEFINITION.—For purposes of this section, the term "date-rape drugs" means gamma hydroxybutyric acid and its salts, isomers, and salts of isomers and such other drugs or substances as the Secretary, after consultation with the Attorney General, determines to be appropriate.

SEC. 8. SPECIAL UNIT IN DRUG ENFORCEMENT ADMINISTRATION FOR ASSESSMENT OF ABUSE AND TRAFFICKING OF GHB AND OTHER CONTROLLED SUBSTANCES AND DRUGS.

Deadline.

(a) ESTABLISHMENT.—Not later than 60 days after the date of the enactment of this Act, the Attorney General shall establish within the Operations Division of the Drug Enforcement Administration a special unit which shall assess the abuse of and trafficking in gamma hydroxybutyric acid, flunitrazepam, ketamine, other controlled substances, and other so-called "designer drugs" whose use has been associated with sexual assault.

(b) PARTICULAR DUTIES.—In carrying out the assessment under subsection (a), the special unit shall—

(1) examine the threat posed by the substances and drugs referred to in that subsection on a national basis and regional basis; and

(2) make recommendations to the Attorney General regarding allocations and reallocations of resources in order to address the threat.

(c) REPORT ON RECOMMENDATIONS.—

(1) REQUIREMENT.—Not later than 180 days after the date of the enactment of this Act, the Attorney General shall submit to the Committees on the Judiciary of the Senate and House of Representatives a report which shall— Deadline.

(A) set forth the recommendations of the special unit under subsection (b)(2); and

(B) specify the allocations and reallocations of resources that the Attorney General proposes to make in response to the recommendations.

(2) TREATMENT OF REPORT.—Nothing in paragraph (1) may be construed to prohibit the Attorney General or the Administrator of the Drug Enforcement Administration from making any reallocation of existing resources that the Attorney General or the Administrator, as the case may be, considers appropriate.

SEC. 9. TECHNICAL AMENDMENT.

Section 401 of the Controlled Substances Act (21 U.S.C. 841) is amended by redesignating subsections (d), (e), (f), and (g) as subsections (c), (d), (e), and (f), respectively.

Approved February 18, 2000.

LEGISLATIVE HISTORY—H.R. 2130 (S. 1561):

HOUSE REPORTS: No. 106–340, Pt. 1 (Comm. on Commerce).
CONGRESSIONAL RECORD:
Vol. 145 (1999): Oct. 12, considered and passed House.
Nov. 19, considered and passed Senate, amended, in lieu of S. 1561.
Vol. 146 (2000): Jan. 31, House concurred in Senate amendments.
WEEKLY COMPILATION OF PRESIDENTIAL DOCUMENTS, Vol. 36 (2000):
Feb. 18, Presidential statement.

○

ATTACHMENT 3

Federal Register Notice (Monday, March 5, 2001; Vol. 66, No. 43)
World Health Organization Scheduling Recommendations

publication of this document in the **Federal Register**. Therefore, a comment is best assured of having its full effect if OMB receives it within 30 days of publication. Written comments and recommendations for the proposed information collection should be sent directly to the following: Office of Management and Budget, Paperwork Reduction Project, 725 17th Street, NW., Washington, DC 20503, Attn: Desk Officer for ACF.

Dated: February 27, 2001.

Bob Sargis,

Reports Clearance Officer.

[FR Doc. 01–5234 Filed 3–2–01; 8:45 am]

BILLING CODE 4184–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00N–1441]

Agency Information Collection Activities; Announcement of OMB Approval; Infant Formula Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a collection of information entitled "Infant Formula Requirements" has been approved by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995.

FOR FURTHER INFORMATION CONTACT: Peggy Schlosburg, Office of Information Resources Management (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–1223.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of November 9, 2000 (65 FR 67388), the agency announced that the proposed information collection had been submitted to OMB for review and clearance under 44 U.S.C. 3507. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. OMB has now approved the information collection and has assigned OMB control number 0910–0256. The approval expires on February 29, 2004. A copy of the supporting statement for this information collection is available on the Internet at http://www.fda.gov/ohrms/dockets.

Dated: February 23, 2001.

William K. Hubbard,

Senior Associate Commissioner for Policy, Planning, and Legislation.

[FR Doc. 01–5158 Filed 3–2–01; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00N–1257]

International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization Scheduling Recommendations for 4-Bromo-2,5-dimethoxyphenethylamine (2C–B); Gamma-hydroxybutyric acid (GHB); 4-Methylthioamphetamine (4-MTA); Zolpidem (INN)

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is providing interested persons with the opportunity to submit written comments concerning recommendations by the World Health Organization (WHO) to impose international manufacturing and distribution restrictions, under international treaties, on certain drug substances. The comments received in response to this notice will be considered in preparing the U.S. position on these proposals for a meeting of the United Nations Commission on Narcotic Drugs (CND) in Vienna, Austria, March 20 to 29, 2001. This notice is issued under the Controlled Substances Act.

DATES: Submit written comments by March 15, 2001.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. To ensure expeditious review of written comments, send a copy by facsimile or e-mail to: James R. Hunter (address below).

FOR FURTHER INFORMATION CONTACT: James R. Hunter, Controlled Substances Staff (HFD–9), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2098, Fax: 301–443–9222, e-mail: hunterj@cder.fda.gov.

SUPPLEMENTARY INFORMATION:

I. Background

The United States is a party to the 1971 Convention on Psychotropic Substances (the Convention). Section 201(d)(2)(B) of the Controlled Substances Act (the CSA) (21 U.S.C. 811(d)(2)(B)) provides that when the United States is notified under Article 2 of the Convention that CND proposes to decide whether to add a drug or other substance to one of the schedules of the Convention, transfer a drug or substance from one schedule to another, or delete it from the schedules, the Secretary of State must transmit notice of such information to the Secretary of Health and Human Services (HHS). The Secretary of HHS must then publish a summary of such information in the **Federal Register** and provide opportunity for interested persons to submit comments. The Secretary of HHS must then evaluate the proposal and furnish a recommendation to the Secretary of State that shall be binding on the representative of the United States in discussions and negotiations relating to the proposal.

As detailed below, the Secretary of State has received notification from the Secretary-General of the United Nations (the Secretary-General) regarding substances to be considered for control under the Convention. The notification reflects the recommendations from the 31st WHO Expert Committee for Drug Dependence (ECDD), which met in June 1998. In the **Federal Register** of April 28, 2000 (65 FR 24969), FDA announced the WHO ECDD review, and the agency invited interested persons to submit information for WHO's consideration.

The full text of the notification from the Secretary-General is provided in section II of this document. Section 201(d)(2)(B) of the CSA requires the Secretary of HHS, after receiving a notification proposing scheduling, to publish a notice in the **Federal Register** to provide the opportunity for interested persons to submit information and comments on the proposed scheduling action.

II. United Nations Notification

The formal United Nations notification that identifies the drug substances and explains the basis for the recommendations is reproduced below.

Notification on 2C-B, 4-MTA, GHB and Zolpidem: Reference: NAR/CL.26/2000 CU 2000/240.

C1971/WHO
UNDCP 42nd CND
TLACSB/CNDS–40/00

The Secretary-General of the United Nations presents his compliments to the Secretary of State of the United States of

America and has the honour to inform the Government that, pursuant to article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances, 1971, he has received a notification from the World Health Organization (WHO) concerning proposed recommendations for international control in respect of the following four substances: 2C-B, 4-MTA, GHB and zolpidem.

In accordance with the provisions of article 2, paragraph 2, of the 1971 Convention, the Secretary-General is transmitting the text of that notification as an annex to the present note.

As will be seen from the notification and the attached assessments and recommendations, WHO recommends that 2C-B be included in Schedule II, 4-MTA in Schedule I, and GHB and zolpidem in Schedule IV of that Convention.

Article 2, paragraph 1, of the Convention reads:

If a Party or the World Health Organization has information relating to a substance not yet under international control which in its opinion may require the addition of that substance to any of the Schedules of this Convention, it shall notify the Secretary-General and furnish him with the information in support of that notification. The foregoing procedure shall also apply when a Party or the World Health Organization has information justifying the transfer of a substance from one Schedule to another among those Schedules, or the deletion of a substance from the Schedules.

Article 2, paragraph 4, reads:

If the World Health Organization finds: (a) That the substance has the capacity to produce (i)(1) a state of dependence and (2) central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function or thinking or behaviour or perception or mood, or (ii) similar abuse and similar ill effects as a substance in Schedule I, II, III or IV, and (b) That there is sufficient evidence that the substance is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control, the World Health Organization shall communicate to the Commission an assessment of the substance, including the extent or likelihood of abuse, the degree of seriousness of the public health and social problem and the degree of usefulness of the substance in medical therapy, together with recommendations on control measures, if any, that would be appropriate in the light of its assessment.

Pursuant to article 2, paragraph 2, of the Convention, the notification, together with the assessments and recommendations from WHO as well as any data received from Governments on any of these substances, will be brought to the attention of the Commission on Narcotic Drugs at its forty-fourth session in March 2001. Any action or decision taken by the Commission with respect to that notification, pursuant to article 2, paragraph 5, of the Convention, will be notified to States Parties in due course.

Article 2, paragraph 5, of the Convention reads:

The Commission, taking into account the communication from the World Health Organization, whose assessments shall be determinative as to medical and scientific matters, and bearing in mind the economic, social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule I, II, III or IV. The Commission may seek further information from the World Health Organization or from other appropriate sources.

The Secretary-General would appreciate it if the Government would submit data on seizures of any of these substances or on the existence of clandestine laboratories manufacturing them. Such data would assist the Commission in its consideration of possible international control of some or all of the substances under review.

In order to further assist the Commission in reaching a decision, it would be appreciated if any economic, social, legal, administrative or other factors the Government may consider relevant to the question of the possible scheduling of these four substances could be communicated by 12 December 2000 to the Executive Director of the United Nations International Drug Control Programme, c/o Commission on Narcotic Drugs Secretariat Section, P.O. Box 500, A–1400 Vienna, Austria, fax: 43–1–26060–5885.

2 November 2000
NAR/CL.26/2000

Annex—Note Dated 4 October 2000 Addressed to the Secretary-General by the Director-General of the World Health Organization

The Director-General of the World Health Organization presents her compliments to the Secretary-General of the United Nations and has the honour to submit, in accordance with Article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances, 1971, assessments and recommendations of the World Health Organization, as set forth on the annex hereto, concerning the proposed international control in respect of 2C-B, 4-MTA, GHB, and zolpidem.

The Director-General of the World Health Organization avails herself of this opportunity to renew to the Secretary-General of the United Nations the assurances of her highest consideration.

2C-B (4-Bromo-2,5-dimethoxyphenylethylamine) Substance identification

2C-B is chemically 4-bromo-2,5-dimethoxyphenylethylamine; 2-(4-bromo-2,5-dimethoxyphenyl) ethylamine (CAS 66142–81–2). Other names include: α-desmethyl DOB; BDMPEA; MFT; Erox; Nexus; Performax. There are no chiral centres; therefore, no stereoisomers or racemates are possible.

Similarity to Known Substances and Effects on the Central Nervous System

2C-B has structural and pharmacological similarities to brolamfetamine and mescaline. 2C–B is a selective partial agonist for 5-HT_{2A}- and 5-HT_{2C}-serotonin receptors. In humans, 2C–B is more potent than mescaline but less potent than brolamfetamine. In low doses it has sensory enhancing effects: skin sensitivity, heightened responsiveness to smells, tastes and sexual stimulation. In higher doses 2C-B is a strong hallucinogen. 2C-B produces particularly marked visual hallucinations with an intense colour play, intriguing patterns emerging on surfaces and distortions of objects and faces. It was reported to enhance sexual feelings, sexual perception and performance.

Dependence Potential

There are no animal or human studies about the dependence potential of 2C-B.

Actual Abuse and/or Evidence of Likelihood of Abuse

In the 1990s, 2C-B was sold as an aphrodisiac in several countries and some abuse of 2C-B has been reported by a number of countries. These suggest that 2C-B has modest abuse liability like other hallucinogens. Although hallucinogens are rarely associated with compulsive use or dependent use, they are known to have modest abuse potential, particularly in polydrug abusers.

Therapeutic Usefulness

Apart from the controversial experimental use to facilitate psychotherapy, hallucinogens, such as 2C-B, do not have any therapeutic usefulness.

Recommendation

Despite the limited availability of studies, the chemical and pharmacological similarity of 2C-B to the hallucinogen mescaline has been demonstrated. The altered state of mind induced by hallucinogens such as 2C-B may result in harm to the user and to

others. Based on its perceived aphrodisiac effects and known modest abuse potential of hallucinogenic drugs in general, it is estimated that 2C-B may be abused so as to constitute a public health and social problem warranting its placement under international control. However, hallucinogens are rarely associated with compulsive use and abuse of 2C-B has been infrequent, suggesting that abuse of 2C–B is likely to constitute a substantial, rather than an especially serious, risk to public health. On these bases, it is recommended that 2C-B be placed in Schedule II of the 1971 Convention on Psychotropic Substances.

4-MTA (4-methylthioamphetamine) Substance Identification

4-MTA is chemically 4-methylthioamphetamine (CAS 14116–06–4) Other names include: α-methyl 4-methylthiophenetylarnine, *p*-methylthioamphetamine; 4-MTA; *p–MTA;* MTA; MK; S5; S_5; Flatliner; The One and Only Dominator. 4-MTA has one chiral centre and can exist in two enatiomers and a racemate. Only the racemic mixture has been reported to have been synthesised.

Similarity to Known Substances and Effects on the Central Nervous System

4-MTA is a potent serotonin-releasing agent and reversible inhibitor of monoamine oxidase-A, and is structurally similar to 4-methoxyamphetamine. Pharmacologically, it is similar to MDA and MDMA; studies suggest that 4-MTA is six times more potent than MDMA and MDA in inhibiting 5-HT uptake.

Dependence Potential

Drug discrimination studies in rats suggest that 4-MTA produces discriminative stimulus effects similar to MDMA. 4-MTA did not substitute for amphetamine, LSD or phencyclidine. Reports from the United Kingdom indicate that 4-MTA is abused for its stimulant/euphoric effects similar to MDMA.

Actual Abuse and/or Evidence of Likelihood of Abuse

4-MTA is mainly abused in Europe. It appears that 4-MTA is part of the dance music culture although its use is relatively less widespread probably because of perceptions by users that the drug is stronger and more harmful than other "club drugs" such as MDMA. 4-MTA has resulted in a number of fatalities and hospital admissions. It appears that toxic effects can be produced directly from the drug and that the presence of other drugs or alcohol may exacerbate such effects.

Therapeutic Usefulness

4-MTA has no recognized therapeutic use.

Recommendation

4-MTA is chemically and pharmacologically similar to MDA and MDMA. 4-MTA is a new synthetic drug which was seized for the first time in 1997. Although evidence of its actual abuse is available only in several countries in Europe, seizures, including those of large quantities reported from a wider range of countries, suggest that the trafficking and abuse of 4-MTA are more widespread than have been reported. Based on this and its similarity to known MDA-type psychotropic substances, as well as data from drug discrimination studies in animals, it is estimated that 4-MTA is likely to be abused so as to constitute a public health and social problem warranting its placement under international control. Taking into consideration that 4-MTA has no recognized therapeutic use and that it has resulted in a number of fatalities, abuse of 4-MTA is estimated to constitute an especially serious risk to public health. It is therefore recommended that 4-MTA be placed in Schedule I of the 1971 Convention on Psychotropic Substance.

