ORPHAN MEDICAL

May 3, 2001

Advisors and Consultants Staff
Center for Drug Evaluation and Research, ORM
Food and Drug Administration
HFD-21, Room 1093
5630 Fishers Lane
Rockville, MD 20852
Peripheral and Central Nervous System Drugs Advisory Committee,
c/o Dr. Sandra Titus; 301-827-7001

Subject: **Xyrem® (sodium oxybate) oral solution, NDA #21-196**
USER FEE NUMBER 3,814, ORPHAN DESIGNATION NUMBER 94-858

Peripheral and Central Nervous System Drugs Advisory Committee
Briefing Booklet for June 6, 2001 Presentation

Dear Advisory Committee Member:

This briefing booklet presents data for the use of Xyrem for treatment in narcolepsy, a seriously debilitating disease. The disease is lifelong after onset, which usually occurs in the second and third decade of life. Historically, diagnosis takes an average of ten years due to low physician awareness. These factors and disease symptomatology negatively affect patients' education, employment potential and interpersonal relationships for the rest of their lives. Current treatments are unsatisfactory, and although approved therapies for daytime sleepiness exist, no therapies are approved for the auxiliary REM-related symptoms of cataplexy, hypnagogic hallucinations, and sleep paralysis. For these reasons Xyrem represents an important new therapeutic advance to meet an unmet medical need.

Narcolepsy affects an estimated 125,000 individuals in the United States, an incidence that qualifies for orphan drug designation. Excessive daytime sleepiness is diagnostic of this disease, while the REM-related symptoms affect 60-90% of patients. About 25,000 individuals have cataplexy of severity requiring pharmacologic intervention.

Limited patient availability has influenced the size of the database. Xyrem safety, efficacy, pharmacokinetics, abuse pharmacology, scheduling and risk management are summarized in this booklet from over 250 volumes of electronic and paper information which has been submitted to FDA for review.

This NDA was designated a priority by the FDA shortly after submission in recognition of the fact that narcolepsy is serious and debilitating with inadequate therapeutic options, particularly for cataplexy. The compelling medical need of narcoleptic patients for additional therapeutic options is summarized in section 2.

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The premise for approval for efficacy is based upon four double-blind controlled clinical trials, two of which were sponsored by the company and two of which were conducted by academics, one in the US and one in the Netherlands. Efficacy is summarized in section 3 of this booklet.

The company has collected data from over 400 patients during the course of its two INDs, including a treatment IND approved by FDA in 1998 (section 4). In addition, an investigator in this country has been treating a small group of patients (N=143) for up to 18 years under his IND. The company has collected information from his database that reflects over 900 patient years of clinical safety data. Information from such a database is not usually available for a new chemical entity. Questions related to this database led to the cancellation of the initial advisory committee review scheduled for March 15th. The company has now addressed these questions and our response is under review by FDA. Overall the safety data set, while not large (604 patients and subjects), supports the safe use of Xyrem for the proposed indication.

The pharmacokinetics and abuse pharmacology are included for completeness in sections 5 and 6 respectively. Also included are sections dealing with scheduling and risk management.

Public health issues related to GHB have been well recognized for over 10 years. FDA took action to remove GHB from the market in 1990 due to public health risks of abuse and its illegal promotion as a 'dietary supplement'. FDA subsequently approached Orphan Medical to develop this compound in narcolepsy in 1994. FDA again took additional action when analogues began to surface over the last 5 years. The scheduling of Xyrem was completed in 2000 following extensive public debate in Congress with advice from FDA, DEA and other stakeholders. A federal law was enacted in 2000 to create a bifurcated schedule for GHB with all illicit use falling under schedule 1 and medical use placed into schedule 3. This law, along with the 2000 World Health Organization expert working committee recommendation for schedule 4, and the HHS recommendation to Congress is included in section 7. Regrettably, these laws do not adequately address promotion of precursor chemicals as abuse alternatives to GHB.

The advisory committee has also been asked to review and discuss the risk management of Xyrem. Risk management refers to minimization of public health issues associated with a pharmaceutical product. There is no evidence that Xyrem has been diverted or used for any purpose but to evaluate its safety and efficacy in treating narcolepsy. We believe that the precautions included in the Company's post-marketing program will constrain in every way possible the risks associated with this medicine while allowing its use by patients to meet their medical needs. These precautions include mechanisms to educate physicians and patients about the proper use of Xyrem, the unique implications of the bifurcated schedule, as well as closed-loop prescription and distribution systems to restrict the opportunity for diversion or misuse. Included with this package of information from Orphan Medical is a short 8-minute video on the prescription process, along with patient and physician education materials (the two binders). The risk of diversion and abuse of Xyrem is further reduced when these post-

marketing processes to which the Company has committed are combined with the scheduling restrictions recommended by FDA and imposed by Public Law 106-172. It should be noted that narcolepsy patients and their physicians are already very familiar with the responsible use of controlled substances since they typically manage symptoms with schedule 2 amphetamine related medications and other medications in schedule 4.

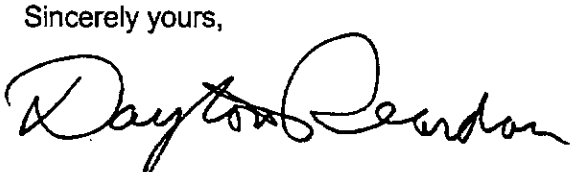
It is an unfortunate fact that illicit GHB substances, not Xyrem, represent a risk to the public health. This risk will neither be increased by approval of Xyrem, nor decreased by denial of approval due to the easy availability of analogues of GHB. While Orphan Medical has no legal responsibility for the illicit use of GHB or its precursor chemicals, we have made a moral and practical commitment to assist the FDA, DEA and other law enforcement and abuse specialists in their efforts to minimize the public health risk of illicit GHB substances.

Sodium oxybate, or gamma hydroxybutyrate, is defined as a new chemical entity since it has never been approved for human use in the United States. Products containing oxybate have been approved in Europe, as an anesthetic since the 1960s, and in Italy for use in treatment of alcoholism since 1994. We believe the data presented herein establish the medical need, efficacy and safety of Xyrem, and provide the basis for our request for approval of the following proposed indication:

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

Should you have any questions not addressed in this briefing booklet, please let us know through Dr. Sandra Titus, the Committee's Executive Secretary.

Sincerely yours,



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Xyrem® (sodium oxybate) oral solution

NDA #21-196

Briefing Booklet for the Peripheral and Central Nervous System Drugs Advisory Committee Meeting

June 6, 2001

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LIST OF ABBREVIATIONS

λ_z	elimination rate constant
5-HT	serotonin
5HIAA	5-hydoxyindolacetic acid
6-OHDA	6-hydroxydopamine
^{14}C	carbon-14
ACh	acetylcholine
NDA	New Drug Application
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AHI	Apnea Hypopnea Index
Alk phos	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ASDA	American Sleep Disorders Association
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{ext}	area under the curve from the time of the last quantified concentration to time infinity
AUC_{inf}	area under the curve from time zero to time infinity
AUC_{last}	area under the curve from time zero to the time of the last quantified concentration
AUC_{SS}	area under the curve at steady-state
A-V	atrioventricular
BDS	bulk drug substance
bpm	beats per minute
BUN	blood urea nitrogen
C	Centigrade/Celsius
C of A	Certificate of Analysis
CAS	Chemical Abstract Services
CBF	cerebral blood flow
CCA	complete cataplexy attacks
CFR	Code of Federal Regulations
CGI-c	Clinical Global Impressions of Change
CGI-s	Clinical Global Impressions of Severity
CHA	cyclohexyladenosine
CL/F	oral plasma clearance divided by absolute bioavailability
Cm	centimeter
C_{max}	observed maximum plasma concentration
CMR_{O2}	cerebral metabolic rate for oxygen
CMR_{glc}	cerebral metabolic rate for glucose
CNS	central nervous system
COSTART	coding symbols for a thesaurus of adverse reactions terms
CRA	Clinical Research Associate
CRF	case report form

CRO	contract research organization
CSF	cerebrospinal fluid
CV	coefficient of variation
CYP2C	cytochrome P450 2C
CYP2C9	cytochrome P450 2C9
CYP2D6	cytochrome P450 2D6
CYP3A	cytochrome P450 3A
CYP3A4	cytochrome P450 3A4
DAGO	(D-Ala^2, *N*-Me-Phe^4, glycinol^5)-enkephalin
DAWN	Drug Abuse Warning Network
DDMAC	division of drug marketing, advertising and communications
DHA	dihydroalprenalol
DOPAC	dihydroxyphenylacetic acid
DP	drug product
DS	drug substance
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	electrocardiogram
ECoG	electrocorticogram
EDS	excessive daytime sleepiness
EEG	electroencephalogram
EMG	electromyogram
ESS	Epworth Sleepiness Scale
°F	degrees Fahrenheit
F	absolute bioavailability
FDA	Food and Drug Administration
FDP	fructose 1,6 diphosphate
FFTs	first fourier transforms
g, G	gram
G6P	glucose-6-phosphate
g/d	grams per day
GABA	gamma aminobutyric acid
GABA-T	gamma aminobutyric acid transaminase
GBL	gamma butyrolactone
GCP	Good Clinical Practice
GLM	general linear model
GHB	gamma hydroxybutyrate
GMP	Good Manufacturing Practice
GTI	Global Therapeutic Impression of Change
HCT	hematocrit
HGB	hemoglobin
HH	hypnagogic hallucinations
HPLC	high pressure liquid chromatography
hr	hour
HVA	homovanillic acid
HZ	Hertz
ICH	International Conference on Harmonization
ICV	intracerebraventricular

ID	identification
IG	intragastric
IND	investigation new drug
IP	intraperitoneal
IR	infrared
IV, iv	intravenous
IRB	Institutional Review Board
k_a	apparent first-order absorption rate constant
kg	kilogram
KF	Karl Fisher
L	liter
LD50	median lethal dose
LDH	lactate dehydrogenase
ln	natural logarithm
LOQ	limit of quantification
MAO	monoamine oxidase
MABP	mean arterial blood pressure
MAX	maximum
MES	maximal electroshock
mg	milligram
MIN	minimum
MK-801	(+)-5-methyl-10,11-dihydro-5H-dibenzo [a,d] cyclohepten-5,10-imine maleate; dizocilpine
mL, ml	milliliter
mm	millimeter
mm Hg	millimeter of mercury
MSE	mean square error
MSLT	Multiple Sleep Latency Test
MWT	maintenance of wakefulness test
n	number
NA	not available
NADDI	national association of drug diversion investigators
NaGHB	sodium gamma–hydroxybutyric acid (sodium oxybate)
NASOA	National Association of State Controlled Substance Authorities
NCS	not clinically significant
NCS-356	γ-*p*-chlorophenyl-*trans*-4-hydroxycrotonate
NCS-382	6,7,8,9-tetrahydro-5-[*H*]benzocycloheptene-5-ol-4-ylidene acetic acid
ND	not determined
NDTI	national disease and therapeutic index
NIDA	National Institute on Drug Abuse
NMDA	N-methyl-D-aspartate
NOAEL	no adverse-effect level
NREM	nonrapid eye movement
NTP	National Toxicology Program
OMI	Orphan Medical, Inc
PBO	placebo
PL	public law

PO	*per os*, oral
PCA	partial cataplexy attacks
PCP	phencyclidine
PSG	polysomnography
PTH	parathyroid hormone
QA	quality assurance
QC	quality control
QNB	quinuclinidinyl benzylate
RBC	red blood cell
REM	rapid eye movement
SAS	Statistical Analysis System
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SEM	standard error of the mean
SGOT	serum glutamic-oxalacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOREMP	sleep onset REM peroids
SqRt	square root
SSA	succinic semialdehyde
SSR	succinic semialdehyde reductase
SSRI	selective serotonin re-uptake inhibitor
SWS	slow wave sleep
SXB	sodium oxybate
$T_{1/2}$	half-life of terminal phase
TBPS	*t*-butylbicyclophosphorothionate
TCA	tricyclic antidepressant
TST	total sleep time
T_{max}	time to observed maximum plasma concentration from dosing
TNCA	total number of cataplexy attacks
V_z/F	apparent volume of distribution divided by oral bioavailability
WBC	white blood cell

DEFINITION OF TERMS

Safety for the clinical trials represented in the original NDA, and all subsequent submissions to date, is based on the following criteria set down during the first of the clinical trials represented:

Adverse Experience:
An adverse experience is any pathologic, noxious, or unintended change in anatomical, metabolic or physiologic function as dictated by physical signs, symptoms, and/or laboratory changes occurring in any phase of a clinical trial, whether or not considered related to study medication and whether associated with study medication or placebo. This includes exacerbation of a pre-existing condition or the significant failure of pharmacologic action.

Adverse experience shall be considered synonymous with the term adverse event.

Severity:
The severity of adverse experiences should be rated as mild, moderate, or severe in accordance with the following guidelines:

1. Mild:
   The adverse experience does not interfere with the patient's normal functioning, although it may be an annoyance.

2. Moderate:
   The adverse experience interferes to some extent with normal functions, but it is not hazardous to health; the event may be uncomfortable or cause embarrassment; the event may require discontinuation of drug as well as other counteractive measures.

3. Severe:
   The adverse experience interferes substantially with normal functions and presents a definite hazard to the patient's health. These experiences virtually always require discontinuation of drug and may require counteractive measures.

Causality:
The relationship between the administration of trial medication and an adverse experience is a judgment based the medical information available at the time of the assessment. The information that is usually considered in making this judgment includes but is not limited to the following.

a) The temporal sequence of the adverse experience with the administration of test medication.
b) The known characteristics of the patient/subjects' clinical state, environment, or toxic factors, or other therapy administered to the patient.

c) The disappearance of the adverse experience on cessation of test medication or reduction in dose (dechallenge).
d) The reappearance of the adverse experience on resuming treatment with test medication (rechallenge).
e) The known response pattern of the test medication.

The relationship between trial medication and adverse experiences will be rated using the following guidelines:

1. Definitely Related:
   This category is usually chosen when the connection between administration of test medication and the adverse experience is certain, based on dechallenge and rechallenge or obviousness (e.g., pain at the site of injection).

2. Probably Related:
   This category applies when the connection between administration of test medication and the adverse experience is considered to be over 50% likely.

3. Possibly Related:
   This category applies when the connection between administration of test medication and the adverse experience is considered to be less than 50% likely.

4. Not Related:
   This category applies to those adverse experiences which are clearly due to non-trial medication causes (e.g., disease, environment).

5. Unknown:
   This category applies to those adverse experiences which after careful consideration of all other categories can not be considered definitely related, probably related, possibly related, or not related usually because of inadequate information.

Frequency:
The frequency of an event was initially rated as either continuous or intermittent. This criteria was later broadened to include the term isolated for events which resolved immediately.

Serious:
A serious adverse experience is defined as an adverse experience wherein the outcome is death, life-threatening, temporarily or permanently disabling, or which results in or prolongs inpatient hospitalization. In addition, an overdose, congenital anomaly, or the occurrence of cancer are considered to be serious adverse experiences.

SECTION 2
MEDICAL NEED

2.0 MEDICAL NEED

2.1 Disease and Pathogenesis

Narcolepsy is among the leading causes of excessive daytime sleepiness (EDS) and is the most common neurological cause (Bassetti 1996). Narcolepsy is now recognized as a prevalent but underdiagnosed neurological disorder (Hubin 1994) that has a socio-economic impact that may be as high as that of epilepsy. The first consensus definition of narcolepsy was produced by the First International Symposium on Narcolepsy, July 1975, in France:

> "A syndrome of unknown origin that is characterized by abnormal sleep tendencies, including excessive daytime sleepiness and often disturbed nocturnal sleep, and pathological manifestations of REM sleep. The REM sleep abnormalities include sleep-onset REM periods and the disassociated REM sleep inhibitory processes, cataplexy and sleep paralysis. EDS and cataplexy and, less often, sleep paralysis and hypnagogic hallucinations are the major symptoms of the disease." (Gulleminault 1976).

Characterized by this descriptive definition, narcolepsy is not just excessive sleep, but rather an inability to maintain either wakefulness or consolidated sleep. Patients are typically excessively sleepy during daytime and insomniacs at night. In addition, narcoleptic patients experience abnormal episodes of REM sleep, such as cataplexy and sleep paralysis representing dissociated manifestations of REM sleep atonia or dream-like hallucinations occurring either in active wake, at sleep onset, or while waking from sleep (Nishino 1997).

Its classic form - narcolepsy with cataplexy - is a distinct neurologic disease with characteristic clinical and paraclinical findings. The definition of the variants of narcolepsy, however, remain a matter of controversy. The International Classification Of Sleep Disorders has defined narcolepsy as:

> "A disorder of unknown etiology, which is characterized by excessive sleepiness that typically is associated with cataplexy and other REM sleep phenomena such as sleep paralysis and hypnagogic hallucinations."

This is the definition adopted by the American Sleep Disorders Association, International Classification of Sleep Disorders, Diagnostic and Coding Manual, Diagnostic Classification Steering Committee, Thorpy MJ (Chairman) 1990.

Thus it remains a purely descriptive disease state in the absence of a defining diagnostic test or investigative measurement and can be a diagnostic challenge in the absence of cataplexy as both EDS and REM phenomena can occur in diseases other than narcolepsy. New information is now emerging as to cause, with the relationship of animal data implicating the hypocretin II receptors to the narcolepsy/cataplexy syndrome in dogs (Lin 1999) and the deficiency of the hypocretin peptide transmitters in a knockout mouse model lacking the hypocretin gene producing abnormalities of sleep control

resembling aspects of narcolepsy (Chemelli 1999). Together these two studies implicate dysfunction of the hypocretin system, or closely related systems, to the pathophysiology of narcolepsy.

Anatomical studies determined that the sources of the hypocretin producing cells were restricted to the hypothalamus and concentrated in the perifornical nucleus and in the dorsal, lateral and posterior hypothalamus. This hypothalamic restriction applies only to the cell bodies and they have widespread neuronal projections to sites centrally related to sleep and arousal. In addition to dense hypothalamic projections, the limbic system, thalamus, subthalamic nucleus, substantia nigra, raphe, locus coeruleus, ventral tegmental area, medullary reticular formation, nucleus of the solitary tract, and other brainstem regions are innervated by these cells (Peyron 1998).

Further pathogenic support for the relationship of the hypocretins and narcolepsy has come from recent discovery of low levels of hypocretin II in the CSF of human narcoleptics (Mignot 2000) and the even more recent discovery of the significant reduction in the number of hypocretin neurons in the brains of narcoleptics (Siegel 2000, Mignot 2000).

Mutations of the hypocretic system may be responsible for some proportion of human narcolepsy cases. However, it is unlikely that most human narcoleptics have a mutation as in the canine model. Most narcoleptics have no narcoleptic relatives, ruling out the autosomal recessive mode of inheritance seen in the dogs. The typical onset of symptoms in the second decade of life or later suggests that damage has occurred to a normally functioning sleep and motor control system. Approximately 75% of the pairs of identical twins examined are discordant for the disease (Partinen 1994) suggesting that environmental factors are critical in the triggering of the disease.

More than 85% of all narcoleptic patients with cataplexy share a specific HLA allele, HLADQB1, 0602, compared with 12% to 38% of the general population (Mignot 1998). Because of the role of HLA gene products in immune regulation, in that most HLA-linked diseases are autoimmune in nature, and because of the possibility of the involvement of environmental triggers, it is speculated that narcolepsy might be an autoimmune disorder. Immune-mediated reduction in the numbers of hypocretin neurons is an exciting new hypothesis requiring research. It is certainly an attractive hypothesis implicating irreversible damage to the hypocretin neurones or to axon terminals as a plausible cause for the disorder. However, there may well be other factors "downstream" of the hypocretin system.

Even though these exciting new discoveries shed some light on the pathogenesis of the disease, treatments remain symptomatic and sodium oxybate provides new potential to favorably modify the debilitating symptom profile that defines narcolepsy.

2.2 History

Although the clinical condition was described as early as 1672 by Willis, by Schindler in 1829, Gélineau gave the first precise description of the disease and coined the term

"narcolepsy" from the Greek meaning "seized by somnolence" in 1880. The term "cataplexy" was proposed in 1902 by Löwenfeld, and confirmed as the clinical term for the loss of muscle tone by Henneberg in 1916.

Hypnagogic hallucinations and sleep paralysis were first linked to narcolepsy in the 1920's (Bassetti 1996).

After World War II, Yoss and Daly (1957) introduced the notion of the narcolepsy "tetrad" – excessive daytime sleepiness, cataplexy, hypnagogic hallucinations and sleep paralysis. In its typical form, narcolepsy patients also experience disturbed nocturnal sleep (narcolepsy "pentad") (Nishino 1997).

Shortly after the discovery of REM sleep (Aserinsky and Kleitman 1953) the discovery that narcoleptic patients often begin their night sleep with a period of REM sleep (Vogel 1960) suggested that narcolepsy might involve abnormal REM sleep. In the same year, Rectschaffen (1963) and Takahashi (1963) independently confirmed that narcoleptic patients often have sleep onset REM periods (SOREMP's), and suggested that cataplexy, sleep paralysis and hypnagogic hallucinations were abnormal manifestations of dissociated REM sleep. This led to the generally accepted model that sleep disturbances seen in narcolepsy are divided into the two distinct categories of disturbance in the sleep/wake distribution (EDS/sleep attacks and fragmented nighttime sleep) and abnormal REM sleep related symptoms (cataplexy, hypnagogic hallucinations and sleep paralysis) (Roth 1969, Takahashi 1971). The fact that EDS and abnormal REM sleep are most often treated to date with distinct medications (stimulants for EDS and antidepressants for REM-related phenomena) also adds credence to this concept of a duality in the symptoms of narcolepsy).

2.3 Epidemiology

Narcolepsy is now recognized as a relatively prevalent but underdiagnosed neurological disorder (Hublin 1994). Following Daniel's classic review in 1934 of 147 patients with narcolepsy seen at the Mayo Clinic in Minnesota, the disease was no longer considered rare. In the same clinic, 241 cases were observed over a five year period of 1950-1954 (Yoss and Daly 1957). The exact prevalence remains unknown, with a reported variation from 0.0002% to 0.50% in different populations (Hublin 1994). The estimated prevalence for narcolepsy with cataplexy is 0.03% to 0.07% of the general adult population in whites (Dement 1973, Hublin 1994, Ohayon 1996).

Narcolepsy often remains undiagnosed or misdiagnosed for several years. In part this may occur because physicians may not include narcolepsy in the differential diagnosis of other diseases with complaints or fatigue, tiredness, problems with concentration, attention, memory and performance, and other illnesses (e.g., seizures, hallucinatory states).

Narcolepsy occurs in both sexes equally, and in all races with a lower prevalence suggested in Israeli-Jews (Wilner 1988). Rigorous clinical and paraclinical testing shows that the percentage of "true" familial narcolepsy does not exceed 4% to 7% (Goode

1962, Billiard 1994, Parkes 1985). The risk of children of narcoleptics developing the disease is about 1% (Bassetti 1996).

2.4 Clinical Picture

2.4.1 EXCESSIVE DAYTIME SLEEPINESS (EDS)

By definition, narcolepsy can be diagnosed only in the presence of EDS, although this symptom rarely appears after the onset of other elements of the tetrad. Sleepiness is usually the most disabling symptom. It most typically mimics the feeling of sleep deprivation, but may also manifest itself as chronic tiredness or fatigue (Nishino 1997). Clinically, narcoleptic and physiologic sleepiness (i.e. after sleep deprivation) are similar in character but differ in temporal pattern and severity. In both, transition from wake to sleep is usually gradual, with increased sleep propensity in the afternoons, in situations of boredom or limited physical activity, post-prandial, and in a warm environment. Narcoleptic sleepiness, however, is usually constant, severe and only transiently and partially improved with sleep.

This continuous sleepiness fluctuates in severity and episodically becomes irresistible, with involuntary brief naps, or "sleep attacks" occurring during such unusual circumstances as talking, eating, standing, walking, driving in traffic, or even during intercourse. Honda and colleagues (1988) reported two or more sleep attacks per day in 68% of 170 patients studied. Naps are usually brief, refreshing, easily terminated by external stimuli and, in one third of cases, are associated with dream experiences (Roth 1980). The duration of the naps may be affected by situational rather than pathophysiologic differences.

Variations in the intensity of sleep attacks, the ability to resist sleep, and in the subjective awareness of sleepiness explain the differences in the phenotypical presentation of EDS. Up to 80% of patients experience fluctuations in vigilance lasting from seconds to hours, during which they can perform semipurposeful, complex acts with no recollection. The perception of the transition from wakefulness to sleep may be altered, and short, involuntary episodes of sleep or decreased vigilance (sometimes referred to as blackouts) may be experienced as paroxysmal loss of consciousness (Bassetti 1996).

2.4.2 CATAPLEXY

Cataplexy is defined as a sudden episode of muscle weakness triggered by emotions, most typically laughter, elation and joy but also anger, annoyance, embarrassment, grief, surprise, and even sexual intercourse. It is normally associated with normal consciousness, is bilateral, and lasts less than a few minutes.