GHB (Gamma-hydroxybutyric acid) Substance Identification

GHB is chemically γ-hydroxybutyric acid; 4-hydroxybutyric acid (CAS 591–81–1). GHB usually exists as either the free acid or as the sodium salt. Sodium oxybate (CAS 502–85–2) is a national nonproprietary name for its sodium salt. There are no chiral centres; therefore, no stereoisomers or racemates are possible.

Similarity to Known Substances and Effects on the Central Nervous System

GHB is an endogenous compound and is structurally similar to the neurotransmitter GABA. Pharmacologically, it produces sedative and anaesthetic effects at high doses. Such depressant effects of GHB appear to be associated with its cataleptic effects and are different from those of barbiturates and benzodiazepines. GHB sedation possessed distinct excitatory properties, which may be due to its effect on the dopaminergic system (increase in intracellular neuronal dopamine). GHB has been found to induce anesthesia (but does not provide pain relief), (slow-wave) sleep, bradycardia, vomiting, random clonic movements, hypothermia, reduction in potassium levels, decrease in ventilatory rate and apnoea. However, the respiratory centre remains sensitive to an increase in carbon dioxide.

Dependence Potential

In drug discrimination studies in animals, none of the known abused drugs has the ability to fully substitute for GHB. Morphine, dexamphetamine, LSD and some benzodiazepines produced, at best, partial substitution. There have been few studies regarding the dependence/abuse potential of GHB. However, during the numerous studies involving administration of GHB to patients at varying concentrations, no dependence has been observed at low doses of GHB. At prolonged high doses, however, a withdrawal syndrome including insomnia, muscular cramping, tremor and anxiety has been noted upon discontinuation in some cases.

Actual Abuse and/or Evidence of Likelihood of Abuse

GHB abuse has been reported in Australia, USA and many countries in Europe. Precursors of GHB, such as γ-butyrolaztone and 1,4-butanediol, which are metabolized to GHB in the body, have also been abused. Although initially abused by body-builders for its apparent growth hormone promoting properties, the more recent primary mode of abuse worldwide has been the use of GHB for its subjective hypnotic, euphoric and hallucinogenic effects, especially in the context of the dance music culture (i.e. "raves"). Some users have also claimed to use GHB as an alternative to alcohol (for relaxation), as a sexual adjunct, appetite suppressant, anti-aging product and has also been implicated in cases of sexual assault.

It appears that toxic effects can be produced directly from the drug and the presence of other depressant or sedative drugs (e.g. opiates, benzodiazepines, alcohol and barbiturates) and possibly other psychoactive compounds (e.g. amphetamine) may exacerbate the effects of GHB. Hospital admissions and deaths have been linked to GHB ingestion and generally involve the onset of coma and respiratory depression.

Therapeutic Usefulness

GHB has been used as an anaesthetic agent and as an aid to alcohol/opiate withdrawal, primarily in France, Germany and Italy, respectively. In USA and Canada it is currently under evaluation for the treatment of narcolepsy-associated cataplexy.

Recommendation

Although GHB is an endogenous compound that exists in the human body, GHB has psychoactive and toxic effects when administered. The pattern and consequences of its abuse in a number of countries in Europe and the USA seem to suggest that its liability to abuse constitutes a significant risk to public health. The current easy availability of GHB and some of its precursors has contributed to its recent abuse. The wide availability is likely to be reduced once GHB is placed under international control. On these bases, it is recommended that GHB be placed in Schedule IV of the 1971 Convention on Psychotropic Substances.

Zolpidem (INN) Substance Identification

Zolpidem is chemically N,N,6-trimethyl-2-p-tolylimidazo [1,2-a]pyridine-3-acetamide; N,N,6-trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetamide (CAS 82626–48–0). Trade names include: Ambien, Bikalm, Niotal, Stilnoct, Stilnox.

Similarity to Known Substances and Effects on the Central Nervous System

Though chemically different from benzodiazepines, zolpidem produces benzodiazepine-like effects. It acts as an agonist binding with high and low affinity to BZ_1 and BZ_2 receptor subtypes, respectively. It is generally believed to produce relatively greater hypnotic effects than other benzodiazepine-like effects.

Dependence Potential

The results of human laboratory studies suggest that zolpidem and triazolam are generally similar in terms of producing subjective reinforcing effects. As with many of the benzodiazepines, there have been a number of case reports describing withdrawal symptoms after cessation of zolpidem administration. Though withdrawal discomfort does not necessarily lead to compulsory drug taking (drug dependence) in humans, there are reports of clinically diagnosed cases of drug dependence resulting from a prolonged use of zolpidem.

Actual Abuse and/or Evidence of Likelihood of Abuse

Epidemiological studies indicate that zolpidem is associated with relatively low incidence of abuse. Sporadic case reports in the scientific literature have indicated that zolpidem is abused, but these cases usually involved patients with histories of drug abuse or chronic psychiatric disorders. Cases of zolpidem overdose requiring emergency treatment have been reported. Death due to zolpidem overdose is rare. Rates of actual abuse and dependence of zolpidem appear to be similar to other hypnotic benzodiazepines in Schedule IV. In terms of the numbers of cases of abuse, dependence and withdrawal reported as adverse drug reactions to the WHO adverse drug reaction database, less than ten benzodiazepines are ranked higher than zolpidem.

Therapeutic Usefulness

Zolpidem is used for treatment of insomnia in more than 80 countries.

Recommendation

Although zolpidem has a somewhat novel neuropharmacological profile relative to classic benzodiazepines, studies of its abuse potential suggest that it may be comparable to that of many benzodiazepines. Furthermore, rates of actual abuse and dependence of zolpidem in medical use, as well as the risk to public health of its abuse, appear to be similar to hypnotic benzodiazepines presently placed in Schedule IV. On these bases, it is recommended that zolpidem be placed in Schedule IV of the 1971 Convention on Psychotropic Substances.

I. Discussion

Although WHO has made specific scheduling recommendations for each of the drug substances, the CND is not obliged to follow the WHO recommendations. Options available to the CND for substances considered for control under the Psychotropic Convention include: (1) Acceptance of the WHO recommendations; (2) acceptance of the recommendations to control, but control the drug substance in a schedule other than that recommended; or (3) rejection of the recommendations entirely.

4-Bromo-2,5-dimethoxyphenethylamine (2C-B) is a Schedule I controlled substance in the United States. The U.S. Drug Enforcement Administration (DEA) placed 2C-B (including salts, isomers, and salts of isomers: isomers include optical, positional, and geometric) in Schedule I of the Controlled Substance Act (CSA) in June 1995. 4-methylthioamphetamine (4-MTA) is not marketed in the United States and is not currently a controlled substance in the United States. Gamma hydroxybutyric acid (GHB) is a Schedule I controlled substance in the United States. GHB, including its salts, optical isomers, and salts of optical isomers, became a Schedule I controlled substance in March 2000. Registered manufacturers and distributors of GHB when it is manufactured, distributed, or possessed in accordance with an FDA authorized investigational new drug exemption under Section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 USC 355(i)) are subject to Schedule III security requirements. If FDA approves a drug product containing GHB for marketing, the approved product will be placed into Schedule III under Public Law 106–172. Zolpidem, its salts, isomers, and salts of isomers, is a Schedule IV controlled substance in the United States. The DEA placed zolpidem in Schedule IV in February 1993. With the exception of 4-MTA, current controls in the United States on the substances under consideration for international control appear to meet the requirements of the recommended Psychotropic Convention schedules.

IV. Comments

Interested persons may, on or before March 15, 2001, submit to the Dockets Management Branch (address above) written comments regarding this notice. This abbreviated comment period is necessary to allow HHS to furnish a recommendation to the Secretary of State in time for the March 2001 meeting of the United Nations Commission on Narcotic Drugs. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Dated: February 27, 2001.

Ann M. Witt,

Acting Associate Commissioner for Policy.

[FR Doc. 01–5218 Filed 2–28–01; 11:36 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Blood Products Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Blood Products Advisory Committee.

General Function of the Committee: To provide advice and

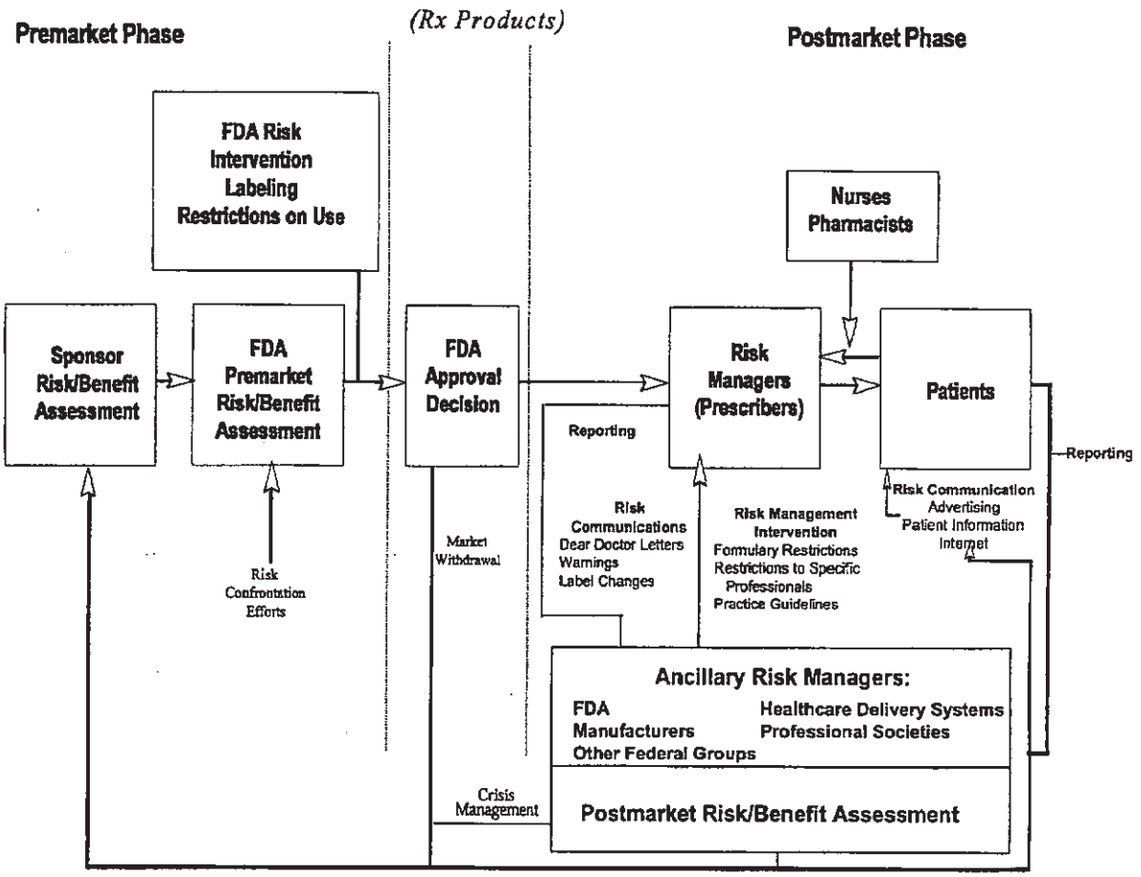
SECTION 8
RISK MANAGEMENT

8.0 RISK MANAGEMENT

8.1 Introduction to Risk Management

The system used to manage the risks presented by medical products during their pre-market and post-market phases involves many different parties with various, and sometimes different, interests. Each party's goal, however, is limitation of the risk a medical product presents to the patient and the public. It is a complex system, presented graphically in Figure 8.1.

Figure 8.1. Complex System for Managing the Risks of Medical Products



Wishing to simplify and update this risk management system, the FDA established a Task Force in 1999 to reconsider the existing system, identify issues, and recommend solutions (Task Force on Risk Management 1999).

One of the major issues highlighted by the Task Force was that each of the partners within this system lacked clearly defined roles and responsibilities. The Task Force further determined that actions of the participants are not well integrated and coordinated.

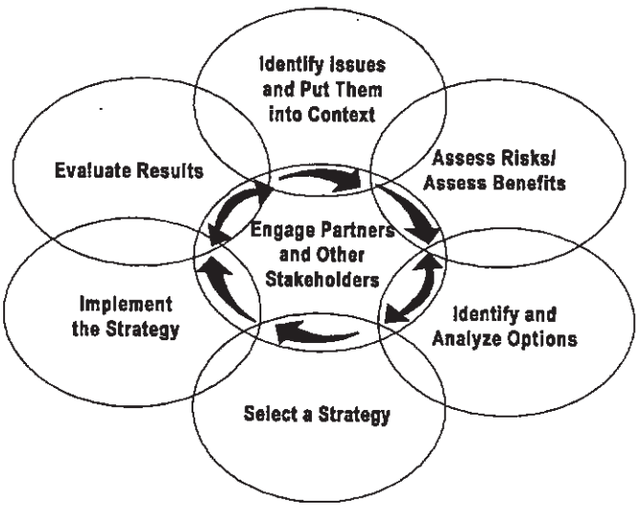
An example is the reporting of adverse events. All pharmacists are trained to identify adverse events, and to report them to the manufacturer, which, in turn, reports them to the FDA. This process is not always effective within the current healthcare environment, in which patients can make several visits to many different physicians, use multiple pharmacies, and take over-the-counter or nutritional products without medical supervision.

Rarely is a thorough medication audit performed on a patient, and consequently, patients may not receive informed counseling regarding potential medication interactions. Resultant adverse events often are not correlated to concomitant medications. While regulations do exist to support counseling of patients by trained pharmacists, many retail pharmacies have addressed this obligation by simply providing written instructions for a given medication, and the opportunity for integration of care is again lost.

Integration of a patient's total care is impossible without all of the care providers working in concert.

The Task Force concluded that "risk confrontation" is key to the effective management of risk associated with medical products. It recommended a simplified model that takes into account the current health care delivery environment (see Figure 8.2).

Figure 8.2. Proposed Risk Management Model



Risk confrontation is the identification of salient risks and the design of methods to address these risks. This model revolves around the participation of relevant partners and stakeholders, that is, interested parties that can contribute to effective risk management. These parties, referred to as the "Interested Community," have to be involved in the risk identification and management processes.

Orphan Medical has embraced and incorporated the conclusions of the FDA Task Force in the design of its risk management system. These are presented in the next sections.