Cataplexy is clinically an extremely variable symptom (Gelb 1994), and only certain muscle groups may be involved. Most often it is mild and occurs as a simple buckling of the knees, head dropping, sagging of the jaw or weakness of the arms. Slurred speech or mutism is also frequently associated. In other cases, it escalates to episodes of muscle paralysis and collapse that may last up to a few minutes. Most often the patient

will have time to seek support or sit down. Long episodes of cataplexy occasionally blend into sleep and may be associated with hypnagogic hallucinations. Its duration exceeded twenty minutes in 2% of a series of 130 patients (Honda 1988). Rare episodes lasting longer than thirty minutes, termed status cataplecticus, can be precipitated by the abrupt discontinuation of antidepressant drugs (Hishikawa 1976) and can render the patient virtually helpless.

2.4.3 SLEEP PARALYSIS

Whereas EDS and cataplexy are cardinal symptoms of narcolepsy, sleep paralysis occurs frequently as an isolated phenomenon affecting 5% to 40% of the narcoleptic population (Dahlitz 1993). Sleep paralysis is best described as a brief inability to perform voluntary movements at the onset of sleep, or upon awakening during the night or in the morning. The patient is unable to perform even a small movement, and the episode may last a few minutes. Sleep paralysis is easily interrupted by noise or other external stimuli. It is present in 20% to 50% of narcoleptic subjects. Episodes are more common with stress, with irregular sleep or sleep deprivation, and frequency varies widely from a few life events to almost daily episodes.

2.4.4 HYPNAGOGIC HALLUCINATIONS

Abnormal visual (most often) or auditory perceptions that occur while falling asleep (hypnagogic) or upon waking up (hypnopompic) are observed frequently in narcoleptic subjects (15% to 66%), and in up to 50% of cases, they occur at least once weekly (Honda 1988). Hypnagogic hallucinations are the expression of a changing state of consciousness in which, as opposed to dreaming, elements of the normal awake mentation are still present, and they may involve one or more senses. Unlike psychotic hallucinations, subjects usually are aware of the unreal nature of the hallucination. The intensity and the accompanying fear and anxiety are sometimes the most distressing symptoms of narcolepsy.

2.4.5 OTHER SYMPTOMS

Disrupted nighttime sleep with frequent awakenings is reported by 60% to 80% of patients with narcolepsy (Billard 1985, Montplaisir 1978). Patients often complain of difficulties with concentration, visual disturbances, problems with memory and perceptual disturbances. Frequently associated problems are periodic leg movements, REM behavior disorder, and other parasomnias.

2.5 Evolution of Narcolepsy

Narcolepsy usually starts around adolescence, occasionally very abruptly, but most often insidiously. Its peak onset is in the second decade of life, with a smaller peak in the third decade. A few cases are recognized in a pediatric context, manifesting as early as five to six years of age (Challamel 1994). In most cases, however, the diagnosis of narcolepsy is made several years after the onset of the clinical condition.

Sleepiness is usually the first symptom to appear, followed by cataplexy, hypnagogic hallucinations, and sleep paralysis. In approximately one-half of the cases, the onset of cataplexy is simultaneous with the appearance of daytime somnolence and within five years in approximately two-thirds of the cases (Honda 1988, Roth 1962). The mean time of the onset of sleep paralysis and hypnagogic hallucinations is also two to seven years later than that of sleepiness.

Sleepiness almost invariable persists over time, although a late decline in severity is not rare, and even short remissions are possible. Conversely, cataplexy, sleep paralysis and hypnagogic hallucinations may disappear spontaneously in 16% to 37% of patients (Billiard 1993).

2.6 Psychosocial Impact of Narcolepsy

Despite dynamic progress in the understanding of narcolepsy, the disease continues to cause the sufferer severe negative life effects. Before and after diagnosis, narcoleptics often experience unrelenting severe psychosocial stress, with differing stresses in each decade of life. Child and adolescent narcoleptics report embarrassment, academic decline and feelings of loss of self-worth related to the symptoms of their disease. Personality characteristics may be adopted that seek to avoid social situations that would precipitate cataplexy or draw attention to the patient's degree of somnolence. More than one-half of narcoleptics believed their symptoms caused poor performances at school (Broughton 1981). Teachers often misinterpret early symptoms and the accompanying irritability, frustration and mood swings as laziness, indifference, or even malingering. Hypnagogic hallucinations may lead individuals to question their own sanity and, at times, these occurrences are mistakenly diagnosed as psychotic episodes (Douglass 1991). Although no inherent memory disturbance has been associated with the disease, somnolence and lapses of concentration (possibly micro-sleeps) may explain the commonly reported problems with memory. Misdiagnosis may result in inappropriate treatment and underestimation of an individual's potential. Denial of the condition may further delay their seeking treatment.

Adult narcoleptics face major concerns, particularly in the workplace, and with secure interpersonal relationships. The effects of sleepiness and cataplexy have major effects on personal and public safety. Broughton (1981) examined the effects on driving. Narcoleptics reported marked increases in the following (percent narcoleptics compared to percent of controls):

	Narcoleptics	Controls
Falling asleep while driving	66%	6.2%
Cataplexy while driving	29%	0%
Sleep paralysis while driving	11.5%	0%
Frequent near accidents	67%	0%
Motor vehicle accidents	37%	5.3%
Increased insurance rates	16%	1%
Suspended drivers' licenses	6.l%	3.9%

In the workplace, narcoleptics face not only danger of accidental injury but the reality of poor performance and job loss. In the 1981 Broughton survey narcoleptics reported the following occupational effects attributed to their symptoms.

	Narcoleptics	Controls
Reduced job performance	78%	9%
Fear of losing job	49%	0%
Decreased earnings	47%	1.2%
Actual job loss	21%	0%
Loss of promotion	3.8%	0%
Disability insurance	11%	0%

Accidental injury in narcoleptics also occurs in the home. Smoking accidents due to narcoleptic symptoms were found in 49% of patients, falls 37%, burns from hot objects 15%, cuts from sharp objects 13%, and "breaking things" 10% were reported by Cohen in 1992.

Interpersonal relations also suffer. Poor self-image and social withdrawal have been mentioned. Narcoleptics frequently feel that others view them as lazy or bored. Sleep attacks during conversations can alienate others.

Marital stress is a major problem and has been reported as high as 72% (Kales 1982). Besides interpersonal problems, financial problems resulting from job loss or accidents add external pressure on the marriage. Sexual dysfunction and loss of libido are commonly reported complaints.

A body of data supports the idea that a large number of narcoleptics also carry diagnosable psychiatric disorders, in most cases thought to result from the symptomatology of the disease and its life effects. In a study by Kales et al in 1982, more than 50% of narcoleptics had a diagnosable psychiatric disorder, all assigned as variants of depression and/or personality disorders.

The psychosocial impacts of narcolepsy disease have been thoroughly detailed in a special journal issue edited by Goswani, Polack, Cohen, Thorpy, Kovey: Psychosocial Aspects of Narcolepsy, Loss Grief Care 1992; 5,1-203.

The culmination of the deleterious effects of narcolepsy upon work, education, occupational and household safety, recreation, personality and interpersonal relations were compared with those of epilepsy and the psychosocial impact of narcolepsy was found to be higher in all categories except driving (Broughton 1984). These data support the medical need for effective treatment.

SECTION 3
EFFICACY

3.0 EFFICACY

Overview of efficacy clinical trials: Four controlled and 3 uncontrolled clinical trials have been performed to evaluate the efficacy of Xyrem for the treatment of narcolepsy. These trials are summarized below:

Controlled Trials: 201 patients

- *OMC-GHB-2* – 136 patients
  Placebo, 3.0, 6.0, 9.0 g/d sodium oxybate
- *Scrima Trial* – 20 patients
  Placebo, 50 mg/kg (4.2 g/d) sodium oxybate
- *Lammers Trial* – 25 patients
  Placebo, 60 mg/kg (4.7 g/d) sodium oxybate
- *OMC-SXB-21* – 55 patients
  Placebo, 3.0, 4.5, 6.0, 7.5, and 9.0 g/d sodium oxybate

Uncontrolled Trials: 323 patients

- *OMC-GHB-3* – 117 patients
  3.0, 4.5, 6.0, 7.5, and 9.0 g/d sodium oxybate
- *OMC-SXB-6* – 185 patients
  3.0, 4.5, 6.0, 7.5, and 9.0 g/d sodium oxybate
- *OMC-SXB-20* – 21 patients
  4.5, 6.0, 7.5, and 9.0 g/d sodium oxybate

3.1 Controlled Studies

3.1.1 OMC-GHB-2

In initial discussions with the FDA in 1995, the Agency indicated that adequate prospective studies to ascertain the appropriate therapeutic dose range of sodium oxybate had not been conducted. This trial was designed to provide that information. The study was designed as a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial with three doses of sodium oxybate and placebo in narcoleptic patients meeting specific American Sleep Disorders Association (ASDA) criteria for narcolepsy. The objectives of the trial were to evaluate and compare the efficacy and safety of three doses (3g, 6g and 9g) of sodium oxybate and placebo in the treatment of the symptoms of narcolepsy. A rating of the change in the severity of the patient's narcolepsy symptoms as measured by the Clinical Global Impression of Change was provided by the investigator at the end of the four-week treatment period, compared to the rating of Clinical Global Impression of Severity of Disease at the end of the baseline period.

Patients who completed this study and continued to meet all other entry criteria except for the minimum number of cataplexy attacks, were eligible to enter a long-term, open label study (OMC-GHB-3) if they desired and if the physician responsible for their care concurred.

3.1.1.1 Study Objectives

Primary Objective: To evaluate and compare the efficacy of three doses (3g, 6g, and 9g) of sodium oxybate and placebo in the treatment of the symptoms of narcolepsy.

Secondary Objective: To evaluate and compare the safety of sodium oxybate and placebo when used in a narcoleptic patient population.

3.1.1.2 Investigational Plan

The study was conducted at sixteen centers, and a total of 136 patients were enrolled. The study was divided into five periods as follows:

Table 3.1 Time Periods of OMC-GHB-2 Trial

Screening	Washout	Baseline	Double-blind Treatment			Follow-up
one day to 4 weeks	5-28 days	2 to 3 weeks	4 weeks			3-5 days
Visit 1	Visit 2	Visit 3	Visits			Visit 7
			4	5	6	
Withdrawal of treatment for cataplexy	No treatment for cataplexy		Placebo or GHB 3g, 6g, or 9g			No treatment for cataplexy

Screening Period: Lasted one day to four weeks. For patients taking tricyclic antidepressants (TCAs) or other drugs used to treat cataplexy, these were gradually withdrawn. Patients not on TCAs proceeded directly to the next study period if they met entry criteria. Patients were permitted to continue taking stable doses of stimulant medication throughout the study.

Washout Period: Lasted five to twenty-eight days. This period allowed time to eliminate any clinical effects of TCAs, for rebound cataplexy (cataplexy that with greater frequency and severity than usual) to abate, and to train patients on the use of the diary. The duration of this period was determined by considering the prior anticataplectic medication, and was five times the half-life of that medication, with a minimum of five days for diary training and a maximum of twenty-eight days.

Baseline Period: Lasted two to three weeks. This period was an opportunity to assess the patients' attacks of cataplexy and to establish a stable number of attacks. Eligibility for admission into the double-blind treatment period required patients to report an average of three or more complete and/or partial cataplexy attacks per week, during the last two weeks of the baseline period.

Double-Blind Treatment Period: Lasted four weeks. Eligible patients were randomly assigned to receive each night 3g, 6g, or 9g GHB or placebo in two divided doses. Patients returned approximately every two weeks during this period for assessment of safety and efficacy.

Follow-up Period: A visit for final assessment three to five days after study medication was discontinued.

Entry criteria included adult patients with a diagnosis of narcolepsy, a history of excessive daytime sleepiness and an average of three or more cataplexy attacks per week during the baseline period. Patients with a diagnosis of sleep apnea, women of child bearing potential (unless using an accepted form of birth control), patients taking hypnotics, tranquilizers, or sedating antihistamines, and patients with a history of seizures or head trauma were excluded from the study.

Approximately 104 patients (26 in each of the four treatment groups) were planned to be enrolled in this study. One hundred and thirty-six patients were actually enrolled and randomly assigned to receive four weeks of treatment with study medication. Additional patients were enrolled to ensure that a sufficient number of evaluable patients completed the study. Medication was packaged in foil pouches and mixed with water. One dose was taken at bedtime, and the second dose was taken 2.5 to 4 hours later. A third party dispenser was employed at each site so that the investigator and the study coordinator did not handle the medication and the integrity of the blind was maintained.

The primary efficacy variable was the change from baseline in the total number of cataplexy attacks (complete + partial) recorded by patients on their diary (the change was calculated from baseline): last two weeks before study medication was started in a patient; to endpoint (the last two weeks a patient was on study medication). Other efficacy variables included the number of complete cataplexy attacks, the number of partial cataplexy attacks, changes in daytime sleepiness, changes in the number and duration of inadvertent naps/sleep attacks, changes in the number of awakenings during the night, change in the total amount of sleep, changes in the incidence of hypnagogic hallucinations, changes in the incidence of sleep paralysis, and the clinical global impressions of change.

3.1.1.3 Discussion of Study Design

Patients naïve to GHB were selected. Patients with a history of excessive daytime sleepiness, cataplexy, a current diagnosis of narcolepsy for at least six months according to Criteria A of the American Sleep Disorders Association were included. Patients were excluded if they had a diagnosis of sleep apnea syndrome or any other cause of daytime sleepiness. Patients were excluded if they were taking hypnotics, tranquilizers, antihistamines (except for non-sedating antihistamines), or clonidine at the start of the baseline period. Patients taking tricyclic antidepressants or other medication to treat cataplexy were withdrawn from those treatments gradually. The list of tricyclic antidepressants and other anticataplexy medication included: protriptyline, imipramine, clomipramine, desipramine, viloxazine, fluoxetine, paroxetine, sertraline or other serotonin reuptake inhibitors or other tricyclic or heterocyclic antidepressants. Patients taking anticonvulsants were not eligible to participate in the study. Patients were allowed to continue taking stimulant medication to include amphetamine, methamphetamine, methylphenidate, or pemoline for the treatment of daytime

sleepiness. Patients were advised not to consume alcoholic beverages during the entire course of the trial and also to use caution in the use of any opioid analgesics or skeletal muscle relaxants. Patients were otherwise free of medication for narcolepsy during the trial. The screening, washout, and baseline periods were variable lengths of time, determined by the investigator within defined limits.

A screening period of one day to four weeks was added to the design for safety purposes. The screening period enabled investigators to gradually withdraw patients from tricyclic antidepressants or other anticataplexy medication. These medications are commonly associated with rebound cataplexy on withdrawal. The rebound cataplexy was perceived to be of sufficient magnitude to constitute a safety concern. The importance of having a companion or other support system available during the screening, washout and baseline periods was stressed to each patient. Patients were instructed to begin keeping daily diaries at the screening period in order to train them on its use prior to the baseline period.

A washout period of five to twenty-eight days was added to the design to eliminate any clinical effects of tricyclic antidepressant or other anticataplexy medication prior to baseline. The washout period started when the last dose of a tricyclic antidepressant or other anticataplexy medication was taken by the patient. The length of the washout period was determined by the investigator by considering the pharmacokinetic and pharmacodynamic profile of the tricyclic antidepressant or other anticataplexy medication being used by the patient during the screening. A minimum of five days of washout was required for patients not taking anticataplexy mediation for the purpose of insuring adequate training on the patient diary. The investigators were required to employ a washout period equivalent to a minimum of five times the half-life of the anticataplexy medication in use (for a maximum of twenty days). The investigators were provided with a list of the drugs typically used to treat cataplexy along with their half-lives and a suggested time for washout for each.

A baseline period of two to three weeks enabled the investigator to assess the patient's cataplexy incidence in the absence of anticataplectic medications, and daily dairy recording habits. The patients qualified for admission to the treatment phase by reporting an average $\geq$ three cataplexy attacks per week during the last two weeks of the baseline period.

The treatment period was four weeks in length with a clinic visit at two weeks. The treatment period was confined to four weeks because it was not ethically sound to continue a symptomatic patient randomized to placebo for a longer period. The investigators contacted each patient on the morning following the first dose of test medication to assess the patient's tolerance of the test medicine. Thereafter patients were contacted at least three times weekly for assessments of compliance, diary completion, and adverse events.

After four weeks of treatment the patients were withdrawn from test medication. The appearance of any rebound cataplexy and other adverse events were noted at a follow-up visit scheduled three to five days following the end of treatment visit.

3.1.1.4 Assignment of Patients to Treatment Groups

At Visit 1, all patients were assigned a unique, four-digit, patient identification number in the order they were seen at the clinic. The first two digits identified the site number and the last two digits identified the patient number assigned sequentially starting with 01. At Visit 4, patients who met the entry criteria were sequentially assigned a unique three-digit randomization number in the order they entered treatment. The patients were dispensed medication labeled with the correct assigned randomization.

3.1.1.5 Selection and Timing of Dose

Individual patient treatment, including the dose of sodium oxybate, was determined by random allocation. No provisions were made in the protocol to permit modification of the dosage regimen. Each patient self-administered two doses of their assigned study medication each day. The first dose was taken at bedtime, and the second 2.5 to four hours later. Patients were instructed to use an alarm to insure that they awakened to take the second dose no more than four hours after the first.

3.1.1.6 Concomitant Medications

Patients were not permitted to take any of the following medications at any time during the study: hypnotics, tranquilizers, antihistamines (except nonsedating antihistamines), clonidine, tricyclic antidepressants, serotonin reuptake inhibitors, monoamine oxidase (MAO) inhibitors, tetracyclic antidepressants, or anticonvulsants. Patients were also not permitted to use alcohol during the study and were cautioned on the use of opioid analgesics and skeletal-muscle relaxants. Women of childbearing potential were permitted to use oral contraceptives. Periodic use of over-the-counter and prescription medicines for treatment of colds, flu, allergies, headaches, etc. required careful review by the investigator prior to use.

3.1.1.7 Primary Efficacy Variable

The primary efficacy variable for this study as defined in the protocol was the total number of cataplexy attacks which is the sum of complete and partial cataplexy attacks that occurred. The median of the total number of cataplexy attacks that occurred in each treatment group during the last two weeks of the baseline period was compared with the median number of events that occurred during the last two weeks of the treatment period (endpoint). Other efficacy measures such as daytime sleepiness and improvement in inadvertent naps were measured along with reduction in the number of episodes of cataplexy.

3.1.1.8 Statistical and Analytical Plans

As described in the protocol, the efficacy analyses were done on the intent-to-treat population. The planned analyses called for an analysis of variance on the change from baseline to endpoint induding in the model the factors of treatment, site, and their

interaction. The interaction term was then to be removed if found to be not statistically significant. In addition, an analysis of covariance (ANCOVA) was planned for the primary efficacy variable (change in total number of cataplexy attacks) using the baseline value as covariate.

Prior to the completion of the study and database lock, an analysis plan was written and approved that detailed performing a log transformation, if the assumptions for ANCOVA were not satisfied. It was anticipated that for many, if not all, of the efficacy variables, the log transformation would result in a more normal distribution conforming to the requirements of the ANCOVA.

At the time of analysis, each of the primary and secondary efficacy variables was assessed for normality and whether a log transformation would improve the distribution. The reassessment was based on using the Wilk-Shapiro test for normality on the residuals from the fitted model and a plot of the residuals against the predicted response, also from the fitted model. If the untransformed data indicated a non-normal distribution, based on the Wilk-Shapiro test, and if the transformed data demonstrated improvement (tending toward a more normal distribution) through both the Wilk-Shapiro test and the plot of the residuals against the predicted, the log transformation was used. Those measures that were analyzed using the log transformation included the following:

- Total number of cataplexy attacks
- Partial cataplexy attacks
- Complete cataplexy attacks
- Duration of inadvertent naps/sleep attacks/day
- Sleep paralysis (episodes/day)
- Hypnagogic hallucinations
- Number of awakenings

For each of these measures, because a 0 was possible, the value 1 was added prior to the log transformation. As a result, the variable analyzed was log (endpoint + 1) – log (baseline + 1). The ANCOVA model used to assess overall treatment group comparisons included treatment, site, and log (baseline + 1). The interaction of treatment and site and treatment with log (baseline + 1) were included in the model and then removed when found to be not statistically significant. Comparisons of GHB dose to placebo were performed using least-squares means with Dunnett's adjustment. The significance of the median change from baseline for each treatment group was assessed using a paired t-test.

Several measures did show a normal distribution without a log transformation. They included:

- Epworth Sleepiness Scale
- Total amount of sleep/night
- Number of inadvertent naps/day

For these variables, the analysis procedures were consistent with those previously described, but were based on the untransformed values.

The Clinical Global Impressions of Change (CGI-c) was assessed by correlation analysis using Cochran-Mantel-Haenszel Test for Nonzero Correlation between the CGI-c score and treatment.

3.1.1.9 Determination of Sample Size

The required sample size for this study was calculated using the change from baseline in the total number of cataplexy attacks (primary efficacy variable) occurring in one week. Previous studies suggested than can effective dose of sodium oxybate would produce a mean reduction of at least 2 cataplexy attacks, based upon the number per week at baseline, in the number of weekly attacks with a standard deviation of 2.5. Using a power of 80% and a two-sided significance level of 0.05, 100 patients were needed, 25 per treatment group, to detect a treatment group difference of 2 with respect to change in cataplexy attacks.

3.1.1.10 Disposition of Patients

One hundred and thirty-six patients were enrolled in the study from sixteen centers, and sixteen patients withdrew from the study before completion, for the reasons shown in Table 3.2.

Table 3.2 Disposition of Patients

Disposition	All patients	Placebo	Xyrem dose (g)		
			3	6	9
Received study medication	136	34	34	33	35
Withdrew from study					
Adverse event	10	1	1	2	6
Protocol deviation	1		1		
Patient request	2		1		1
Lost to follow-up	1			1	
Lack of efficacy	2		1	1	
Total withdrawals	16	1	4	4	7
Completed the study	120	33	30	29	28

The primary reason for withdrawal from the study was the development of adverse events (10 patients). Patient withdrawals for adverse events were more frequent in the 9g GHB dose group than in the other three treatment groups. Patients who withdrew

from the study were followed until adverse events or laboratory abnormalities resolved or were fully characterized.

3.1.1.11 Data Sets Analyzed

Since the analysis performed in this study was an intent-to-treat analysis, no patients were excluded from the analysis.

3.1.1.12 Demographic and Other Baseline Characteristics

The demographic characteristics of the 136 patients who received study medication are summarized in Table 3.3.

Table 3.3 Demographic Characteristics of Study Population

Characteristic	All Patients	Placebo	Xyrem dose (g)			p-value*
			3	6	9	
Age						0.2737
n	136	34	34	33	35	
mean (years)	43.06	40.82	47.06	43.52	43.91	
SD	15.03	14.33	16.89	14.98	13.53	
Gender						0.0027
Male	57	12	7	21	17	
Female	79	22	27	12	18	
Race						0.1379
Caucasian	124	29	33	31	31	
African American	9	4	0	1	4	
Asian	1	0	0	1	0	
Other	2	1	1	0	0	
Height						0.0283
N	131	31	33	33	34	
mean (cm)	170.91	171.97	166.7	173.1	171.9	
SD	9.53	8.18	8.78	10.39	9.64	
Weight						0.4847
N	134	34	33	33	34	
mean (kg)	82.87	83.98	78.86	85.04	83.56	
SD	17.36	18.89	15.65	15.54	19.08	

*p-value based on ANOVA (GLM)

Significant between group differences in gender and height were noted. The 6g GHB group was predominantly male, while the placebo and 3g GHB groups were predominantly female. Consistent with the large difference in distribution of males and females in the 3g GHB group, the height of this group was less than the other treatment groups.

The severity of narcolepsy in the patient population was assessed by documenting the historical frequency of symptoms that were reported in the three months prior to screening.

Table 3.4 summarizes the narcolepsy symptom profile recorded in the patient diaries during the last two weeks of baseline, representing narcolepsy symptoms in the absence of anticataplectic or sedative/hypnotic medications, but with continued stable stimulant medication.