8.1.1 RISK MANAGEMENT OF XYREM USING THE RISK CONFRONTATION MODEL

8.1.1.1 Identify Issues and Put Them Into Context

The first step in the risk confrontation model is to identify issues and understand their real-world implications. Orphan Medical invited stakeholders to participate in a series of meetings, between 1998 and 2001, in order to discuss Xyrem and its potential risks. Stakeholders included in these meetings were:

- Narcolepsy patient organizations
- Narcolepsy patients
- Physicians expert in treating narcolepsy
- Drug abuse experts
- Criminal prosecutors
- Forensics experts
- Sexual assault investigators

- Drug abuse trend experts
- Legislative personnel
- Field law enforcement
- Various law enforcement officers who train other officers in drug recognition issues
- Emergency room physicians
- Toxicologists and Poison Control Center directors
- The National Association of State Controlled Substance Authorities (NASCSA)
- The National Association of Drug Diversion Investigators (NADDI)
- Rape crisis centers and advocates

The objectives of the meetings were to:

1. Identify all of the key risks relating to the use of Xyrem as well as illicit GHB and related chemicals; and to
2. Propose methods to contain the risks identified.

The stakeholders first agreed on the following list of facts and issues.

- Narcolepsy is a disabling disease estimated to affect fewer than 140,000 people in the United States. Since it is a difficult disease to diagnose, only an estimated 75,000 individuals with narcolepsy have received an accurate diagnosis and are receiving treatment.
- Cataplexy, a disabling symptom of narcolepsy, is distinguished by a loss of muscle tone when the patient is confronted by emotional stimulus. It is estimated that the number of diagnosed/treated narcolepsy-with-cataplexy patients in the U.S. is approximately 25,000. Current treatments for cataplexy are limited in their effectiveness and can have troubling adverse effect profiles, leading to their discontinuation by some patients.
- Physicians and narcolepsy patients are familiar with the restrictions and risks associated with controlled substances. Schedule II and IV medicines are typically used in the attempt to control the symptoms of narcolepsy.
- The results of clinical trials in which Xyrem was evaluated indicate that it is safe and efficacious when used to treat narcolepsy.
- Illicit use of GHB and related chemicals is growing, with serious physical consequences to users being identified (Zvosec 2001).
- The sources of illicit GHB and related chemicals range from home made products and "reagent kits" sold on the Internet to two industrial chemicals, of which 100 million gallons were produced in the US last year (Caruso 1997). Illicit GHB and related chemicals can also be obtained as nutritional supplements from health food stores. All illicit products vary in purity, content, and dose.
- Xyrem has never been reported as a source of abused GHB by toxicologists, ER personnel, or law enforcement personnel.

- Poly-drug use is common in the abuser population (Galloway 2000), with little known about drug interactions among various illicit drugs. Use of alcohol in combination with GHB is common, leading to dangerous, potentially synergistic, effects (McCabe 1971).
- In general, toxicologists, emergency medicine personnel, and other medical personnel lack knowledge of GHB and related chemicals and training in how to treat their misuse, especially when ingested with alcohol or other illicit drugs.
- Law enforcement personnel also usually lack knowledge and training in how to identify illicit GHB and related chemicals.
- State laws addressing illicit GHB and related chemicals are not uniform. Differences also exist between federal and state laws.
- Within the Interested Community, very little scientific information regarding abuse of GHB, drug diversion investigations, law enforcement training, identification, activities, and state efforts dealing with controlled substances exists, and even less is shared.
- Currently, diversionary activities are difficult to identify and investigate due to the lack of integration in pharmacy reporting systems.
- Often investigations are initiated many months after a crime occurs, owing to the need to collect extensive data. Thus, illicit use is simply "caught" versus prevented.
- Widespread distribution of controlled substances through community pharmacy increases the potential for diversion.
- Sexual assault investigation protocols do not include screening or testing for illicit GHB and related chemicals.
- Most hospital diagnoses are presumptive. Very few laboratories identify or quantify GHB, GBL and 1,4-Butanediol in blood or urine. These drugs are not part of routine drug screening methodologies in hospitals.
- Urine screening for illicit GHB and related chemicals is not specific enough to distinguish between the ingested agents: all are identified as GHB.
- Available on-line and other information resources that report sanctions of physicians accused of diversion are not used by appropriate parties.
- Legislation has reduced the illicit use of GHB-containing products, however, readily obtained chemicals such as GBL and 1,4BD are increasingly being used as substitutes.
- Further state legislation is needed to apply penalties to the misuse of these substitute sources of GHB.

After identifying these facts and issues, the groups reached these conclusions:

- Xyrem should be made available for patients who need it, but must be handled responsibly by all involved parties.
- A comprehensive approach, involving key stakeholders and partners, is needed to manage the risk that Xyrem could become a source of abused product while allowing access to it by patients whose conditions can be improved by its medicinal properties.
- To reduce the threat to public health posed by illicit GHB, information about GHB must be shared within and among the scientific, medical, and law enforcement communities.

8.1.1.2 Assess Risks/Assess Benefits

The second step in addressing risk management, as described by the FDA Task Force, is to assess the overall benefits and risks of a given medical product. Elsewhere in this document, the medical need for Xyrem is presented, as are data regarding the safety and efficacy of Xyrem.

It should noted that after review of controlled trials assessing Xyrem in narcolepsy patients, the FDA asked Orphan Medical to initiate a Treatment IND. By definition, Treatment IND protocols are granted only when medicines under clinical evaluation treat patient populations whose medical condition is "life threatening or debilitating" and where no acceptable therapeutic alternative exists.

The medical need, efficacy, safety, and Treatment IND information was also shared with the stakeholders and partners that Orphan Medical involved in the development of its risk management approach.

The law enforcement stakeholders involved were initially skeptical about the need for this medication, but, upon learning about narcolepsy and the clinical results of Xyrem, these parties agreed that the therapeutic need for Xyrem was compelling. They continue to be very concerned, of course, about the use of illicit GHB and related chemicals and asked that Orphan Medical address both the potential for inappropriate prescribing of Xyrem and the potential for diversion, two factors which could contribute to the complexity of the illicit GHB drug environment.

Other stakeholders voiced concern about the addictive potential of illicit GHB and related chemicals and whether there is a risk of addiction among narcolepsy patients from their use of Xyrem. Orphan Medical has, and will continue to share, information it has about the abuse or addiction potential of Xyrem. The Abuse Liability and Overdosage section in this document addresses these issues. Orphan Medical has also pledged to assist, where it can, efforts to evaluate the abuse and addictive properties of other GHB related compounds. All of the stakeholders understand that these compounds do not fall under the responsibility of the Company, but that the Company's current and future data may be helpful in efforts to contain the risk presented by these illicit compounds.

All stakeholders agreed that it was important for Orphan Medical to consider risk management solutions that will allow Xyrem to reach the intended population of narcolepsy patients while minimizing the risk that Xyrem may be obtained by those seeking to misuse it.

8.1.1.3 Identify and Analyze Options

Orphan Medical presented to the stakeholders options it could have followed to date, but were dismissed since the options did not combine the goals of providing Xyrem to those who need it, managing risk associated with Xyrem in a responsible manner, and

assisting the stakeholders where possible to reduce the risk of illicit GHB and related chemicals.

Clearly, Orphan Medical could have chosen to ignore risk issues around illicit GHB and related chemicals, and instead focus solely on the medical use of Xyrem. It could have attempted to shift the focus of attention to problems with alcohol, Ecstasy, amphetamines, Rohypnol and other club drugs with greater frequency of use and levels of abuse than GHB. It could have designed its risk management system in a manner that assumes physicians, patients and pharmacists will work together to minimize risks once Xyrem is approved.

Instead, Orphan Medical has invested substantial resources to address issues around Xyrem, and around illicit GHB and related chemicals that are not, strictly speaking, the Company's responsibility. Along with stakeholders and partners, Orphan Medical has pro-actively developed approaches and solutions to these issues. These were arrived at through consideration of possible alternatives available to Orphan Medical, listed below.

8.1.1.3.1 Distribution Options

- Use a traditional pharmaceutical distribution model that relies on current controls to prevent, minimize, and prosecute diversion.
- Establish a specialty distribution model that includes customized controls to meet the needs of the stakeholders.

8.1.1.3.2 Scheduling Timing Options

- Wait for Xyrem approval and scheduling designation at the time of NDA approval, the customary administrative approach.
- Prior to the Xyrem NDA submission, support and move for the legislative scheduling of Xyrem, illicit GHB and related chemicals, which allows greater control over these compounds and allows prosecution of illicit use sooner.

8.1.1.3.3 Scheduling Designation Options

- Support Schedule II designation that allows prescription monitoring and strong penalties for illicit use, but entails a much broader distribution system, thereby creating many more points of potential diversion.
- Support Schedule IV designation that permits use of a centralized mail order-based distribution system serving small patient populations, but offers minimal penalties for illicit use.
- Support Schedule III designation that allows for centralized mail order-based distribution to small patient populations, and offers greater penalties for illicit use.
- Support the HHS recommended "bifurcated schedule" of Schedule I/Schedule III, that allows central, mail order-based distribution to small patient populations, and offers the strongest possible penalties for illicit use.

8.1.1.3.4 Prescribing Options

- A system that allows investigation of inappropriate use/action based on verification and/or identification of:
    - A patient's diagnosis
    - A physician's appropriateness
    - Prescription and dispensing of an appropriate dose
    - Appropriate frequency of prescription
    - Inappropriate use

- A system that relies on state or federal authorities to investigate based on their verification and/or identification of:
    - A patient's diagnosis
    - A physician's appropriateness
    - Prescription and dispensing of an appropriate dose
    - Appropriate frequency of prescription
    - Inappropriate use

- A prescription system that relies on the physician, patient, and pharmacist to oversee verification and/or identification of:
    - A patient's diagnosis
    - A physician's appropriateness
    - Prescription and dispensing of an appropriate dose
    - Appropriate frequency of prescription
    - Inappropriate use

8.1.1.4 Select a Strategy

The fourth step identified by the Task Force in the risk confrontation model is to select a strategy. After much discussion with stakeholders and partners, and consideration of alternatives, Orphan Medical has developed the following risk management strategy. (The key elements of this strategy are in italics.)

8.1.1.4.1 Strategy Selected

Confront issues of risk regarding Xyrem and co-develop risk management solutions with other stakeholders.

Pharmaceutical companies often seek to minimize the perception of risk associated with their products by highlighting problems with other products or allowing risk management of products to be addressed by other stakeholders, such as physicians or pharmacists once the product is commercially available. Orphan Medical concluded this approach was not appropriate for Xyrem.

A closed distribution system has been designed to address risk management of Xyrem. In addition to assigning responsibility for some risk management to the traditional

stakeholders, the system also places more than usual responsibility on the patient, state authorities, and federal authorities.

Assist stakeholders in confronting the risks associated with illicit GHB, and related chemicals.

The risks associated with illicit GHB and related chemicals originate from the distribution of raw chemicals, home-made formulations, and the sales of nutritional supplements and of "reagent kits" over the Internet. Most pharmaceutical companies would refuse help to efforts to curb these risks since there is little that the pharmaceutical company, physicians, and pharmacists can do in regard to illicit GHB. Orphan Medical, however, has pledged its help to efforts to contain the public risk associated with illicit GHB and related chemicals. The Company has shared its data with NIDA, forensic science groups, toxicologists and emergency medicine physicians. Orphan Medical is involved in collaboration and sponsorship of studies relating to abuse pharmacology.

Orphan Medical has tried to set an example of how a company can help advance the science and understanding of an abuse substance and work with physicians, drug abuse specialists, law enforcement and other stake holders to better address risks posed by illicit substances.

8.1.1.4.2 Development Option Selected

Develop Xyrem for a small patient population where adequate therapy does not exist, understanding its importance in that population.

While conventional wisdom in the pharmaceutical industry is to develop a medication for the largest possible indication, Orphan Medical's mission is to develop and market pharmaceuticals of high medical value for patients with rare diseases for which few, or inadequate, therapeutic alternatives exist. Larger pharmaceutical companies typically ignore such diseases and conditions because the potential revenue is inadequate to generate acceptable returns.

Orphan Medical, on the other hand, has conducted trials and collected data that it believes demonstrate Xyrem's safety and efficacy in this small patient population. Xyrem will be marketed only for the approved label claim, with DDMAC (FDA's Division of Drug Marketing, Advertising and Communications) having "jurisdiction" over promotional activities.

8.1.1.4.3 Scheduling Timing Option Selected

Pro-actively support, prior to any approval of Xyrem, the legislative scheduling of GHB compounds, including Xyrem, illicit GHB and related chemicals, to allow greater control and prosecution of misuse.

Traditionally, consideration of a medication's schedule status occurs during the NDA review and its definitive schedule is designated at the time of approval. Due to the

widespread availability of illicit GHB and its growing chemical abuse in the late 1990's, many states began to legislatively schedule GHB. In those states which enacted GHB scheduling initiatives, the "street use" quickly shifted from GHB to GBL, 1,4BD or other related chemicals. Due to the metabolism of these agents in the body to GHB, these agents were used not only to make illicit GHB, but eventually they were simply ingested in order to obtain a "GHB-like" effect. Thus, well-intentioned legislation was ultimately ineffective since it was too narrow and did not also include GHB precursor chemicals.

Orphan Medical, along with stakeholders, concluded it would be in the best interest of the overall risk management of Xyrem to support Federal legislation to schedule GHB and related chemicals. Orphan Medical worked with other interested parties and stakeholders to help obtain legislation as quickly as possible. In early 2000 President Clinton signed into effect PL 106-172, The Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000 (Public Law 106-172).

8.1.1.4.4 Scheduling Designation Option Selected

Support congressional scheduling based on the HHS recommended "bifurcated schedule" of schedule I/schedule III that allows for central, mail order-based distribution of Xyrem to a small patient population, and also provides for the strongest possible penalties for illicit use.

One of the main issues raised by stakeholders was the application of the schedule that would apply the harshest penalties possible for the illicit use of GHB and related chemicals, yet allow access to Xyrem for narcolepsy patients who need it. PL 106-172 followed the recommendations of FDA and as presented to the DEA by the Department of Health and Human Services on May 19, 1999 (Satcher, written communication).

This bifurcated schedule made illicitly used GHB a Schedule I substance and provided Schedule III designation for medicines containing GHB that might be approved by the FDA in the future. It is important to note that the Schedule I provisions apply to approved products if they are used illicitly.

The HSS report, submitted to the DEA by David Satcher, M.D., Ph.D., Assistant Secretary for Health and Surgeon General, is based on a document prepared by FDA's Drug Abuse Evaluation Staff. That document includes an eight-factor analysis regarding the recommended scheduling of Xyrem. The following information is excerpted from that documen (US Department of Justice 1997).

> "GHB products are currently being studied under FDA authorized investigational new drug applications. None of the reports of actual abuse of GHB that support the scheduling recommendation in part I has involved GHB that was diverted from an authorized study. Moreover, given the ease with which GHB can be synthesized from readily available materials, it is considerably less likely that these authorized studies will become a source for unlawful use or abuse of GHB. In essence, the widespread availability of clandestinely produced GHB decreases the

> abuse liability and potential for abuse of the products being studied in authorized research programs and well-supervised clinics. For this reason, a GHB product or substance that is the subject of an authorized protocol and is being studied under a carefully designed research protocol has "low potential for abuse relative to drugs or other substances in schedule III." (Emphasis added.) (see U.S.C. 12 (b)(4)(A)".