Table 3.4 Summary of Baseline (Visit 4) Narcolepsy Symptoms by Treatment Group

		Xyrem Dose (g)			
Type of event	Placebo	3	6	9	p-value Kruskal-Wallis
Total cataplexy attacks/week					0.7749
N	34	33	33	35	
Mean	34.27	28.57	38.85	34.60	
Median	20.21	20.00	23.00	23.50	
SD	46.63	30.53	55.04	33.92	
Complete cataplexy attacks/week					0.5151
N	34	33	33	35	
Mean	6.86	7.08	15.26	8.61	
Median	1.12	4.50	4.85	2.00	
SD	12.37	8.50	27.53	14.01	
Partial cataplexy attacks/week					0.7289
N	34	33	33	35	
Mean	27.44	21.49	23.59	26.12	
Median	15.03	15.00	16.15	18.79	
SD	42.08	28.30	29.01	26.14	
Hypnagogic hallucinations/day					0.9766
N	34	33	33	34	
Mean	0.57	0.58	1.14	0.53	
Median	0.23	0.43	0.33	0.29	
SD	0.74	0.68	3.72	0.70	
Sleep paralysis episodes/day					0.9597
N	34	33	33	35	
Mean	0.51	0.42	0.73	0.41	
Median	0.26	0.14	0.08	0.10	
SD	0.74	0.55	1.84	0.60	
Inadvertent naps/day					0.7008
N	34	33	33	35	
Mean	1.71	1.91	1.70	1.72	
Median	1.57	1.93	1.45	1.27	
SD	0.96	1.43	1.12	1.56	

3.1.1.13 Excessive Daytime Sleepiness

Daytime sleepiness was the subjective assessment of a patient's ability to remain alert and awake. Excessive daytime sleepiness was defined as difficulty remaining awake and was usually accompanied by rapid entrance into sleep when the patient was sedentary. This variable was assessed through the use of the Epworth Sleepiness Scale (ESS). The ESS is a subjective report of propensity to sleep, difficulty in maintaining an alert awake state, usually accompanied by a rapid entrance into sleep when the person is sedentary. The ESS was used at the end of baseline (Visit 4), at the end-of-treatment (Visit 6), and again at the last follow-up visit (Visit 7). Patients were to rate their "chance of dozing" on a scale of 0-3 (never, slight, moderate, and high chance of dozing) in each of eight possible situations:

- Sitting and reading
- Watching TV
- Sitting, inactive in a public place (i.e. a theater or a meeting)
- As a passenger in a car for an hour without a break
- Lying down to rest in the afternoon when circumstances permit
- Sitting talking to someone
- Sitting quietly after lunch without alcohol
- In a car, while stopped for a few minutes in traffic

The ESS measures sleep propensity based on the retrospective report of the subject's dozing behavior in eight everyday situations. This brief, self-administered questionnaire asks that the subject rate the chances that over the recent past (i.e. since the last prior rating) whether he or she would have dozed in each of the eight situations. The relative soporific nature of these situations has been described both for "sleepy patients" and a normal population of medical studies and are known to remain stable within individuals over a period of months (Johns 1991). The ESS score is the sum of eight individual item scores and ranges from 0 to 24. In one study ESS scores for narcoleptics averaged 16.8, general sleep disorder patients averaged 10.2, and healthy medical studies averaged 7.4 to 7.6 (Johns 1991).

Excessive daytime sleepiness at baseline as assessed by the Epworth Sleepiness Scale is presented in Table 3.5. This mean Epworth score can be considered in the moderately severe to markedly severe range, in spite of maintained stable stimulant medication.

Table 3.5 Summary of Excessive Daytime Sleepiness at Baseline as Assessed by the Epworth Sleepiness Scale

		Xyrem Dose (g)		
Statistic	**Placebo**	**3**	**6**	**9**
N	34	34	32	35
Mean	18.47	17.06	17.28	16.66
SD	3.13	3.71	3.49	4.07

3.1.1.14 Clinical Global Impression of Severity (CGI-S)

This parameter was the investigator's assessment of the severity of a patient's narcolepsy and was recorded at Visit 4. It was made in relation to the investigator's total experience with the narcoleptic population using the following assessments:

- Not assessed
- Normal – no signs of illness
- Borderline ill
- Slightly ill
- Moderately ill
- Markedly ill
- Among the most extremely ill

The CGI-severity score is an expert clinical measure of the patient's general condition at baseline. The majority of patients were judged to be markedly or extremely ill, followed by those who were judged moderately ill and with much fewer patients in the borderline, slightly, or normal categories as seen in Table 3.6 below. There were no significant differences in the percentage of patients enrolled in any severity response category. Subsequent changes from the baseline CGIs score are captured in the Clinical Global Impression of change (CGI-c) score.

Table 3.6 Baseline Clinical Global Impression of Severity (CGI-S)

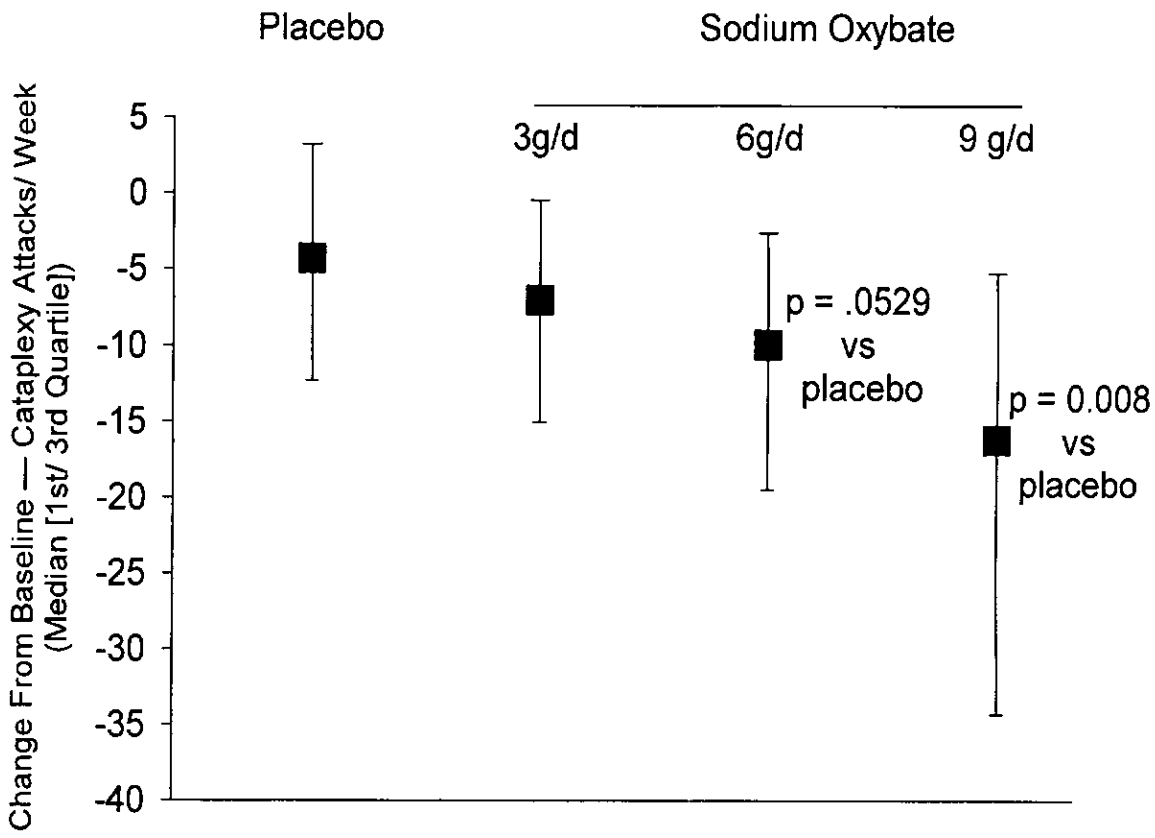
Treatment	Normal	Borderline	Slightly ill	Moderately ill	Markedly ill	Extremely ill
Placebo	0	2	2	8	12	10
3g Xyrem	0	1	1	11	17	4
6g Xyrem	1	1	0	14	11	6
9g Xyrem	0	1	2	13	15	4
Total	1	5	5	46	55	24

3.1.1.15 Analysis of Efficacy

3.1.1.15.1 Primary Efficacy Variable

The primary efficacy variable was the change from baseline in the total number of cataplexy attacks. As shown in Table 3.7, the median and mean values for total cataplexy attacks/week were noted to be similar across dose groups. As noted in Table 3.7, there was a significant (p=0.0021) difference among treatment groups in change from baseline to endpoint in total number of cataplexy attacks/week with treatment. The change in total number of cataplexy attacks exceeded placebo, and was in the clinically meaningful range in all Xyrem treatment groups (Table 3.7 and Figure 3.1). Like most neuropharmacology studies, there was also considerable placebo response, potentially in part the consequence of the disciplined sleep hygiene imposed by the protocol and diary recording of sleep habits during the treatment period. As a result, the difference between Xyrem treatment groups compared to placebo response showed marginal significance in the 6g Xyrem group (p=0.0529), and unambiguous statistical significance in the 9g Xyrem group (p=0.0008).

Figure 3.1 Changes in Total Number of Cataplexy Attacks (Baseline to Endpoint) — OMC-GHB-2



However, these results still indicate an important clinical response to the three dosages of sodium oxybate. The median frequency of cataplectic events at the end of four weeks of treatment shows similarity in the three dosage groups (3 g/day = 9.5, 6 g/day = 8, 9 g/day 8.7), all of which differ markedly from the median placebo response of 16.3 (see Table 3.7).

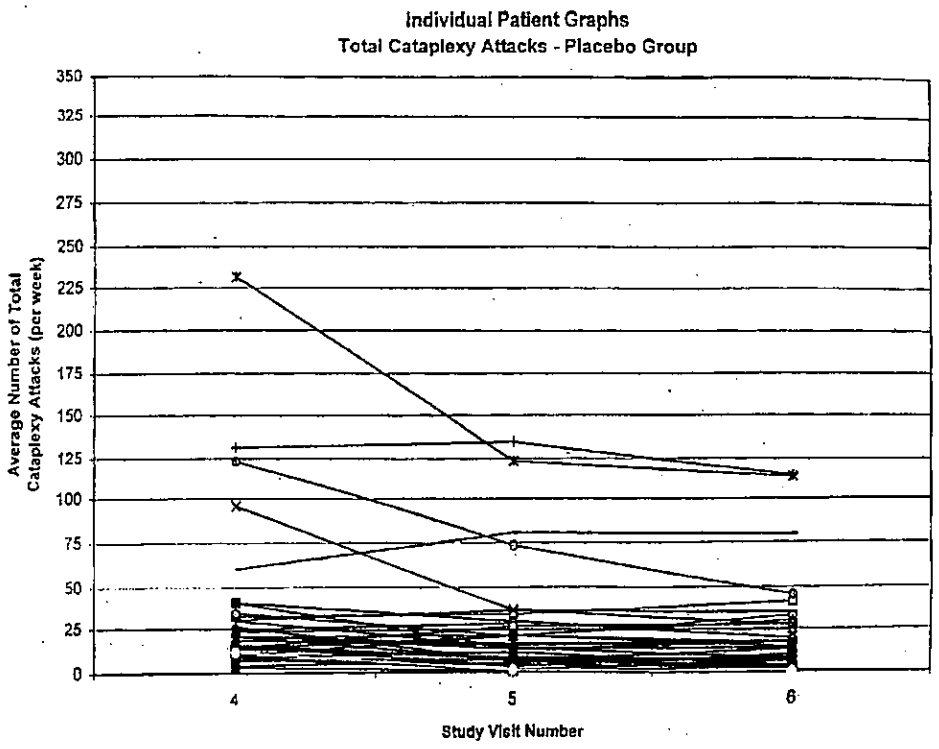
Table 3.7 Total Number of Cataplexy Attacks

Dose group	Statistic	Observed		Change from baseline to endpoint	Comparison with placebo (p-value)
		Baseline	Endpoint		
Placebo	N	33	33	33	
	Mean	35.1	24.0	-11.1	
	Median	20.5	16.3	-4.3	
	SD	47.1	28.4	27.7	
	p-value			0.028	
3g	N	33	33	33	
	Mean	28.6	19.5	-9.1	
	Median	20.0	9.5	-7.0	0.5235
	SD	30.5	27.5	22.4	
	p-value			0.026	
6g	N	31	31	31	
	Mean	33.8	24.6	-9.2	
	Median	23.0	8.0	-9.9	0.0529
	SD	45.6	62.9	27.3	
	p-value			0.070	
9g	N	33	33	33	
	Mean	35.7	14.4	-21.3	
	Median	23.5	8.7	-16.1	0.0008
	SD	34.5	19.3	29.8	
	p-value			<0.001	

P=0.0021 for overall treatment group comparison

Interpretation of this data clinically is complicated by the fact that frequency of cataplexy attacks in this trial is not normally distributed data (incidence ranging from 2.8 cataplexy attacks/week to 249/week at baseline, with a median frequency of 21.0/week). When plots of individual patient data are considered it is possible that outlier data such as one patient in the 6 g dosage group may have represented ongoing REM rebound phenomena, directly affecting statistical interpretations. The consideration of these individual patient responses in the spaghetti plots (Figures 3.2, 3.3, 3.4, and 3.5) indicated the dose response in all dosage groups.