8.1.1.4.4.1 Medical Use

Dr. Satcher's report goes on to address the medical use of GHB:

> "A GHB product, however, has recently been granted a protocol under 21 CFR 312.34 to allow for expanded, treatment use of the product in patients who suffer from cataplexy associated with narcolepsy. In this instance the study and development of a GHB product is sufficiently far along to suggest that authorized formulations of GHB may be considered as having a "currently accepted medical use with severe restrictions" under the CSA (see 21 U.S.C. 812 (b)(2)(B); see also 47 FDA 281241, June 29, 1982)".

8.1.1.4.4.2 Physical or Psychological Dependence

Dr. Satcher also states,

> "There is no well-developed evidence from clinical studies to suggest that GHB leads to psychological dependence. The few available anecdotal case reports suggest only mild withdrawal symptoms that may be indicative of 'low risk of physical dependence.' Similarly, from these few anecdotal reports, instances of escalation of GHB dose, increased frequency of use, and continued use despite adverse consequences, are only suggestive of dependence production. There is no evidence to suggest that abuse of GHB leads to 'severe' dependence (see 21 U.S.C. 812 (b)(2)(C)). When compared to substances in Schedules II and III, GHB's physical and psychological dependence producing effects appear to be 'limited' (see 21 U.S.C. 812 (b)(4)(C))."

The Assistant Secretary for Health and Surgeon General concludes:

> "Formulations of GHB currently are being studied under FDA-authorized INDs. At least one sponsor's formulation has been granted Orphan Drug status under section 526 of the Food, Drug, and Cosmetic Act, and is available under a treatment use protocol under 21 CFR 212.34. None of the reports of actual abuse of GHB that support the Schedule I recommendation has involved GHB diverted from an authorized study. Given the ease with which GHB can be synthesized from readily available materials, it is unlikely that authorized studies will become a source of GHB for abuse. Rather, the abuse potential of GHB, when used under an

> authorized research protocol, is consistent with substances typically controlled under Schedule IV. Information on the dependence producing effects of GHB is limited, but can suggest that its potential for physical and psychological dependence is also consistent with control under Schedule IV". (Emphasis added.)
>
> "Authorized formulations of GHB, however, do not meet the 'accepted medical use' criteria set forth in Schedule IV. At best, an authorized formulation of GHB is far enough along in the development process to meet the standard under Schedule II of a drug or substance having a 'currently accepted medical use with severe restrictions.' Under these circumstances, FDA recommends placing authorized formulations of GHB in schedule III, a level of control higher than Schedule IV to take into account the lack of an accepted medical use and a level of control lower than schedule II to take into account the abuse and dependence liability findings for authorized formulations of GHB." (Emphasis added)

Stakeholders, potential specialty medications distribution partners, drug diversion investigators, State Boards of Pharmacy, legal experts and others were consulted on the issue of scheduling. They strongly supported a schedule III designation because it allows for a "closed loop" distribution system. A "closed loop" system provides for the confirmation of the shipment and receipt of medicine. Prescribing information, including frequency and dosing data, can be accessed from a single source. With this system, Xyrem's distribution can be monitored and controlled relatively easily and accurately since product is distributed from a single location, unlike a typical pharmaceutical distribution system that allows for widespread distribution through multiple retail pharmacies.

Such a centralized, mail order-based system is very well suited to minimize diversion and related risk issues. Narcolepsy is limited in its incidence so the number of patients is easily managed. Moreover, since the disease is chronic, prescriptions are repetitive and usage can be monitored for unusual patterns.

In practice, some state pharmacy laws do not allow for mail order distribution of Xyrem. (Mail order is legal, but prescriptions for Schedule II agents have to be submitted in person.) The Schedule III designation was necessary to implement this system of direct-to-patient delivery. The closed distribution system for Xyrem, along with the physician and patient education components of the program, will be addressed at length later in this document.

Another issue addressed in PL 106-172 was the "listing" of the industrial chemical GBL, requiring special reporting by chemical manufacturers. Unfortunately, this legislation did not address other related chemicals. Orphan Medical is actively supporting efforts on a state-by-state basis to include GHB precursor chemicals in various analog and sexual assault statutes[1].

[1] various state analog laws

8.1.1.4.5 Prescribing Options Selected

Confront risk by targeting promotional and selling efforts to those physicians (and physician specialties) identified as most likely to treat narcolepsy patients, and develop a system of responsible distribution that includes physician and patient education programs to help minimize physician off-label prescribing and patient misuse of Xyrem.

Certain stakeholders asked if Orphan Medical could somehow control who prescribes Xyrem, and control how Xyrem is prescribed. Orphan Medical cannot dictate or directly limit who prescribes Xyrem as it does not have accrediting jurisdiction over physicians. Further, it cannot limit the indications for which Xyrem might be prescribed, as this would constitute an imposition on the practice of medicine, for which Orphan Medical is not licensed.

Orphan Medical can, however, attempt to address this issue by prospectively identifying and targeting those physicians and physician specialties most likely to treat narcolepsy. This will be accomplished by utilizing a number of research sources and analyzing selected data. (Note that, because narcolepsy is a rare disease with a small patient population, most research sources provide limited information and/or data. Furthermore, these sources of information and data are highly unreliable because survey sample sizes are small. However, certain assumptions can be made.)

The first source consulted was the American Board of Sleep Medicine (ABSM). This organization issues certificates of special knowledge in sleep medicine to physicians and PhDs in related fields. The knowledge base of sleep medicine is derived from many disciplines, including neuroanatomy, neurophysiology, respiratory physiology, pharmacology, psychology, psychiatry, neurology, general internal medicine, pulmonary medicine, pediatrics, and others. As of February 2001, there were 1,517 professionals identified by ABSM as certified sleep specialists.

According to the American Medical Association (AMA), many clinicians practice sleep medicine under their primary specialty, such as neurology, pulmonology, psychiatry. Sleep medicine, however, is not listed as one of the 24 major board specialties recognized by the AMA, and only 48 physicians within the United States have identified themselves to the AMA as practicing sleep medicine. While this group of physicians is certainly qualified to prescribe Xyrem, it clearly does not treat the entire narcoleptic population.

The National Disease and Therapeutic Index (NDTI), identifies physician specialties that prescribe medications for a given disease. The NDTI data, like the ABSM information, report the involvement of numerous medical specialties in treating narcolepsy. NDTI data for 1999 and 2000 (January-June) identified the following specialties that prescribe medication for patients with a diagnosis of narcolepsy: neurology, pulmonary diseases, psychiatry, family practice, osteopathic medicine, internal medicine, and general practice.

IMS HEALTH Information Services, through its National Prescription Audit information, tracks prescribers of Provigil (modafinil). Since Provigil is indicated for the treatment of daytime sleepiness associated with narcolepsy, it could be presumed that Provigil prescribers are physicians treating narcolepsy patients. Again, it was noted that the number of medical specialties is large; Provigil prescribers are classified as follows: neurology, pulmonary diseases, psychiatry, internal medicine, sleep medicine, and 24 other specialties.

All of these data sources corroborate; that is, physicians who practice sleep medicine, diagnose and treat sleep disorders (narcolepsy, in particular), and prescribe medicines for these disorders fall within a defined range of medical specialties. As part of its marketing strategy, and consistent with its risk management goals, Orphan Medical has identified, within this group of specialties, key physicians on whom to focus initial marketing and sales efforts.

Prior to the launch of Xyrem, these physicians will be checked with the AMA and with the National Prescribers Databank (NPD) to determine if they are medical license holders and further licensed to prescribe controlled substances. Because the NPD is updated quarterly, State Medical Boards will be searched on-line to determine if disciplinary actions have been taken against any of these physicians which have not yet been reported to the NPD database. If any of the physicians has had privileges revoked, the central database will be flagged and the physician will be removed from Orphan Medical's list, with no mailings or detail calls made to them. In addition, the central pharmacy will be instructed not to fill prescriptions received from such physicians. These database checks (AMA, NPD and State Medical Boards available on-line) will periodically occur to ensure that physician eligibility has not changed.

At the launch of Xyrem, each of the key physicians identified by Orphan Medical will receive a traditional "detail call" from an Orphan Medical sales representative. During this call, a Xyrem Physician Success Program℠ will be reviewed with the physician and left behind. This educational program outlines the prescription and distribution process for Xyrem. DDMAC-approved information, regarding the benefits and risks of Xyrem in the intended patient population, will also be provided to these physicians.

Because a single, central pharmacy will handle distribution of Xyrem, as well as its educational materials, it will be possible to keep consolidated records of which physicians and patients have received educational materials on Xyrem. In addition, pharmacy data on prescribing physicians will be collected. It will be the pharmacy's role, not Orphan Medical's, to share with appropriate state and federal authorities the data regarding the prescribing of Xyrem. Available data, including physician name, physician specialty, and frequency of prescribing will assist appropriate authorities in an investigation, should one become necessary. The centralized, real-time nature of these data will allow for rapid identification in the rare case of diversion.

The second issue raised around the risk management of Xyrem is that of "off label" prescribing. It is important to note that an NDA holder has the responsibility to

manufacture and promote a medication consistent with its label claim. All promotions are subject to FDA review, and U.S. laws permit no off-label promotion.

Orphan Medical is a manufacturer and marketer, not a pharmacy or distributor. Orphan Medical will sell Xyrem to the specialty pharmacy, which is then responsible for filling prescriptions according to the laws governing the practice of pharmacy in each state.

According to stakeholders in the areas of pharmacy practice and law, there is no state or federal territory in which confidentiality laws allow for a manufacturer to know the name of a given patient or the dose of a given prescription. Orphan Medical has no legal means to ascertain if a given physician has accurately diagnosed a patient's disease. Nor is the pharmacist in a position to approve or disapprove of the use of Xyrem in a given patient. The practicalities of how prescriptions are filled in the U.S. do not allow for a specialty pharmacy to "police" the practice of medicine by a given physician. The role of the central pharmacist will be to fill the prescription; perform a medication audit to determine what other ethical medications, over the counter products, and nutritional supplements the patient may be taking; and given the doctor-patient-pharmacist relationship, enter into a dialog with the physician about the treatment of a given patient if appropriate.

Fortunately, the current system used in the U.S. for managing the risks associated with controlled substances allows for appropriate stakeholders to police individual physician and patient behavior. The Xyrem system preserves this important feature.

In every state in the U.S., a pharmacy is required by law to cooperate with state and federal authorities, including State Medical Boards, DEA and FDA, in any investigation dealing with physician or patient behavior. The controlled substance tracking system has been designed to provide data on both patient use and physician prescribing of controlled substances.

According to the stakeholders familiar with drug diversion, however, the current systems do not work prospectively; they identify inappropriate use long after it happens. Consider the "patient" who is an abuser, seeking various narcotics. This patient may visit an emergency room one day and be prescribed a narcotic, which is filled at a local pharmacy. This same patient may travel to a neighboring town the next day and be prescribed a second narcotic, which is filled at that local pharmacy. This cycle could be repeated in town after town for a long period of time before triplicate prescription forms identify the situation. If the patient is able to obtain different identification for each visit this activity may never be caught.

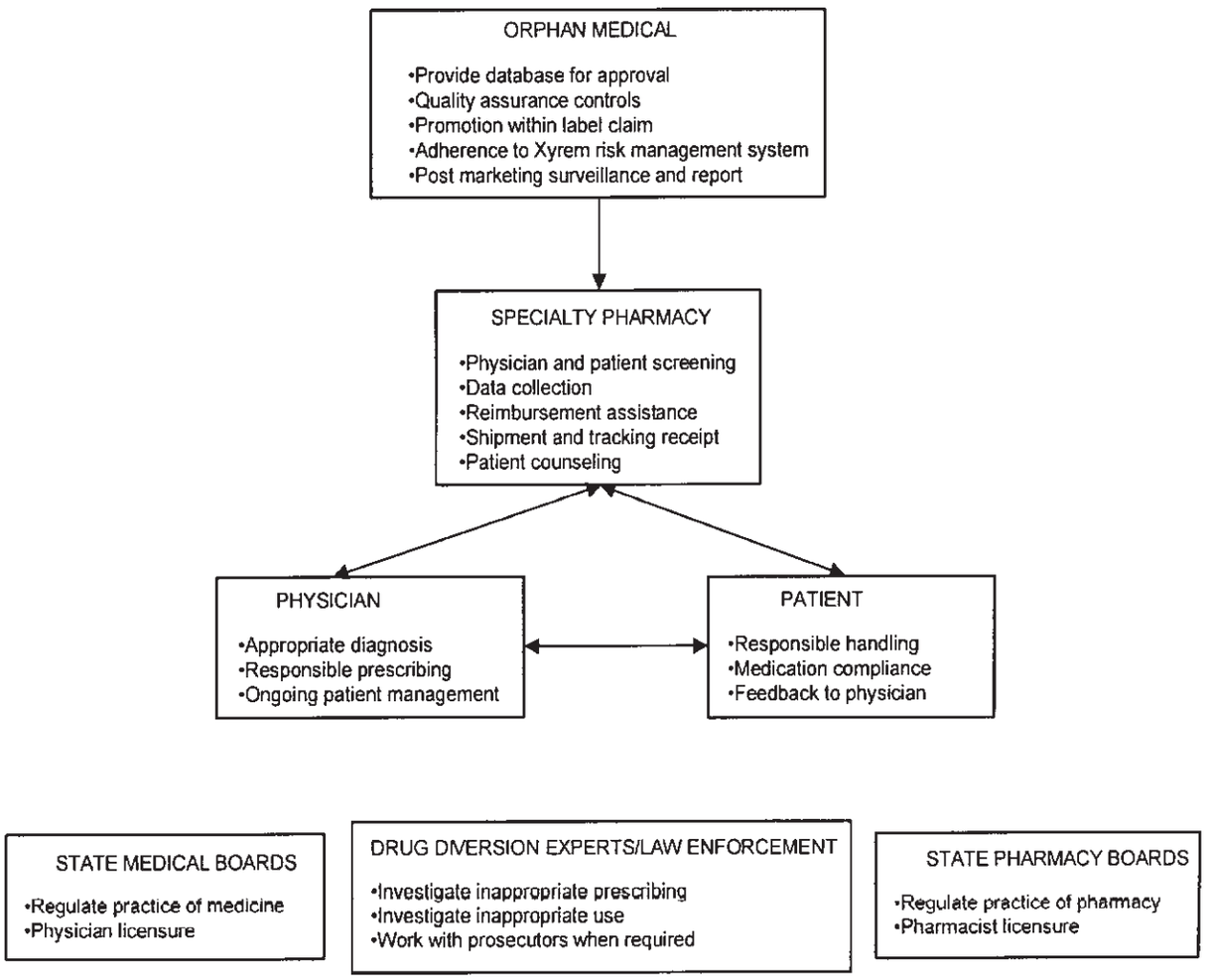
The Xyrem risk management system ensures that the centralized pharmacy will identify patients who are attempting to duplicate prescriptions. All data collected will be available to state and federal authorities, on whatever timeframe they determine to be appropriate. This allows law enforcement agencies to more easily fulfill their responsibility for which they have the training and authority to perform. Incidentally, individuals caught trying to manipulate health care systems for illicit purposes as described above will be subject to Schedule I penalties as outlined in PL 106-172.

This briefing book contains an 8 minute video demonstrating the specific prescription process for Xyrem. Viewing it will aid in understanding the systems Orphan Medical will use to fulfill its stated risk management goals:

- **Make Xyrem available in a responsible manner to patients who need it;**
- **Keep Xyrem out of the hands of those who would use it illicitly; and**
- **Provide responsible assistance to law enforcement investigation and prosecution efforts if illicit use occurs.**

Figure 8.3 describes the roles and responsibilities of each of the involved parties in the Xyrem risk management system.

Figure 8.3. Xyrem: Risk Management Roles and Responsibilities



Stakeholders involved in developing this system strongly support that a risk management system similar to Orphan Medical's be required of any manufacturer who submits an ANDA (generic application) or NDA for any GHB-containing product.

The Xyrem risk management system has been designed to confront risk through responsible distribution as well as through patient and physician education programs. Details of this program follow.

The Xyrem risk management system has been designed with the input of stakeholders to confront and minimize the potential risk of both unintended and intended misuse of Xyrem.

Starting from the Risk Confrontation model outlined by the FDA Task Force, Orphan Medical developed the Xyrem risk management system. It reflects the input and involvement of stakeholders and partners in the identification of risk issues, of potential solutions, and of the final selection of strategies. FDA and DEA input on the program has been sought and has not yet been received.

Bulk drug for Xyrem is manufactured at a single site and it is formulated into finished product at a separate, single site. From there, finished Xyrem is shipped to a central pharmacy.

Each of these facilities meets FDA and DEA requirements for controlled substances: the bulk drug manufacturer meets Schedule I requirements; the drug product manufacturer meets Schedule I and Schedule III requirements; and the central pharmacy is compliant with Schedule III requirements. Each facility is designed to provide secure storage of controlled substances.

Using a central pharmacy is more costly than using conventional distribution channels and systems. Using a single pharmacy also eliminates the opportunity to "fill the retail distribution pipeline." (Generally, pipeline sales of pharmaceuticals are significant, and generate initial sales.) Orphan Medical is foregoing this pipeline opportunity because it feels Xyrem can be better managed through a single pharmacy, rather than on the shelves and loading docks of, perhaps, thousands of pharmacies and distribution centers around the country.

Receiving, storage, and shipping controls are in place to ensure that the amount of Xyrem shipped from the manufacturer is equal to that received at the pharmacy. Discrepancies are investigated and reported appropriately. Xyrem, once received at the specialty pharmacy, goes into a secure holding area dedicated solely to storage of Xyrem and accessible only to authorized employees. Measures such as cages, security alarms, cameras and key cards are used to ensure security. On a weekly basis, the specialty pharmacy determines the amount of Xyrem it is likely to need for fulfillment of prescriptions, and the appropriate amount of product is transferred to "owned inventory".

This is the point at which Xyrem is "sold" by Orphan Medical to the specialty pharmacy. This transfer of ownership allows the specialty pharmacy to collect confidential data such as patient names and medication doses. This is information that Orphan Medical will not have, but the specialty pharmacy can collect because of the doctor/pharmacist/patient relationship.

As was discussed previously, physicians most likely to prescribe Xyrem will be identified and "pre-screened" prior to the launch of Xyrem. When the FDA approves Xyrem, the Xyrem Physician Success Program will be shared with those physicians who have met the screening criteria.

The Xyrem Physician Success Program contains details about Xyrem's unique prescription process, its distribution, the reimbursement program, and physician responsibilities regarding Xyrem. Approximately 25 Orphan Medical sales representatives nationwide will begin making "detail calls" on these physicians. These representatives will have been trained to present efficacy and safety information within the approved label claim as directed by DDMAC. At the first detail call, the sales representative will leave behind the Xyrem Physician Success Program, giving the physician a lasting source of information regarding Xyrem's unique distribution system and special handling process. At no time will samples of Xyrem be carried by sales representatives or left with physicians.

Once a physician decides that Xyrem is appropriate for a given patient, he or she will write a prescription for Xyrem and fax it to the specialty pharmacy. Upon receipt, the specialty pharmacy will verify the physician's eligibility by checking the AMA, DEA, or State Medical Board on-line databases, as previously described. This step will ensure that the prescription was written by a "real" physician with current privileges to prescribe controlled medications.

After physician verification is complete, the specialty pharmacy will contact the physician's office to confirm patient information. By adding this step, the process is likely to "catch" any prescriptions written on stolen or counterfeit prescription pads. During the call, the patient's name, social security number, telephone number and insurance information will also be obtained. The specialty pharmacy will also ask for an assignment of benefits form, so it can work on the patient's behalf to obtain insurance coverage, and for a letter of medical necessity, if it is needed from the insurance company.

While the patient's specific information is needed for insurance purposes, the collection of it by the specialty pharmacy assists in the building of a patient registry which also aids in diversion prevention. The prescribing physician will also be contacted if a prescription appears to be a duplicate or if the dosing frequency appears unusual.

Once the insurance reimbursement is obtained, the Xyrem shipping process begins. The specialty pharmacy will contact the patient to notify him/her of coverage, and arrange a time for a next-day delivery when the patient or his/her designee is to be

present. Xyrem will not be left with anyone other than the patient or the designee (who cannot be a minor), and it will not be left unattended.

Once the shipment designee and time of delivery is determined, the Xyrem prescription and the Patient Success Program℠ is shipped via Federal Express. Federal Express offers real-time tracking so packages can be tracked from point of shipping to point of receipt, and points in-between.

If a shipment becomes lost, the appropriate state/federal authorities will be contacted, and the investigation can begin at the point of loss. If the patient or designee is not available at the location and time designated, the package will not be left on the doorstep, or with a neighbor. Finally, the package will not be returned to the local Federal Express station, but after a same-day redelivery attempt will be returned to the specialty pharmacy.

When the proprietary tracking system shows that the patient has received the shipment, the pharmacist at the specialty pharmacy will contact the patient to:

- confirm receipt of the Xyrem prescription;
- confirm receipt of the Patient Success Program;
- counsel the patient regarding Xyrem administration, dosing and compliance; and
- confirm the patient's understanding of the contents of the Xyrem Patient Success Program and the patient's responsibilities.

This system allows documentation of a patient's receipt of educational materials and communication with the patient about responsibilities and any other matters brought up in the conversation with the pharmacist.

The centrally located, real-time data collected by the specialty pharmacy will be invaluable to the identification of suspicious prescribing or use, and will aid appropriate state and federal investigation and prosecution.

Orphan Medical is grateful for the contributions and efforts of the many stakeholders who have diligently helped identify issues, proposed options, and assisted the company in selecting means to confront and manage the potential risks associated with Xyrem. With their assistance, Orphan Medical has designed a comprehensive system to effectively and responsibly manage risk, while giving narcolepsy patients and their physicians an important medicine to treat this debilitating disease.

SECTION 9
INTEGRATED SUMMARY OF BENEFITS AND RISKS

9.0 INTEGRATED SUMMARY OF BENEFITS AND RISKS

9.1 Background and Rationale for Use of Xyrem® (sodium oxybate) oral solution in the Treatment of Narcolepsy

Narcolepsy is a relatively rare neurologic disease of unknown origin with an incidence of approximately 0.05% (Mignot 1998). It is a debilitating, lifelong disorder following its usual presentation in the second or third decade of life. It is unique in being the only known neurological disorder to specifically affect the generation and organization of sleep (Nishino 1997).

There are currently no therapies approved for the REM related phenomena of narcolepsy, and those currently used clinically (typically the TCA or SSRI antidepressants) are chosen because of REM suppressant properties. This modulation invokes the homeostatic "pressures" to precipitate REM rebound on interruption of therapy, with consequent symptomatic increase in severity, even rarely to status cataplecticus (Scrima 1990, Bassetti 1996). The side effect profile of the tricyclic antidepressants also presents a significant problem. These are mostly due to their anticholinergic effects (dry mouth, tachycardia, urinary retention, constipation, weight gain, blurred vision, sexual dysfunction, tremors) but rarely can extend to severe complications (conduction abnormalities, seizures, exacerbation of glaucoma [Nishino 1997]). The more recent introduction of the selective serotonin reuptake inhibitors (SSRIs) provided a therapeutic alternative to avoid anticholinergic effects, raising the hope of cataplexy control with fewer side effects. In general, however, sleep clinicians have been less impressed with their efficacy in treating the symptoms of narcolepsy.

The mainstay of therapy for excessive daytime sleepiness has been the stimulants, indirect sympathomimetic drugs such as methylphenidate, pemoline, and d-amphetamine that increase the synaptic availability of norepinephrine and dopamine. The rationale for stimulant treatment seeks to maximize alertness at selected times of the day (i.e. work, school, driving) while minimizing side effects and without compromising the potential for satisfactory nocturnal sleep. With all these stimulant agents tolerance develops in up to 30% of cases, more commonly at high doses, and patients may benefit from "drug holidays" of one to two days per week with lower doses or no medication in some patients. The most common side effects include headaches, nervousness, irritability, tremor, insomnia, anorexia, gastrointestinal disturbances and palpitations; however, psychosis, hypertension and myocardial ischemia have been reported (Bassetti 1996). Severe but rare hepatotoxicity is precipitated by pemoline as well.

The recently approved agent, modafinil, is a "wakefulness promoting" agent that is indicated for the treatment of the excessive daytime sleepiness symptoms of narcolepsy. This drug is unrelated both chemically and in its mechanism of action to the other stimulant drugs and has the advantage of an improved side effect profile, as well as less potential for abuse. Its therapeutic response, however, rarely returns the patient to normal values in objective and subjective assessments for daytime sleepiness as was

represented in the randomized blinded trial for modafinil in 283 narcoleptic subjects (U.S. Modafinil in Narcolepsy Multicenter Study Group, 1998).

There is obvious clinical need beyond existing therapies which are clearly divided in efficacy between daytime sleepiness (stimulants and modafinil) and REM suppressant agents (TCAs, SSRIs) that provide limited therapeutic potential for the REM related symptoms of cataplexy, hypnagogic hallucinations, and sleep paralysis for which no approved treatments exist. All have the potential for the development of tolerance as the benefits of treatment wane in time, and although dosage increases provide temporary therapeutic gain, the risk of side effects increases.

Oxybate is a four carbon hydroxy fatty acid that is naturally occurring and widespread in most tissues of the body. Extensive scientific attention has been paid to its central effects and functions. When administered therapeutically as the sodium salt, it is a neuroactive drug with specific effects on sleep architecture. It has been shown to increase slow wave non-rapid eye movement (nonREM or NREM) sleep, with no suppression of rapid eye movement (REM) sleep, and to decrease REM latency (Mamelak 1997, Lapierre 1990).

The unique beneficial effects of sodium oxybate treatment in narcoleptic patients with cataplexy have been previously reported from several open-label, uncontrolled clinical studies (Broughton 1979, Broughton 1980, Scharf 1985, Mamelak 1986, Montplasir 1986). For example, Scharf and colleagues (1985) treated 30 narcoleptic patients for 4 to 30 weeks with average nightly doses of 5 to 7 grams. They reported significant decreases from baseline in the frequency of cataplexy attacks, daytime sleep attacks, hypnagogic hallucinations and sleep paralysis. In addition, sodium oxybate has been shown to produce marked improvement in nocturnal sleep disturbance in narcoleptic patients, with EEG findings supported by subjective improvement (Broughton 1980, Scharf 1985, Montplaisir 1986).

Narcolepsy is a relatively rare disease affecting approximately 0.05% of the general adult population of the United States and in various European countries (Nishino 1997). Review of its prevalence has resulted in Orphan Drug designation by the FDA. This 0.05% prevalence has limited the size of the clinical trial database in the development of Xyrem, along with further patient limitation by the required entry criterion of cataplexy. Whereas excessive daytime sleepiness with sleep attacks affects 100% of narcoleptics, the REM-related symptoms occur with lesser frequency (cataplexy 60-90%, hypnagogic hallucinations and sleep paralysis 30-60% of narcoleptics, as reported by Mitler, 1997).

9.2 Benefits of Xyrem (sodium oxybate) oral solution

The effectiveness of Xyrem in the treatment of narcolepsy has been documented in this application by three basic methods: (1) by patient daily diary records of the occurrence of narcolepsy symptoms along with patient self-rating of daytime sleepiness [e.g., the validated Epworth Sleepiness Scale] (2) by principal investigator rating of overall clinical improvement [e.g., the Clinical Global Impression of Change Rating] and (3) by objective recording of changes in sleep architecture [e.g., overnight PSG,MWT and MSLT].

Taken together these well-established methods have been utilized in four adequate and well-controlled trials (OMC-GHB-2,OMC-SXB-21, Scrima and Lammers) and in one long-term supportive trial (OMC-GHB-3) to validate the benefits of Xyrem in treating the symptoms of narcolepsy. Table 9.1 summarizes the statistical evidence that supports this statement.

9.2.1 CATAPLEXY

Statistical evidence of the reduction in cataplexy incidence has been established in two pivotal trials, OMC-GHB-2, and Scrima.

In OMC-GHB-2, patients represented the broad spectrum of disease severity, with cataplexy ranging in incidence from 2.8/week up to 250/week, but the severity at baseline was well balanced and not statistically different between groups, averaging approximately 34/week. Because of this wide spread and skewed distribution, log transformation was performed when data failed to show normal distribution according to the Wilks-Shapiro Test. Thus, group data are represented as medians rather than the more common means. The median number of cataplexy attacks was approximately 22 per week at the start of double-blind drug treatment in OMC-GHB-2. Therefore, the patients in this trial had moderate to severe cataplexy.

A significant dose-related reduction in the overall occurrence of cataplexy attacks per week is clearly shown in Table 9.1. Statistical reduction relative to baseline was demonstrated across all treatment groups (P=0.0021), but comparison to placebo showed clear efficacy at the 6 g (P=0.0529) and 9 g (P=0.0008) doses. The majority of reduction occurs in the first two weeks of treatment, but response does not maximize in this four-week treatment period.

Another secondary clinical benefit of Xyrem is demonstrated by the data derived from the abrupt cessation of drug after the 4-week treatment period in the OMC-GHB-2 trial. An expected increase in cataplexy incidence followed, showing regression toward, but not exceeding, baseline levels. This lack of acute rebound cataplexy, as occurs with abrupt cessation of tricyclic antidepressants, (described as a consequence of the homeostatic "REM pressure"), separates Xyrem from the medications currently used.

With respect to the Scrima study, the results in Table 9.1 again indicate an appreciable placebo effect in the reduction of the incidence of cataplexy, but this did not reach statistical significance (P=0.117). In contrast, the change from baseline to endpoint for patients receiving 50 mg/kg sodium oxybate (average dose 4.2 g/d) was significant (P=0.007). There were significantly fewer cataplexy attacks/day during sodium oxybate treatment overall compared to placebo (P=0.013) with significant differences at week 3 (P=0.005) and week 4 (P=0.004).