Figure 3.2


Individual Patient Graphs
Total Cataplexy Attacks - Placebo Group
Average Number of Total Cataplexy Attacks (per week)
350
325
300
275
250
225
200
175
150
125
100
75
50
25
0
4
5
6
Study Visit Number

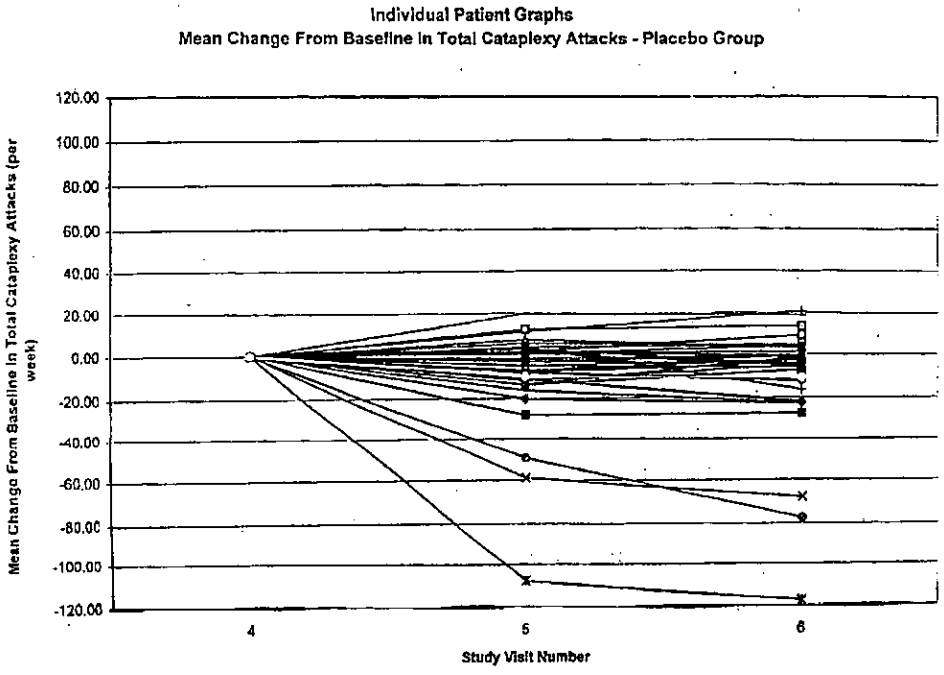
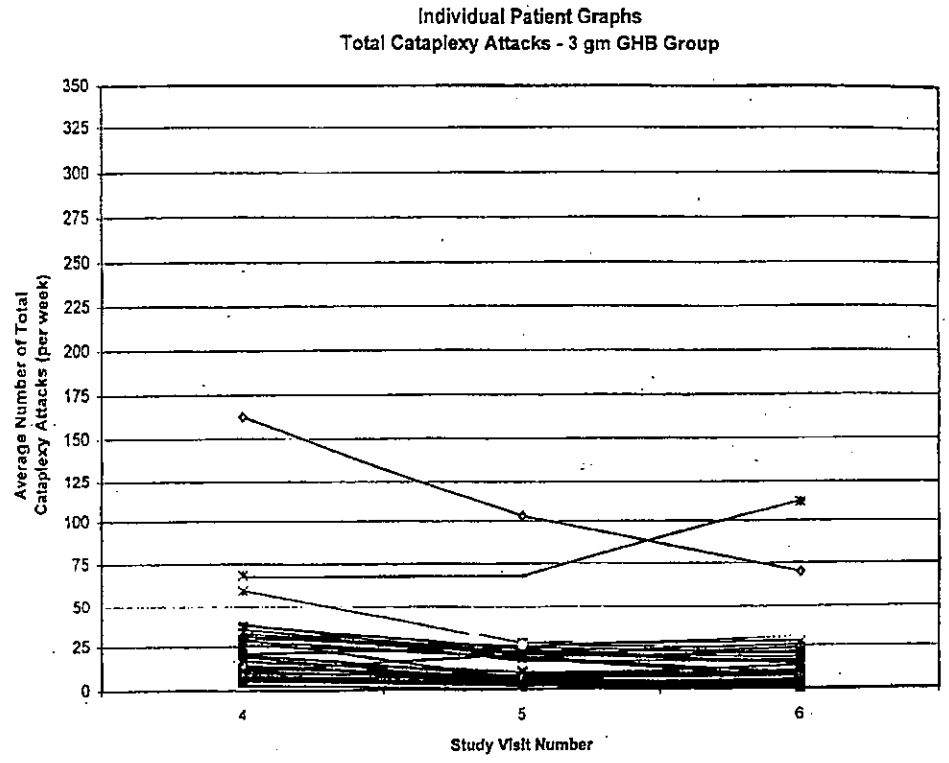

Individual Patient Graphs
Mean Change From Baseline in Total Cataplexy Attacks - Placebo Group
Mean Change From Baseline in Total Cataplexy Attacks (per week)
120.00
100.00
80.00
60.00
40.00
20.00
0.00
-20.00
-40.00
-60.00
-80.00
-100.00
-120.00
4
5
6
Study Visit Number

Figure 3.3


Individual Patient Graphs
Total Cataplexy Attacks - 3 gm GHB Group
Average Number of Total Cataplexy Attacks (per week)
350
325
300
275
250
225
200
175
150
125
100
75
50
25
0
4
5
6
Study Visit Number

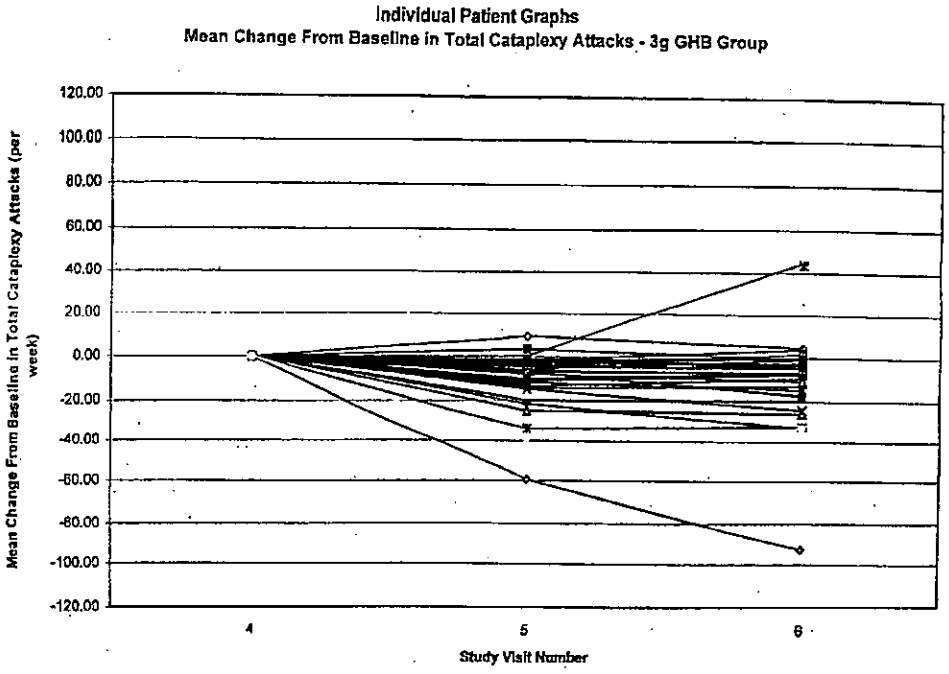
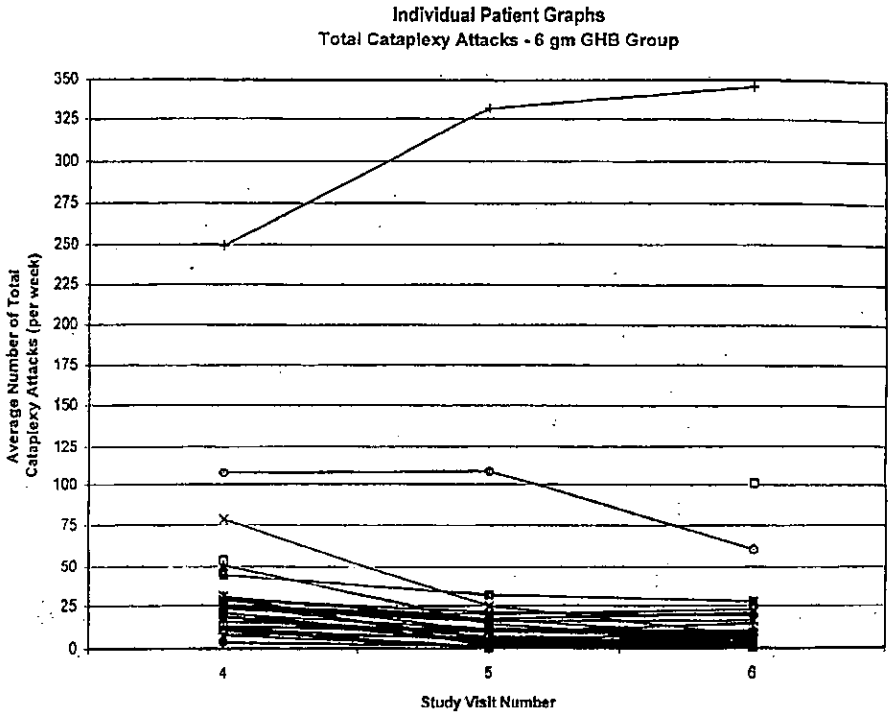

Individual Patient Graphs
Mean Change From Baseline in Total Cataplexy Attacks - 3g GHB Group
Mean Change From Baseline in Total Cataplexy Attacks (per week)
120.00
100.00
80.00
60.00
40.00
20.00
0.00
-20.00
-40.00
-60.00
-80.00
-100.00
-120.00
4
5
6
Study Visit Number

Figure 3.4



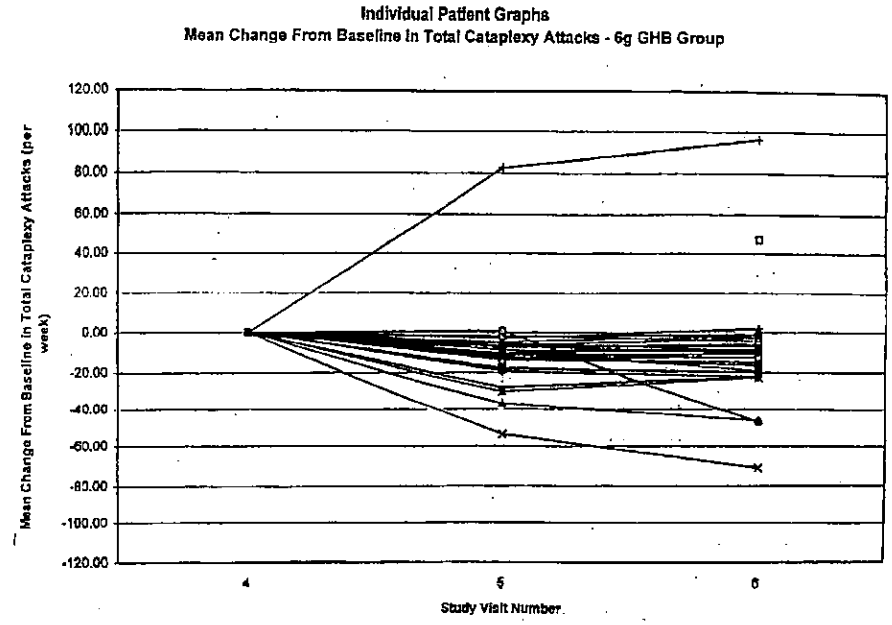
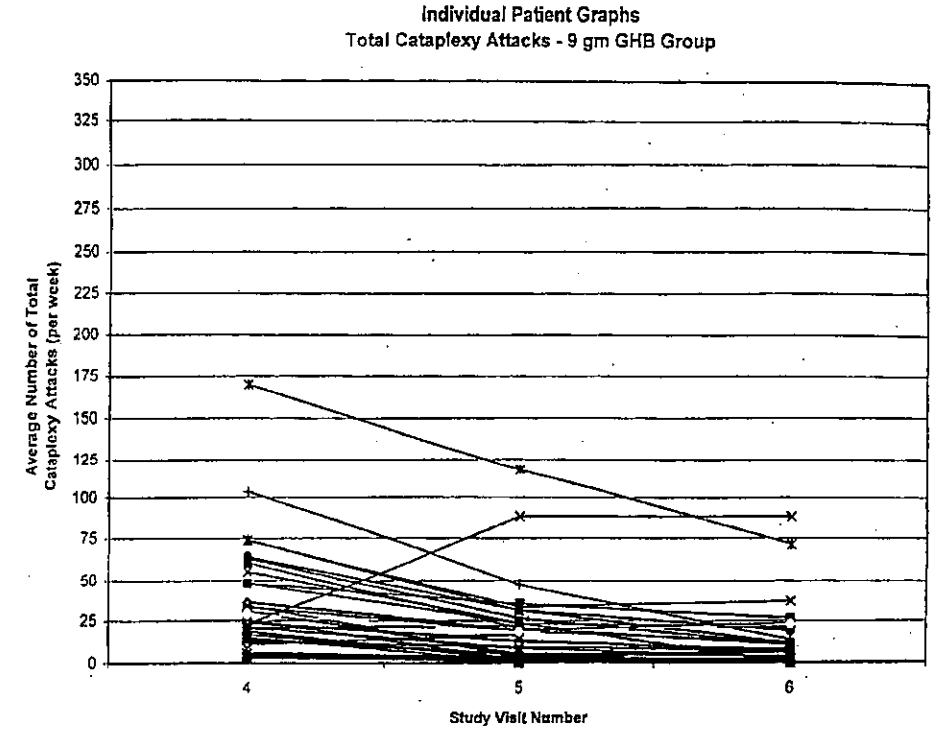
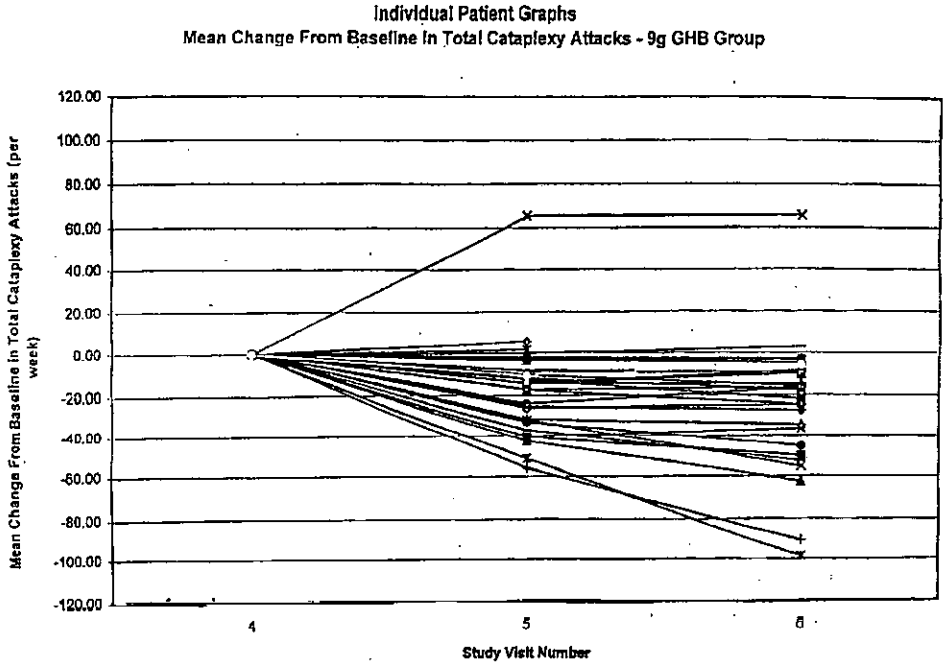


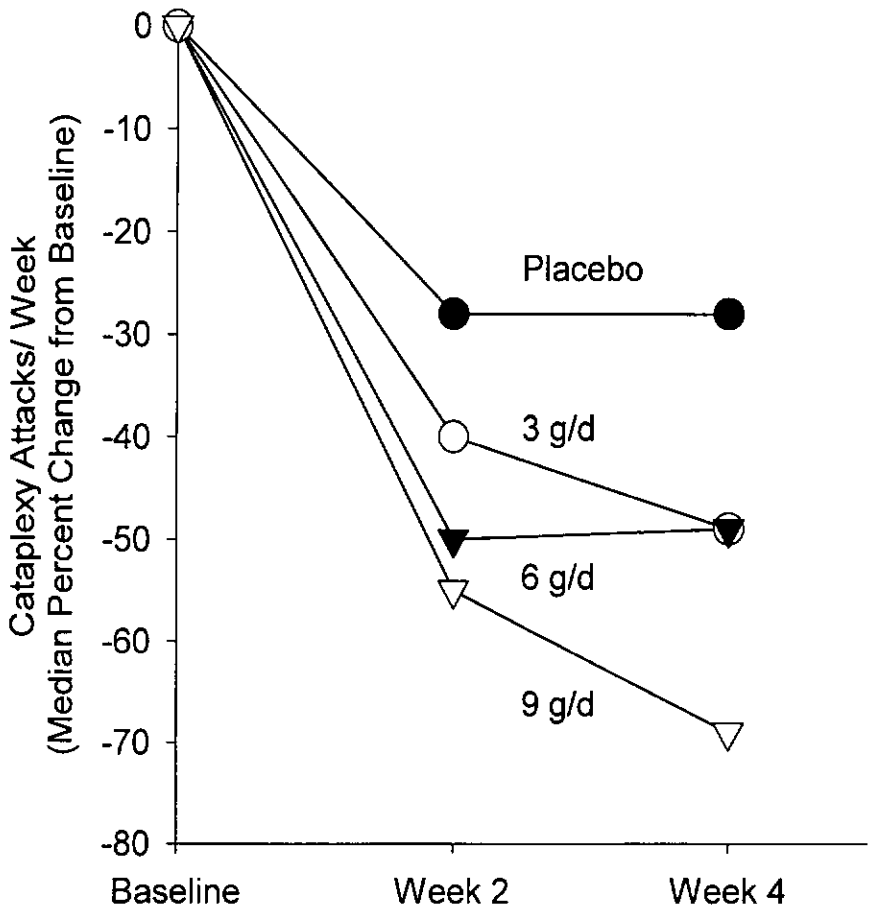
Figure 3.5


Individual Patient Graphs
Total Cataplexy Attacks - 9 gm GHB Group
Average Number of Total Cataplexy Attacks (per week)
350
325
300
275
250
225
200
175
150
125
100
75
50
25
0
4
5
6
Study Visit Number


Individual Patient Graphs
Mean Change From Baseline in Total Cataplexy Attacks - 9g GHB Group
Mean Change From Baseline in Total Cataplexy Attacks (per week)
120.00
100.00
80.00
60.00
40.00
20.00
0.00
-20.00
-40.00
-60.00
-80.00
-100.00
-120.00
4
5
6
Study Visit Number

In Figure 3.6, the percentage change in the total number of cataplexy attacks from baseline (median) was calculated on the distribution of change values for each individual patient at baseline, two weeks, and four weeks of treatment. This indicates that with the exception of the 9g treatment group, the majority of the reduction in cataplexy attacks occurred during the first two weeks of treatment, as is also represented by the previous graphs of individual patients.

Figure 3.6 Changes in Number of Cataplexy Attacks by Dosage Group Over Time — OMC-GHB-2



3.1.1.15.2 Secondary Efficacy Variables

3.1.1.15.2.1 Complete Cataplexy Attacks

As shown in Table 3.7, at baseline the median number of complete cataplexy attacks was 1.2, 4.5, 4.7, and 2.0 in the placebo, 3g, 6g and 9g treatment groups respectively. Complete cataplexy attacks were much less frequent than partial cataplexy attacks although clinically they are particularly dangerous. At endpoint the median number of complete cataplexy attacks changed by 0, -1.00, -1.62, and –1.62 in the placebo, 3g, 6g and 9g treatment groups respectively. While there appears to be a dose response, none of the decreases reached statistical significance when compared to placebo, although the pattern of changes were in a dose response manner.

3.1.1.15.2.2 Partial Cataplexy Attacks

Also shown in Table 3.7, at baseline the median number of partial cataplexy attacks was 15.05, 15.00, 15.15, and 18.79 in the place, 3g, 6g and 9g treatment groups respectively. From baseline to endpoint the median number of partial cataplexy attacks changed by –2.72, -3.69, -6.35, and –10.00 in the placebo, 3g, 6g, and 9g treatment groups respectively exhibiting a dose response relationship that was statistically significant from placebo at 9g (p=0.0009). Hence the patterns of change were similar in complete and partial cataplexy attacks although the much more frequent partial cataplexy attacks were statistically more powerful in showing the dose response.

3.1.1.15.2.3 Clinical Global Impression of Change (CGI-c)

The Clinical Global Impression of Change was an integrated clinical measure based on the investigator's overall impression of the change in the patient's condition. This measure was based on comparison of the patient's condition at the time of a comprehensive baseline interview defining the severity of patient illness at the time of entry into the study captured in the Clinical Global Impression of Severity (CGI-s). The CGI-c focused on overall clinical change in severity including all narcolepsy symptoms and effectiveness in activities of daily living and incorporating any problems in overall functioning deriving from adverse experiences.

During Visit 6 (the last treatment visit) and Visit 7, investigators rated their impressions of any change in the severity of the patient's overall condition of narcolepsy using the CGI-c rating scale as follows:

- Very much improved
- Much improved
- Minimally improved
- No change
- Minimally worse
- Much worse
- Very much worse

As shown in Table 3.8 and Figure 3.7 below, a highly significant treatment effect was noted on the CGI-c scale. The majority of placebo patients were observed to have a modal value of *no change*, with 35% *no change*. The placebo population distributed mainly into the *no change*, *minimally improved* and *much improved* brackets with the population distribution weighted to the *no change/minimally improved* group. The majority of placebo patients fell in the combined *no change/minimally improved* brackets. A similar distribution was noted in the 3g group although with higher proportions in the *minimally improved* and *much improved* groups and a model value at the *much improved* group and half the patients in the *no change/minimally improved* brackets. In the 6g dose group, the distribution is seen to have shifted upwards with fewer *no change* and more *very much improved* patients and a majority of patients in the *minimally improved/much improved* brackets. In the 9g dose group a marked shift of distribution is seen with a large majority of patients in the *much improved* (43%) and *very much improved* (37%) brackets. Hence a global clinical assessment measure incorporating all aspects of the patient's disease strongly demonstrates the dose response trend to Xyrem.

Table 3.8 Summary of Clinical Global Impression of Change at Endpoint by Treatment Group

		Xyrem Dose (g)		
Impression	**Placebo**	**3**	**6**	**9**
Very much improved	3 (9%)	3 (10%)	5 (16%)	11 (37%)
Much improved	8 (24%)	11 (37%)	11 (35%)	13 (43%)
Minimally improved	8 (24%)	9 (30%)	9 (29%)	3 (10%)
No change	12 (35%)	6 (20%)	5 (16%)	1 (3%)
Minimally worse	0	0	0	0
Very much worse	1 (3%)	0	1 (3%)	0

P=0.0010 for overall treatment group comparison based on Cochran-Mantel-Haenzel Test for Nonzero Correlation

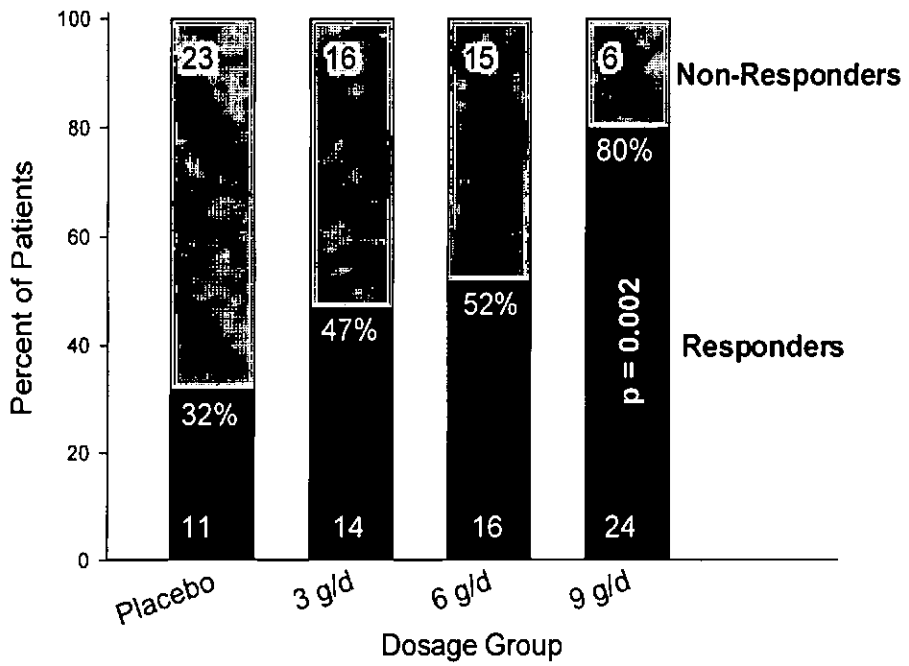
The CGI-c data can also be viewed in another manner as defining a responder analysis (see Table 3.9 and Figure 3.7). Given that the majority of placebo patients fall into the *no change/minimally improved* brackets, a responder was defined as a patient falling into the *much improved* or *very much improved* category. This responder definition also has the virtue of defining patients who, on face value, showed a clear clinical benefit since an experienced clinician rated them as *much improved* or *very much improved*. For this post hoc analysis, responders included the *very much improved* or *much improved* categories; and nonresponder included all other categories of CGI-c except not assessed. Patients not assessed or with missing CGI-c scores were not included in Table 3.9.