In the Lammers randomized crossover trial in 25 narcoleptics, patients were administered 60 mg/kg/day (average dose 4.7 g/d) or placebo for four weeks, separated by a four-week washout period. This study differs from the previous two in that sodium oxybate treatment was added to existing medications, including anti-cataplectic therapy

in some patients, for an incremental treatment response. Most importantly and in contrast to the patient populations in the OMC-GHB-2 and Scrima trials, the narcoleptic patients in this study presented a much lower cataplexy incidence at baseline (median 5/week). Thus, the Lammers trial represents narcoleptics with relatively mild cataplexy. As reported in the publication of these data (Lammers 1993), the change in cataplexy incidence over the four-week treatment period failed to reach statistical significance but showed a strong trend in favor of the active drug treatment.

The analysis of the published data discussed above employed a non-parametric statistical model that treated each of the two drug administration periods as though they comprised two independent patient samples. When those data were reanalyzed by Orphan Medical using a statistical model more appropriate to a crossover design (ANCOVA) that included treatment order, period, and baseline cataplexy rate, the difference between placebo and oxybate treatment periods was found to be statistically significant (P=0.002).

Strong additional support for the efficacy of Xyrem in cataplexy reduction comes from the GHB-3 open-label extension study, in which 117 patients from the GHB-2 entered a long term open label study, during which daily diary recording of symptoms provided opportunity for longer term efficacy analysis. Patients entered the treatment phase at the 6 g dose, and titrated to clinical efficacy at doses between 3-9 grams. This prolonged treatment period indicated a further marked reduction in cataplexy incidence, with maximal reduction achieved after eight weeks of treatment in OMC-GHB-3, and maintained reduction over the remainder of the twelve-month period. There was no difference in dose response across all doses when expressed as median percentage change from baseline, confirming the appropriateness of the available dose range to optimize clinical response.

In OMC-SXB-21 study, the long-term efficacy of Xyrem was demonstrated in patients who had received treatment with Xyrem for 6 months to 4 years by the return of cataplexy when randomized in blinded fashion to placebo, compared to the blinded continuation of treatment. No change was seen in the incidence of cataplexy attacks in the Xyrem group (median change 0.0 each week), while cataplexy attacks increased in the placebo group by a median of 4.2 in week 1, and 11.7 in week 2. The overall median increase in cataplexy in the blinded study period was 0.0 in the Xyrem group, and 21 in the placebo group. These data strongly support the long-term efficacy of Xyrem in the control of cataplexy in narcolepsy.

In a six-month safety study conducted under the Treatment IND in 185 patients (OMC-SXB-6), treatment with Xyrem was initiated at a 4.5 g nightly dose, added to any existing medications for narcolepsy. This protocol recommended dose titration between 3-9 g/day in 1.5 g increments to optimize clinical response as recorded in a Narcolepsy Symptom Questionnaire. Withdrawal of concomitant anti-cataplectic medications (TCAs or SSRIs) was encouraged once stable Xyrem dosage was reached, unless antidepressant medication was required for treatment of depression. This study established that at stable doses of Xyrem that produce clinical response, the side effect profile does not change when treatment is initiated as concomitant medication, and that

the REM-suppressant antidepressants can be safely and effectively discontinued or decreased in dosage without an increase in the frequency of cataplexy, or the precipitation of rebound cataplexy.

Table 9.1. Summary of Outcomes in Clinical Trials Supporting the Efficacy of Sodium Oxybate

Trial[a]/ Dosage Group (n)	Baseline	Endpoint	Comparison to Placebo *P*-value
Cataplexy Attacks			
OMC-GHB-2 (median attacks/wk; n = 130)			
Placebo (33)	20.5	16.3	—
3.0 g/d (33)	20.0	9.5	NS
6.0 g/d (31)	23.0	8.0	0.0529
9.0 g/d (33)	23.5	8.7	**0.0008**
Scrima (mean attacks/wk — daily x 7)			
Placebo (18/19)	20.3	13.3	—
4.2 g/d (18/19)	20.3	8.4	**0.013**
Lammers (median attacks/wk — daily x 7)			
Placebo (24)	5.5	3.0	—
4.7 g/d (24)	4.0	1.5	NS **(0.002)**[b]
OMC-GHB-3 (median attacks/wk — endpoint = 12 months)			
3.0 g/d (7)	32.85	2.13	**0.016***
4.5 g/d (9)	13.50	0.88	**0.004***
6.0 g/d (24)	23.25	0.55	**< 0.001***
7.5 g/d (14)	33.50	2.76	**< 0.001***
9.0 g/d (21)	34.50	2.67	**< 0.001***
Daytime Sleepiness			
OMC-GHB-2 — Epworth Sleepiness Scale Range 0 to 24 (median)			
Placebo (33)	19.0	17.0	—
3.0 g/d (31)	17.0	16.0	NS
6.0 g/d (30)	17.0	13.5	NS
9.0 g/d (28)	17.0	12.0	**0.0001**
Scrima — MSLT Sleepiness Index: abnormal > 75, borderline 50 to 75, normal < 50 (mean)			
Placebo (20)	88.5	89.6	—
4.2 g/d (20)	88.5	85.8	NS
Lammers — patient rating of severity 0 = no sleepiness, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe (median)			
Placebo (24)	1.50	1.57	—
4.7 g/d (24)	1.67	1.16	**0.028 (0.034)**[b]

(continued)

Table 9.1. Summary of Outcomes in Clinical Trials Supporting the Efficacy of Sodium Oxybate

Trial[a]/ Dosage Group (n)	Baseline	Endpoint	Comparison to Placebo *P*-value
Daytime Sleepiness (continued)			
OMC-GHB-3 Epworth Sleepiness Scale Range 0 to 24 (median — endpoint = 12 months)			
3.0 g/d (7)	17.00	13.00	**0.019***
4.5 g/d (9)	19.00	15.00	**0.005***
6.0 g/d (24)	16.50	12.00	**< 0.001***
7.5 g/d (14)	18.00	11.50	**< 0.001***
9.0 g/d (20)	17.50	13.00	**< 0.001***
Inadvertent Naps/Sleep Attacks[c]			
OMC-GHB-2 (median naps/attacks/day)			
Placebo (33)	1.50	1.07	—
3.0 g/d (33)	1.93	1.14	NS
6.0 g/d (31)	1.45	0.92	**0.0497**
9.0 g/d (33)	1.27	0.50	**0.0122**
Scrima (mean sleep attacks/day)			
Placebo (17)	2.8	2.1	—
4.2 g/d (17)	2.8	1.9	NS
Lammers (median sleep attacks/day)			
Placebo (24)	1.83	2.14	—
4.7 g/d (24)	2.17	1.36	**0.001 (<0.001)[b]**
Number of Awakenings/Night[c]			
OMC-GHB-2 (median)			
Placebo (33)	2.05	2.14	—
3.0 g/d (33)	2.88	2.57	NS
6.0 g/d (31)	2.93	2.57	NS
9.0 g/d (33)	2.89	2.18	**0.0035**
Scrima (mean)			
Placebo (17)	3.0	3.7	—
4.2 g/d (17)	3.0	2.4	**0.042**
Lammers (median)			
Placebo (24)	2.71	3.31	—
4.7 g/d (24)	3.39	2.00	**NS (0.011)[b]**

(continued)

Table 9.1. Summary of Outcomes in Clinical Trials Supporting the Efficacy of Sodium Oxybate

Trial[a]/ Dosage Group (n)	Baseline	Endpoint	Comparison to Placebo *P*-value
Clinical Global Measures of Change[d]			
Trial	**Non-Responders[e]**	**Responders[f]**	**Comparison to Placebo p-value**
OMC-GHB-2 – Investigator's Clinical Global Impression of Change in Severity			
Placebo (34)	23 (68%)	11 (32%)	—
3.0 g/d (30)	16 (53%)	14 (47%)	NS
6.0 g/d (31)	15 (48%)	16 (52%)	NS
9.0 g/d (30)	6 (20%)	24 (80%)	**0.0002**
Lammers — Patient's Global Therapeutic Impression of Change			
Placebo (24)	22 (92%)	2 (8%)	—
4.7 g/d (24)	9 (38%)	15 (63%)	**<0.001 (<0.001)[b]**
OMC-GHB-3 Investigator's Clinical Global Impression of Change in Severity			
3.0 g/d (7)	1 (14%)	6 (86%)	—
4.5 g/d (8)	1 (13%)	7 (88%)	—
6.0 g/d (24)	1 (4%)	23 (96%)	—
7.5 g/d (14)	1 (7%)	13 (93%)	—
9.0 g/d (21)	3 (14%)	18 (86%)	—

[a] OMC-SXB-6 did not measure change from baseline numerically and is not included in this presentation.

[b] *P*-value reported by Lammers (1993) followed in parentheses by *P*-value obtained by reanalysis of data by Orphan Medical, Inc. using ANCOVA.

[c] OMC-GHB-3 did not present number of naps/sleep attacks/week or number of awakenings/night.

[d] Scrima did not have a clinical global measurement of change and is not included in this presentation.

[e] Non-responders in OMC-GHB-2 and OMC-GHB-3 = "minimally improved," "no change," "minimally changed," and "much worse"; in Lammers = "no beneficial effect."

[f] Responders in OMC-GHB-2 and OMC-GHB-3 = "very much improved" and "much improved"; in Lammers = "beneficial effect."

* Comparison of endpoint to baseline for open-label trials only; double-blind placebo-controlled trials comparison is oxybate-treated vs placebo.

Epworth Sleepiness Scale measures sleep propensity based on the retrospective report of the subject's dosing behavior in 8 everyday situations.

— = not applicable. MSLT = multiple sleep latency test. NS = not statistically significant, $p > 0.05$.

Data Source: Trial reports: OMC-GHB-2 — in-text Tables 10, 12, 13 and Summary Tables 20 and 22; Scrima — Tables 6A, 7A, 8A, 23; Lammers — 14a, 16a, 18a; OMC-GHB-3 — Tables 10, 16, 23. Publication: Lammers 1993.

9.2.2 EXCESSIVE DAYTIME SLEEPINESS

The measures employed to monitor excessive daytime sleepiness (EDS) in the Orphan-sponsored clinical development program have been the validated and widely-used patient representation of daytime feeling of somnolence, the Epworth Sleepiness Scale (ESS) and patient recordings in daily diaries of the number of inadvertent naps or sleep attacks occurring each day during daytime.

In the blinded, randomized study in 136 patients (OMC-GHB-2), there was again a clear dose-related ESS decrease across the three doses studied, with this change reaching statistical significance (P=0.0001) in patients in the 9 g/day dose group compared to placebo response. These data represent three important considerations: First, stimulant medication was held constant throughout this trial, so the change in daily feelings of somnolence was incremental beyond that of maintenance stimulant medication. Second, in spite of the continued stimulant therapy, the baseline measure in all groups showed severe subjective sleepiness (mean ESS score of approximately 17, maximum ESS score=24) indicating a real need for additional therapeutic options in the treatment of daytime sleepiness. Lastly, this incremental improvement has been sufficient to improve some patients in all three treatment groups to a reduced ESS score no longer in the defined range for narcolepsy (13 to 24). Approximately one quarter of the patients in the 9 g/day dosage group achieved Epworth scores in the normal range ($\leq$ 10).

The second component of daytime sleepiness, the number of inadvertent sleep attacks during the day, were also significantly reduced versus placebo at the 6 g/day dose (P=0.0497) and the 9 g/day dose (P=0.0122).

In OMC-SXB-20, the objective measure of Maximal Wakefulness Test (MWT) was employed on the day following overnight polysomnographic recording. This study was primarily conducted to define the dose-related EEG characteristics of Xyrem, but again supported the efficacy of Xyrem to reduce the symptom of daytime sleepiness by the objective measure of increased sleep latency under standardized soporific conditions. The mean (SD) sleep latency time in minutes increased from 4.5 (6.01) minutes at baseline by 3.7 (7.68) minutes after 4 weeks of 4.5g/day dosing, and by 6.1 (6.82) minutes at the 9g/day dose. Both of these changes were statistically significant, and represent incremental increases beyond the effects of maintained stimulant therapy.

In the Scrima trial, efficacy measures for excessive daytime sleepiness included the objective measure of Multiple Sleep Latency Test (MSLT) and the number of daytime sleep attacks. In this small group of twenty patients, statistically significant changes were not observed although both measures showed a positive trend with respect to oxybate.

In the Lammers Study, a patient assessment of sleepiness during the day was recorded on a 5-point scale in daily diaries. This measure showed significant improvement in the oxybate treatment phase (P=0.028) compared to placebo. Daytime sleep attacks were

again significantly reduced (*P*=0.001) further confirming efficacy at this dose of 60 mg/kg (average actual dose = 4.7 g/d).

In the OMC-GHB-3 follow-on study in 117 patients continuing from OMC-GHB-2, the subjective assessment of somnolence represented by the Epworth Sleepiness Scale mirrored the changes seen in cataplexy, with maximal changes across all doses seen after eight weeks of treatment, and then sustained across the 12 months of treatment. This sustained response strongly supports this parameter as a representation of pharmacodynamic significance, since one would certainly expect subjective measures of less significance to regress toward baseline over such a prolonged time course. Because the patients were titrated to clinical effect, no significant differences were seen amongst the dose groups from 3 to 9 g/day.

9.2.3 OTHER SYMPTOMATIC BENEFITS

Sleep paralysis was recorded in relatively low incidence in all controlled trials, so no meaningful analysis was feasible. In both the Lammers and Scrima trials, hypnagogic hallucinations were reduced in a statistically significant manner (p=0.008 in both trials). In the OMC-GHB-2 & 3 studies, a consistent trend in the reduction of hypnagogic hallucinations was seen that did not reach a level of significance.

9.2.3.1 Clinical Global Improvement

Finally, in OMC-GHB-2 and in the Lammers study, the clear clinical benefit of Xyrem therapy in narcolepsy was confirmed by two measures of overall assessment, one by the clinician and the second by the patient. In OMC-GHB-2 the Clinical Global Impression of Change (CGIc) was the instrument used by the clinical investigator to assess the overall change in disease severity at the end of the blinded four-week treatment period compared to an assessment of disease severity recorded at the end of baseline. The change in status utilized a standard seven-point rating scale from "very much worse" to "very much improved". Based on the CGIc rating, only patients rated as "very much improved" or "much improved" were classified as responders, with all other classifications grouped as non-responders. A clear dose response was seen for this parameter with a 32% responder rate for placebo-treated patients, 47% and 52% in the 3 g and 6 g groups, respectively, and an 80% responder rate for patients in the 9 g high dose Xyrem group. Only the 9 g group responder rate was statistically significantly different from the placebo group (*P*=0.0002).

In addition, this same CGIc rating instrument was continued through to the twelve-month assessment in OMC-GHB-3. Even though this was an open-label study, there was a clear indication of high responder rates across all doses, sustained over time, when Xyrem was titrated to optimal clinical effect.

A different means of assessing overall dinical response was used in the Lammers crossover study, where the patient's opinion on the overall benefit of the double-blind medication was recorded (as a dichotomous Global Therapeutic Impression: "beneficial effect" versus "no beneficial effect") at the end of each four-week treatment period.

Sixty-four percent of the patients (16 of 25) reported overall beneficial effect following sodium oxybate treatment. In comparison, after placebo treatment, only 8% reported beneficial effect (2 of 25). This difference was highly significant (*P*=0.001).

9.2.4 BENEFICIAL CHANGES IN SLEEP ARCHITECTURE

Pre- and post-treatment polysomnogram (PSG) analyses were not included in the OMC-GHB-2 trial but were a part of both the Scrima and Lammers trials. Orphan Medical did not have access to the Lammers PSG raw data and, therefore, was not able to include the PSG data in the full clinical report in this application. Thus, the statements below regarding Lammers' findings with respect to PSG-based sleep architecture are based solely upon his published paper (Lammers 1993).

In the Scrima trial, polysomnographic recordings at the end of baseline and again at the end of the active and placebo treatment periods yielded very useful objective data regarding the beneficial effects of sodium oxybate on sleep architecture. Sleep consolidation was confirmed by enhancement of both the depth (increased slow wave sleep) and continuity of sleep. Compared to placebo, treatment with sodium oxybate increased slow wave sleep (especially Stage 3) with a correspondingly significant decrease in light (Stage 1) sleep. The number of objectively measured awakenings decreased significantly (*P*=0.042). This enhanced sleep continuity was supported by the significant reduction in stage shifts associated with oxybate treatment. Lastly, oxybate did not suppress REM sleep, a characteristic of other hypnotic drugs such as the benzodiazepines.

In the OMC-SXB-20 study, overnight polysomnographic studies demonstrated the dose-related effects on sleep architecture. There was the characteristic increase in slow-wave sleep (Stage 3 & 4) across all four doses, reaching significance at the 9.0 g/night dose, and a reduction in Stage 1 sleep. Delta power, a derived index of all slow wave signals, showed a dose related increase that was highly significant on the first night of dosing at 4.5 g as well as after 2 weeks of dosing at 6 g, 7.5 g and 9 g/night. A dose-related decrease in the number of nocturnal awakenings was recorded, which was significant at the 7.5 g and 9.0 g/night Xyrem doses.

Unlike previous studies, a decrease in total REM sleep duration at all 4 doses followed an initial acute increase at 4.5 g dosing. No significant change in REM latency was observed.

A decreasing trend in the number of shifts in sleep stages was seen, but total sleep time and time awake after sleep onset did not change.

In the publication of the Lammers trial, several effects of sodium oxybate on PSG sleep parameters were reported (Lammers 1993). Compared to placebo, sodium oxybate significantly reduced the number of awakenings from, and the percentage of wakefulness during, REM sleep. During oxybate treatment the amount of nocturnal slow wave sleep also was increased considerably and to a significant degree (*P*=0.053). Other PSG parameters were not significantly altered by oxybate treatment.

These sleep EEG effects are consistent with and supportive of the open-label published trials previously discussed at the beginning of this section.

9.3 Observed and Potential Risks of Xyrem® (sodium oxybate) oral solution

9.3.1 SAFETY

9.3.1.1 Adverse Event Profile

The overall safety profile of sodium oxybate during the controlled, double-blind and open-label trials in narcolepsy has been favorable, with most adverse events reported as mild to moderate in severity, and not considered to be serious. The most frequently reported adverse events included headache, nausea, dizziness and pain (without causality association). When the occurrence of adverse events was considered in terms of dose at onset of the event, there were no apparent differences across the proposed therapeutic dosage range from 3 to 9 grams per day.

There are 181 patients included in the three randomized, blinded, controlled trials. OMC-GHB-2 is the largest parallel design trial of 136 patients and patients were assigned to the treatment groups of 3 g, 6 g, 9 g or placebo in blinded fashion, without regard for physical characteristics or disease severity, and, as in proposed clinical practice, without any dose titration. One hundred of the patients reported one or more adverse events during the treatment period. Many occurred within the first few days of initiation of double-blind medication and were not reported again during the study period. The adverse events that suggested a dose relationship included nausea, vomiting (only reported in the 6 and 9 g dose groups), dizziness, and enuresis. Although not statistically dose-related, headache was a prominent adverse event (induding the placebo group). Enuresis is of special interest, since this and, more rarely, somnambulance (sleepwalking) have been uniquely associated with sodium oxybate therapy.

In the Scrima Trial of crossover design, 20 patients received 50 mg/kg and placebo in divided dose at night for 29 days. In general, most adverse events occurred either with similar frequency during placebo and oxybate treatment or only once during the trial with the exception of dizziness (four events on active treatment, none with placebo). The most common events with oxybate were headache (n=5), dizziness (n=4), nervousness (n=3), and somnolence (n=3). Most events were of mild severity, with no deaths or discontinuations, or serious adverse events.

In the Lammers Study of crossover design, 25 patients received active drug treatment in a nightly divided dose of 60 mg/kg for 28 days. Sodium oxybate was well tolerated with adverse events few in number and mild in severity, with only 3 of 6 events occurring during active drug therapy.

In the uncontrolled extension trial, OMC-GHB-3 patients could continue the study for up to 24 months. This was analyzed in detail for the 12-month duration as in the initial

protocol and, in summary, from up to 18 and 24 months. Patients entered the study at the 6 g dose and were titrated to clinical efficacy at doses between 3 g and 9 g, with dose titration generally achieved in 2 to 5 weeks. By the end of the trial, >75% of patients had titrated to dosages between 6 g/d and 9 g/d, while stimulant medication dosage was maintained.

Of the 117 patients receiving drug, 109 reported any adverse event in the first 12-month treatment period. The most common events were headache (33.3%), nausea (28.2%), viral infection (27.4%), dizziness (26.5%), pain (25.6%) and somnolence (19.7%). Of these events, only dizziness occurred across treatment groups at a statistically significant level (P=0.015), but was not a dose-related event, since most events occurred in the lower dose groups. Weight decrease occurred in five patients (3 in 7.5 g group, 2 in 9 g group).

In the second 12 months of the study (to two years exposure), no additional patients experienced adverse events.

Overall, a positive safety profile of long-term Xyrem administration was observed. Adverse events appeared to initiate within the first 12 months of drug exposure, and the great majority (> 90%) were classified by the investigators as mild or moderate. There was no dose relationship for severity.

In the OMC-SXB-6 Treatment IND Protocol, 185 patients enrolled, and started Xyrem at 4.5 g in divided dose at night as additional therapy for narcolepsy. Dose was titrated to optimize clinical response with the option to gradually withdraw TCAs or SRIs, while maintaining stimulant medication constant. The majority of patients (70%) were receiving doses $\geq$ 6 g/d by the time of their last observation. In this trial 144/185 (78%) of patients reported adverse events over the 6-month treatment period and these were rated as mild to moderate in 114 patients (62%) and severe in 30 patients (16%), with possible association with drug rated in 53% of patients overall.

There were no apparent dose related trends for adverse events. Most frequently reported over the 6-month period were headache (22%), nausea (16%), pharyngitis (11%) and sleep disorder (10%). Six patients reported an event coded in the COSTART dictionary as "convulsion", but all of these were cataplexy events and, therefore, part of the disease symptomology. Weight variation was reported in 5 patients, 3 with weight increase and 2 with weight loss.

Of the adverse events that occurred with a frequency of $\geq$ 5% overall or in any one-dose group, only headache (6 patients) was classified as severe in $\geq$ 3 patients for the overall population. There was no apparent dose-relationship for severity.

Of the adverse events classified as "sleep disorder" the majority were at 4.5 to 6 g dosage at onset, and mostly represented somnambulism (sleep walking), with 12 patients reporting 13 episodes, and 2 reporting somniloquence (sleep talking).

Thirteen patients reported urinary incontinence, all as single episodes except for 1 patient (2 episodes) and all representing enuresis except for 2 reports that were unclassified in terms of temporal diurnal relationship.

The longer-term treatment IND study (OMC-SXB-7) into which patients transferred from previous trials (OMC-GHB-3, OMC- SXB-6, or Scharf IND patients) provides longer-term evidence of safety. Patients entering this trial had previously received sodium oxybate for up to 2 years in GHB-3, for 6 months in OMC-SXB-6, or for up to 16 years under the Scharf IND. Of the 145 patients enrolled in this trial to the date of interim cut-off of December 31, 1999, 44 (30%) had 1 or more adverse events, with 7 (5%) reporting severe adverse events, but only 13 (9%) having adverse events considered possibly related to trial medication. Two patients reported serious adverse events, one leading to patient discontinuation, and no deaths occurred.

The same profile of adverse events was seen in this trial with the most common adverse events reported as nausea (4%), sleepwalking, vomiting, back pain and pain (each 2%). The majority of reported adverse events were classified by the investigator as mild (45%) or moderate (39%). Again, there was no dose relationship in the severity of adverse events.

9.3.1.2 Scharf Report

Orphan Medical was aware of the long experience of Martin Scharf, PhD, Cincinnati, in the use of sodium oxybate. He treated 143 patients with the drug during a period of over 16 years under his Investigator IND. Orphan Medical was granted access to this database by Dr. Scharf and we have included this data to provide a profile of long-term clinical experience with sodium oxybate. This data was collected by the site more in the form of clinical records than as drug development research and, hence, there exists some compromise in interpretation (i.e. laboratory measures were generated from many different laboratories, dose titration extended to as high as 12.5 g/day [greater than 9 g in four patients]), but this data does provide useful experience in long-term treatment exposure. The exposure to drug includes 121 patients with data $\geq$ 6 months, 104 for $\geq$ one year, 74 $\geq$ 5 years and 46 $\geq$ 10 years.

During the study, any adverse event was reported by 136 (95.1%) patients, with a higher evidence of reporting in the first 6 months (87.4%) than in the remaining treatment period (77.6%). This suggests that long-term exposure to sodium oxybate is not associated with higher levels of adverse events.

Many of the adverse events were those expected as a temporal relationship with a long-term clinical study, the most common being associated with frequent symptomology (flu syndrome, headache, viral infection, accidental injury, pain, nausea, pharyngitis and rhinitis). For the entire study, 44% of the adverse events occurred in only 1 or 2 patients and, hence, does not support a strong association with sodium oxybate.

Many of the frequent adverse events were judged not related to study medication by the investigator. In the first 6-month treatment period, the reports of dizziness and nausea

were frequently assigned as related (8.4% and 5.6%, respectively). All instances of sleep disorders (9.1%), mainly somnambulism, were considered related to treatment. When this time period is compared to the similar time period in the long-term studies conducted by Orphan Medical to create accurate comparative temporal relationship, the adverse event profile was very similar in incidence and profile.

For the continued long-term treatment period beyond 6 months, all instances of sleep disorders [40, (28%)] and urinary incontinence [31, (21.7%)] were considered treatment related.

The term "convulsions" was used to code events reported in 9 patients, but 5 of the 9 patients had events that were more appropriately coded as "cataplexy", and, therefore, symptomatic of the primary disease of narcolepsy. Four patients had events that were correctly coded as convulsions. At least one of these patients had a history of seizures prior to oxybate treatment and one patient had a known intracranial lesion. There was no dose response relationship evident.

In 1991, a 49-year old female patient in the study developed clinical symptoms of arthritis, after treatment with sodium oxybate continuously for over 5 years at an average nightly dose of 6 g. An anti-nuclear antibody (ANA) test and two repeat tests were all positive raising concern for the possibility of drug-related lupus. She was withdrawn from the drug with a subsequent fall in ANA titers, followed by an increase again 1 year later.

At this time, Dr. Scharf began to collect ANA profiles on all patients active in the ongoing study. Over the next 2 years, 19 of 65 patients were shown to have ANA elevations ranging from 1:40 to 1:2560. Some of these elevations were intermittent and no correlation was found between ANA titer positivity and duration of oxybate treatment, age or gender. Antihistone antibodies were also determined for 15 of the 19 ANA-positive patients. Only 1 patient showed a "borderline" positive result.

These data indicate that long-term use of sodium oxybate may result in elevations in ANA antigen profiles without the corresponding increase in antihistone antigens that is characteristic of most reported cases of drug-induced lupus. Secondly, narcoleptic patients with positive ANA findings did not present or subsequently develop symptoms suggestive of lupus-related disease. Lastly, no patients in the Scharf long-term study have developed systemic lupus erythematosus during treatment with sodium oxybate for over 16 years.

9.3.1.3 Clinical Laboratory Test Evaluations

In consideration of blood chemistry values in the five clinical trials discussed, mean changes for all parameters were small and similar across all 5 doses of sodium oxybate and placebo. Similar observations were made for hematology values, where changes were again small and similar across all 6 treatment groups.

A slight increase in urinary pH was seen in OMC-GHB-2, where this change was postulated to relate to the urinary excretion of the sodium load sourced from Xyrem (in this sodium salt, 18.23% by weight of each dose is sodium).

When considering specific values, shifts from baseline to last observation occurred in ≥ 10% of patients for calcium and total bilirubin. A shift from normal to low calcium was seen in 14 of 132 patients in whom this was measured over 1 year as in OMC-GHB-3 and OMC-GHB-2. This laboratory value shifted significantly from normal to abnormal (low) within the 6 g dose group, but was considered probably due to natural variability as there was no observed dose effect and the change was not considered clinically significant.

Of 23 patients with a normal serum calcium at baseline in OMC-GHB-3 that recorded a value lower than the normal range, 15 patients recorded a subsequent serum calcium within the normal range while still on Xyrem therapy, confirming laboratory variability rather than study medication. In a further 8 patients, values remained in the hypocalcemic range, in spite of normal renal function, proteins and phosphate levels, with no clinically significant reports to explain the finding. In all cases, the reduction was mild and would not be considered clinically significant.

A shift from normal to high values was seen in some patients with respect to glucose blood levels, but since these were frequently non-fasting levels, clinical interpretation is difficult.

9.3.1.4 Deaths

There has been one death (suicide) reported in the studies conducted by Orphan Medical. This death occurred from overdose of multiple drugs not involving Xyrem, and was considered unrelated to study medication. No deaths were reported in the Scrima or Lammers studies. This includes 366 patients, plus 144 subjects or patients in the pharmacokinetic/drug interaction studies. Subsequent to the cut-off date of data included in the NDA, a second suicide death has occurred in a patient with a long history of depressions and progression to bipolar disorder.

During the 16-year period of the Scharf trial, 11 patients died. These deaths were causally related to: 5 deaths from cardiovascular-related causes, 5 deaths from malignancy (3 lung, 1 colon, 1 bladder). One death resulted from a boating accident (study medication discontinued 4 months prior to the accident). A significant prior history of contributory disease was present in all 5 cardiovascular related deaths. In 2 of the patients succumbing to malignancy, a prior medical history of the malignancy was known. No symptoms were recorded prior to diagnosis of the malignancy for the remaining two patients. None of the deaths were considered as causally related to study drug.

9.3.1.5 Serious Non-Fatal Adverse Events

In the randomized, controlled trials, there was one serious adverse event (OMC-GHB-2), and 17 recorded during the longer term, open-label studies. Of these, 2 patients reported the SAEs prior to beginning sodium oxybate therapy.

The SAE's classified as related to study medication occurred in 5 patients (1 in OMC-GHB-2, 1 in OMC-GHB-3, and 3 in OMC-SXB-6). In the OMC-GHB-2 study, a female patient randomized to the 6 g dose experienced a severe confusional episode in the afternoon of the 7th day after her 6 g dose of Xyrem the preceding night. This episode resulted in hospitalization where she was treated with haloperidol, and the episode resolved. She was permanently discontinued from the study, and the event was categorized as possibly related to study drug.

Another patient in OMC-GHB-3 on 9 g dosing experienced severe agitation in the middle of the night on day 678 of treatment, leading to temporary cessation of treatment. The event resolved spontaneously.

A third patient in the OMC-SXB-6 experienced dizziness, confusion, nausea, vomiting, vertigo and asthma on day 99 of treatment at the 9 g dose. This patient was permanently discontinued from the trial.

Another patient in OMC-SXB-6 experienced a possibly related event at the 4.5g dose on day 170. The episode was coded as thinking abnormal, apnea, and unconsciousness. He collapsed soon after the first nightly dose (un-witnessed) recognized by the sound of hitting the floor. He was transferred to the hospital, requiring intubation and ventilation. He soon regained consciousness and respiratory depression resolved. Extensive neurological and cardiac assessment failed to identify a cause. Final expert opinions suggested some type of cardiac or neurological event, most likely cataplexy with resultant head injury, but with possibility of overdose. Symptoms resolved without sequelae, but he was permanently discontinued from the study.

The last report also came from OMC-SXB-6 and the patient was permanently discontinued from the trial on day 66 because she reported pregnancy, an exclusion criteria. Forty-two days later she experienced a spontaneous abortion which was rated by the investigator as "possibly" related to Xyrem.

In the Scharf patients, a total of 205 serious adverse events were reported by 54 patients over 16 years, representing 155 unique SAEs. However, the evidence for recurring SAEs was minimal, and the majority of events appeared consistent with the illness profile of older patients with narcolepsy and cataplexy.

Twelve serious adverse events were judged by the investigator to have been related to study medication. These 12 events occurred in 6 patients and 6 of these events were associated with higher doses than recommended as the therapeutic range (11.3 g, 12 g, and 3 instances of overdose at 18 g and 1 further event considered probably related to a high dose). These events were classified as overdose (2 instances), comatose, stupor,

unsuccessful suicide attempt, and potential overdose. One of these patients had associated hypoxemia, one had an accidental fall down a flight of stairs with consequent injuries, and one had "convulsive like seizures" and urinary incontinence. As several of these SAEs imply acute major psychiatric illness, this will be addressed separately in this report.

9.3.1.6 Discontinuations Due to Adverse Events

There were 38 withdrawals due to 1 or more AEs in the seven clinical trials excluding the Scharf database. These included 37 patients on sodium oxybate, 1 patient receiving placebo and, of those on drug, 32 experienced AEs considered related to trial medication. Four of these have been described in the SAE section, including the patient incorrectly listed as withdrawal due to pregnancy (protocol violation) with subsequent spontaneous abortion 42 days later. In these discontinuations due to AEs classified as related to study medication, there was no dose relationship seen, with 17 of the 32 events occurring at doses of 3-4.5 g/d, and 15 reported at doses of 6, 7.5, or 9 g/d.

Many of these events are related to the established side effect profile of sodium oxybate, such as dizziness, nausea, urinary incontinence, and headache. Others relate to other components of sleep disorders such as somnolence and movements during sleep (periodic limb movements), COSTART listed as hyperkinesias.

One subject also withdrew from one of the pharmacokinetic studies (OMC-SXB-11) investigating the effect of a high-fat meal on the bioavailability of Xyrem. This event consisted of respiratory depression, severe obtundation, and fecal incontinence when administered 4.5 g Xyrem as a single dose after an overnight fast. This patient responded to simple supportive measures, but chose not to continue in the second portion of the study.

In the Scharf study, 19 patients discontinued treatment with sodium oxybate because of an adverse event. These included eight patients whose symptoms were associated with their subsequent deaths, the attempted suicide, the 6 patients listed earlier as SAEs, 1 patient with difficulty sleeping and a psychiatric problem, elevated ANA titer, hypertonia, swelling and weight loss.

9.3.1.7 Drug Interactions

Orphan Medical sponsored three separate drug interaction studies evaluating the effects of Xyrem on co-medication and vice versa (Zolpidem, Protriptyline and Modafinil). The 3 co-medications chosen represent 3 classes of drugs (hypnotics, antidepressants and stimulants) commonly used in the treatment of narcoleptic symptoms. These studies concluded that sodium oxybate had no clinically important effect on the pharmacokinetics of these medications. Conversely, these 3 co-medications do not have any clinically significant impact on oxybate pharmacokinetics.

Invitro studies with pooled human liver microsomes show that oxybate does not significantly inhibit or enhance the activities of the human P450 isozymes: CYP1A2,

CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A. Given this fact and that the degradation of GHB is mediated by enzyme systems not related to the P450 oxidative systems, the lack of in-vivo drug-drug interactions are not surprising.

No reports of interactions with other concomitant medications were recorded during the drug development program. The clinical safety experienced with the wide range of medications, the expected lack of metabolic interaction resulting from independence from the cytochrome P450 oxidative enzyme system, and the fact that oxybate is an endogenous substance provide a satisfactory risk profile in terms of drug-drug reactions.

Special consideration should be given to interaction with alcohol. Animal data suggests that potential synergy resulted from coadministration of alcohol and GHB on the sleep time in rats (McCabe 1971). Kinetic interactions have been suggested by Vree (1975,1978), and so the warning must be issued that concomitant use of alcohol with Xyrem must be avoided.

9.3.1.8 Vital Signs and Electrocardiograms

No significant changes in vital signs or ECGs from baseline to the end of double-blind treatment were found in the four treatment groups (Placebo, 3, 6, and 9g/day) in OMC-GHB-2. Dose-related decreases detected in body weight and blood pressure were not considered to be clinically significant. Likewise, in the 6 PK studies conducted in healthy subjects, no clinically significant changes were observed in heart rate, respiration rate, or blood pressure.

9.3.2 SPECIAL CONSIDERATIONS

9.3.2.1 Seizurogenesis and Incontinence

Since enuresis has been an event reported in several of the studies (15 events in 8 patients in OMC-GHB-2, 51 events in 13 patients in OMC-GHB-3, 33 patients in the Scharf database), it is considered worthy of special address. In addition, 1 patient in OMC-GHB-2 reported fecal incontinence (considered due to diabetic diarrhea), as did 1 subject in the effect-of-food PK study (described earlier), and 1 patient in the Scharf trial.

At the time of review by FDA of OMC-GHB-2 in October 1998, FDA suggested that a relationship of incontinence and seizurogenesis should be considered and, hence, investigation was initiated into these early patients. This was done by:

- A questionnaire to all Investigators to review any observed abnormal nocturnal observations suggestive of seizures, urologic history preceding oxybate therapy, and any new neurologic symptoms.

- Correlation of any other CNS AEs correlating with incontinence (either urinary or fecal) that could be related to seizures.

- Subjecting 6 patients who had reported incontinence to overnight EEG (full-montage) recording at 9 g Xyrem dosing. These recordings were then referred to Nathan E. Crone, M.D., Neurologist, Johns Hopkins Medical Case, along with case reviews.

- Discussions with Martin Scharf, Ph.D. and Mortimer Mamelak, M.D., University of Toronto, Canada, regarding this long-term prior experience with sodium oxybate therapy.

In animal studies at high dose, GHB has been associated with EEG changes and behavioral presentation of symptomatology representing absence-seizure-like states. This has been developed as a model for absence seizures by Snead (1978) in primates, when high doses of GHB (600mg/kg) were administered intravenously. Myoclonus has been described as an occasional accompaniment of anesthesia induction with GHB intravenously.

In review of the data, there was no evidence to support seizurogenesis in our clinical trials. No bed partner has ever reported a seizure-like event in the treated patients. When the full-montage EEG studies were conducted in the patients with an incontinence history with Xyrem, it was serendipitous that 1 patient had urinary incontinence during the recording. Neither in this case nor with the other patients was there EEG evidence of seizure activity. There was no correlation with other CNS AE's that would correlate with incontinence to suggest neurologic disorder. Finally, 2 patients in the OMC-SXB-10 pharmacokinetic study at 4.5 g dosing as a single dose, experienced enuresis while under observation, and no seizure activity was seen. Pre-existing nocturia was a frequently reported symptom in these patients in their questionnaire.

Hence, in spite of the potential for partial seizures at doses far in excess of the human therapeutic dose in primates (when administered intravenously), there is no support for a relationship between seizures and the incontinence reported in this NDA submission, or from literature reporting human experience in therapeutic doses. Some associated seizure or tonic-clonic activity has been associated with presentation of some overdose and abuse experiences, where polypharmacy is common, and dose relationship determinations are impossible.

9.3.2.2 Psychopathology

The reporting of depression, and acute psychiatric symptomatology, such as frank psychosis, intentional overdose and suicide in the long-term studies, prompts a review of the literature associating psychopathology with narcolepsy as a disease. An association between psychopathology and narcolepsy was proposed by John Sours in 1963 when he reviewed clinical records of patients admitted to a New York hospital in the period from 1932 to 1964 that were coded under categories of hypersomnia, somnolence and narcolepsy. He identified eight patients with schizoid personality disturbances and another ten patients that developed frank schizophrenic psychoses that required prolonged hospitalization. Similar association was established in 1985 with an eleven-year sex- and age-matched review at the University of Iowa by James Wilcox that concluded a relationship between narcolepsy and psychosis. Such associations

have led to discussions as to whether psychiatric findings are epiphenomenal to, or inherent in the expression of narcolepsy.

A review of the emotional and psychosocial correlates of narcolepsy in fifty adults by Kales in 1982 indicated a "high level of psychopathology compared to controls", but he concluded that this resulted primarily as a reaction to the disorder and its effects.

An association between the HLA antigens related strongly to narcolepsy-cataplexy (HLA-DR2, DQ1) and its subdivision HLA-DR15, DQ6 has been suggested with schizophrenia. Douglass (1991, 1993) found that in 56 schizophrenic patients and 56 controls, the incidence of narcolepsy-associated antigens was 3.89 times higher in the schizophrenic patients. Also, that the patients with the narcolepsy-associated antigens had more hospitalizations and higher Brief Psychiatric Rating Scale scores, suggesting a severity association.

As was suggested by Kales, studies using self-report as well as traditional psychiatric measures have found significant depression among narcoleptics. People newly diagnosed with narcolepsy have reported that depression was the personality change they noted at disease onset (Broughton 1976). Recurrent episodes of depression have been reported by 51% of people with narcolepsy (Broughton 1984).

Seven hundred narcoleptics chosen randomly from the patient rolls of the American Narcolepsy Association were surveyed (response rate = 61.4%) with anonymous responses to the Center for Epidemiologic Studies Depression Scale (CES-D), indicating again that a high proportion of narcoleptics (49%) were experiencing depressive symptoms.

Analeptic-induced paranoid psychoses have been reported to occur in the treatment of narcolepsy (Leong 1989). Certain predisposing factors, such as pre-treatment paranoid ideation, family history of psychosis, significant head injury, or previous excessive use of stimulants, may provide "triggers" for psychiatric progression from long-term high dose stimulant therapy (Pawluk 1995).

Patient status in narcolepsy is obviously a complicated and dynamic representation of:

- Disease-associated psychosocial morbidity.
- Stimulant-induced changes and "trigger" influences
- Stress variations in daily life.
- Treatment-related co-morbidities

Such a possible commonality in pathogenesis and biochemical mechanism must be included in assessment of adverse events in a narcoleptic population and, in this context, there is little support for an association between sodium oxybate and the precipitation of the acute psychopathology recorded during the clinical trial periods.

9.3.2.3 Abuse Liability

There has been no evidence of tolerance development requiring dose escalation to maintain clinical efficacy in our clinical trials, and hence it has been possible to exclude suggestion of dose escalation for reasons of social pleasure. Absence of kinetic tolerance with chronic dosing was established in an appropriate study in narcoleptic patients. Although drug abuse has emerged as a significant public health issue for GHB wherein dose escalation both in terms of total dose and frequency of dosing is a real issue, we have seen no evidence of any such tendency in our clinical studies. Strict drug compliance has been monitored, and neither non-prescribed dose escalation nor diversion of clinical trial supplies was evidenced. As with the stimulant medications routinely used by narcoleptics, there was no documentation of euphorogenic properties at therapeutic doses used over the long periods of administration. No withdrawal symptomatology was reported following abrupt discontinuation of therapy.

Pre-clinical studies of the abuse potential using standard animal models have not yielded a picture of a highly abusable substance, but minimal human testing has yet been done. It is therefore difficult to separate the pharmacologic contributions to the public health problems of abuse from the sociologic issues, particularly in light of the ease of clandestine manufacture, the ease of access to starting materials, recipes, and "kits" for home manufacture via the Internet, and the wide availability and use of precursor chemicals such as gamma butyrolactone, and 1,4-butanediol.

9.4 Conclusions

Sodium oxybate offers a new and major therapeutic improvement in the management of narcolepsy when titrated to optimal clinical effect between the doses of 3 and 9 g nightly in divided dosing. It has great facility to reduce the incidence of cataplexy and, in combination with stimulants, reduce the subjective feelings of daytime somnolence. The added benefit in the reduction of inadvertent naps/sleep attacks was established in two double-blinded studies, with useful effects on the other ancillary REM-related symptom of hypnagogic hallucinations. Prolonged, sustained efficacy was established in the long-term study, OMC-GHB-3, and by the OMC-SXB-21 protocol.

The primary beneficial effects of sodium oxybate on sleep architecture previously described in the literature were confirmed in the Scrima trial, where a decrease in the number of awakenings, decreased Stage I with increased slow wave sleep, and a decrease in the number of stage shifts was measured in this double-blinded, placebo-controlled study. This confirms the increased delta-wave sleep seen in the OMC-SXB-20 protocol, where a clear dose-response increased in Stage 3,4 sleep along with a dose-related increase in delta power was established. The objective measure of Maximal Wakefulness Test increase confirmed the effects of Xyrem on daytime sleepiness that had been extensively measured by use of the Epworth Sleepiness Scale.

These benefits of therapy are seen in relation to low potential risks when used under prescribed medical care. Since the proposed dosing regimen requires therapy initiation at the low dose of 4.5 g in divided dose nightly with slow titration to achieve optimum

clinical benefit, the side effects that are usually mild (most frequently nausea, dizziness, headache, with occasional enuresis and somnambulism in susceptible individuals), can be minimized relative to clinical benefit. These benefits are offered as an alternative to the current off-label treatments of tricyclic and SSRI antidepressant medications used in addition to the stimulant medications. Sodium oxybate is the first drug product with the therapeutic potential to bridge the duality of treatments used to manage the symptoms of narcolepsy that are conceptually divided into the two mechanistic presentations of excessive daytime sleepiness and the ancillary REM-related symptoms of hypnagogic hallucinations, sleep paralysis and cataplexy.

SECTION 10
LIST OF REFERENCES

10.0 LIST OF REFERENCES

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