Table 3.9 Summary of Clinical Global Impression of Change to Endpoint by Treatment Group for Responders and Nonresponders

		Xyrem Dose (g)			
Category	Placebo	3	6	9	p-value* (overall comparison)
Responders	11 (32%)	14 (47%)	16 (52%)	24 (80%)	0.0014
Nonresponders	23 (68%)	16 (53%)	15 (48%)	6 (20%)	
p-value (group vs placebo)		0.3075	0.1368	0.0002	

*Based on Fisher's Exact Test

Figure 3.7 Summary of CGIc at Endpoint by Treatment Group — OMC-GHB-2



In Figure 3.7 the percentage of responders improved across the treatment groups in a dose response manner with a particularly sharp improvement to 80% in the 9g group (p=0.0002) as compared to 32% in the placebo group.

This post hoc responder analysis detects the same dose response trend evident in the inspection of the categorical analysis of the patients seen in Table 3.9.

3.1.1.15.2.4 Excessive Daytime Sleepiness

The Epworth data provide another independent confirmation of the dose response of narcoleptic symptoms to Xyrem. The Epworth Sleepiness Scale draws on the patient's subjective assessment of their propensity to fall asleep in different circumstances. As presented in Table 3.10, Figure 3.8 below, excessive daytime sleepiness as assessed by the Epworth Sleepiness Scale improved in all Xyrem treated groups and the improvement compared with placebo was highly significant in the 9g group (p=0.0001) where the change from baseline was nearly twice that seen in the 3g and 6g groups.

Figure 3.8 Daytime Sleepiness (Baseline to Endpoint)

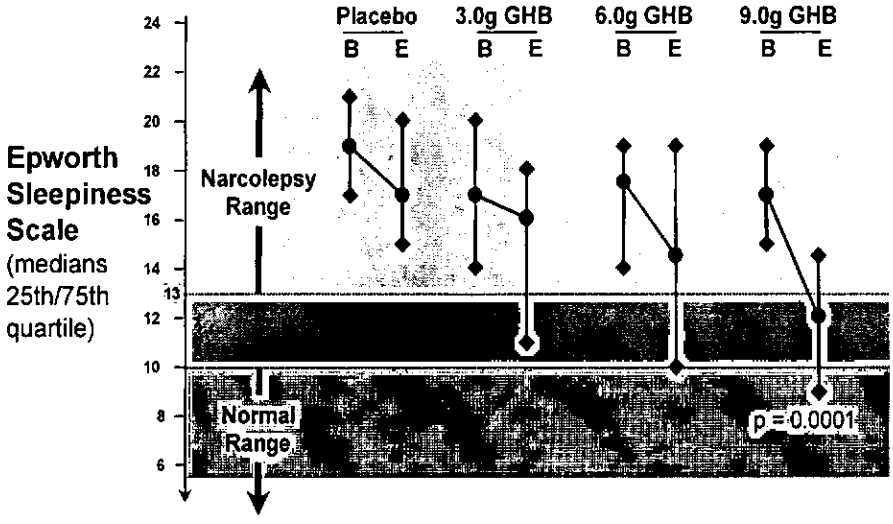


Table 3.10 Summary of Changes from Baseline to Endpoint in Excessive Daytime Sleepiness as Assessed by Epworth Sleepiness Scale

Dose group	Statistic	Observed		Change from baseline to endpoint	Comparison with placebo (p-value)
		Baseline	Endpoint		
Placebo	N	33	31	33	
	Mean	18.4	17.3	-1.1	
	Median	19.0	17.0	-1.0	
	SD	3.2	3.6	3.1	
	p-value			0.043	
3g	N	31	31	31	
	Mean	17.1	14.6	-2.5	
	Median	17.0	16	-1.0	0.1137
	SD	3.7	5.2	3.8	
	p-value			0.001	
6g	N	30	30	30	
	Mean	16.9	14.6	-2.4	
	Median	17.0	13.5	-2.0	0.1860
	SD	3.3	4.6	3.5	
	p-value			0.001	
9g	N	28	28	28	
	Mean	16.4	11.8	-4.7	
	Median	17.0	12.0	-3.5	0.0001
	SD	3.9	4.2	4.3	
	p-value			<0.001	

P= 0.006 for overall treatment group comparison

The reduction in ESS from baseline to endpoint was observed in all treatment groups, with again a dose-response trend as with cataplexy response. This change reached statistical significance (p=0.0001) in patients in the 9g/day dosage group compared to placebo. The first and second quartile lines represent that some patients in all three treatment groups have reduced ESS scores to the extent that they no longer reach the level considered characteristic of narcolepsy (13 to 24; Johns 1991). The median score in the 9g/day dosage group was outside the narcoleptic range, and over 25% of these patients had scores that were within the "normal" range (≤ 10), indicating a highly clinically significant reduction in patients' subjective rating of somnolence, and this change was incremental beyond the status achieved with stable dosages of stimulant medications continued during the trial.

3.1.1.15.3 Other Secondary Efficacy Measures

As presented in Figure 3.9 and Figure 3.10, compared with placebo a significant decrease in the number of inadvertent naps/sleep attacks was seen in both the 6g and 9g Xyrem groups (p=0.0497 and p=0.0122, respectively), and a significant decrease in the number of awakenings was seen in the 9g Xyrem group (p=0.0035). These data are consistent with the dose response pattern of reduced excessive daytime sleepiness reflected in the Clinical Global Impression of change and the Epworth Sleepiness Scale. No significant differences between treatments were seen in the change from baseline in the median number of hypnagogic hallucinations, sleep paralysis episodes, total amount of sleep, and duration of inadvertent naps/sleep attacks.

Figure 3.9 Median Changes for Number of Inadvertent Naps/Sleep Attacks From Baseline to Endpoint

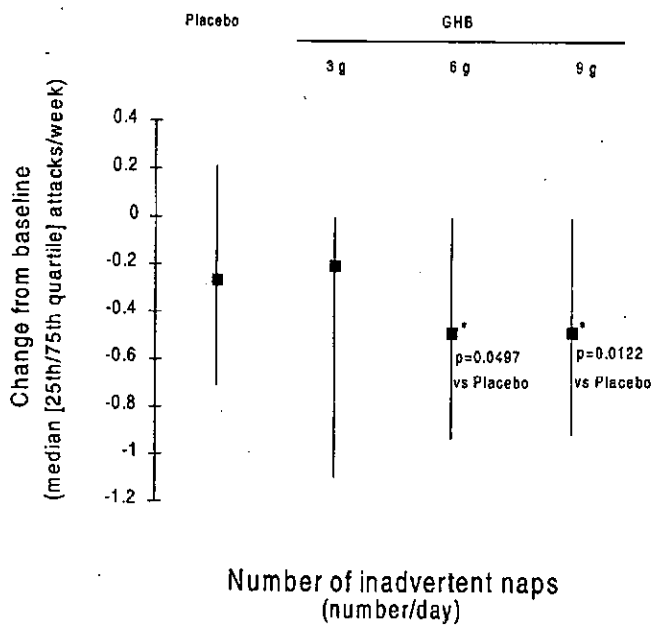
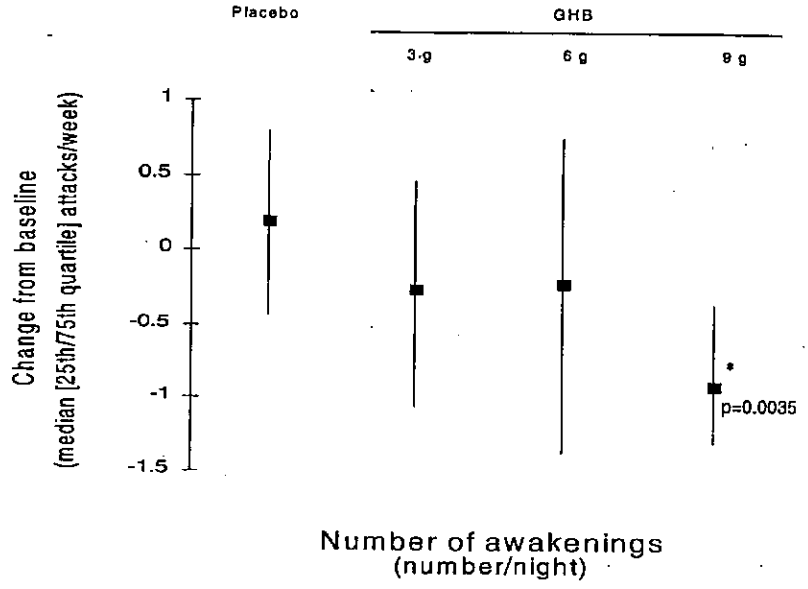


Figure 3.10 Median Changes for Number of Awakenings From Baseline to Endpoint



An exploratory analysis was conducted of the changes from baseline to endpoint in the parameters of subjective rating of quality of sleep, level of alertness, and ability to concentrate as rated by the patients. These parameters were measured on a four-point scale: 1-excellent, 2-good, 3-fair, 4-poor. For the 6g and 9g dose groups, there was a statistically significant increase in the subjective quality of sleep (p=0.0028 and p=0.0010), level of alertness (p=0.0006 and p=0.0004), and overall reported ability to concentrate (p=0.0229 and p=0.0007).

3.1.1.15.4 Abrupt Cessation of Double-Blind Medication

The change in incidence of cataplexy attacks that occurred following discontinuation of double-blind treatment (Visit 6) through the end of the trial three to five days later (Visit 7), and from baseline to Visit 7 was calculated. Only patients for which there were data at baseline (Visit 4), Visit 6 and Visit 7 were included in this analysis.

Table 3.11 Total Cataplexy Attacks per Week by Treatment Group – Medians Change from Visit 6 to Visit 7 and from Baseline to Visit 7

					V6-V7		Baseline to V7	
Treatment Group	N	Baseline	V6	V7	Change	P-Value	Change	P-Value
Placebo	30	20.6	16.5	17.5	1.9	0.06	-3.8	0.10
3g	29	18.7	9.5	13.0	2.3	0.09	-5.4	0.07
6g	29	23.0	8.0	16.3	6.1	0.0001	-3.3	0.13
9g	27	29.2	8.0	14.0	4.7	0.0017	-11.6	0.0001

Total cataplexy attacks per week were determined by first calculating the average daily number of cataplexy attacks based on the numbers recorded in the patient diaries, then multiplying this number by seven to get Total Cataplexy Attacks per Week.

Patients discontinued sodium oxybate treatment at Visit 6 (Week 4) and were to return to the clinic for assessment of cataplexy at Visit 7, three to five days later. According to their daily diary recordings, the median number of total cataplexy attacks per week for all patients in all treatment groups trended toward their higher baseline values. A significant change from Visit 6 to Visit 7 in the median number of cataplexy attacks per week occurred in the 6g group (p=0.0001) and 9g group (p=0.0017). The 9g dose group exhibited a significantly lower median number of weekly cataplexy attacks at Visit 7 than at baseline (p=0.0001).

In all treatment groups, acute rebound cataplexy was not in evidence as the median number of attacks at Visit 7 was lower than their baseline values.

Adverse events, for the time period of up to five days prior to Visit 6 and up to five days prior to Visit 7, were compared to determine if REM rebound effects (i.e. rebound cataplexy) occur on withdrawal of Xyrem. Adverse events suggestive of REM rebound

(sleep disturbance, hallucinations, and dream abnormal) which were present at up to five days before Visit 6 were compared with those adverse events that occurred up to five days before Visit 7. There was not an exacerbation of adverse events suggestive of REM rebound effects corresponding with the cessation of treatment with Xyrem at Visit 6. The difference in the number of events between these two periods is not statistically significant. REM rebound effects did not appear when stopping Xyrem for three to five days

3.1.1.16 Efficacy Conclusions

Table 3.12 OMC-GHB-2 Efficacy Conclusions

Parameters	Treatment	Baseline (median)	Endpoint (median)	P-value (vs. Placebo)
Total Number of Cataplexy Attacks Per Week	Placebo	20.5	16.5	--
	3g	20.0	9.5	n.s.
	6g	23.0	8.0	0.0529
	9g	23.5	8.7	0.0008
Excessive Daytime Sleepiness (Epworth Sleepiness Scale)	Placebo	19.0	17.0	--
	3g	17.0	16.0	n.s.
	6g	17.5	14.5	n.s.
	9g	17.0	12.0	0.0001
		Change in Medians		
Frequency of Inadvertent Naps/Sleep Attacks/Day	Placebo	-0.26		--
	3g	-0.20		n.s.
	6g	-0.48		0.0497
	9g	-0.48		0.0122
Number of Awakenings at Night	Placebo	+0.20		--
	3g	-0.25		n.s.
	6g	-0.21		n.s.
	9g	-0.91		0.0002
Clinical Global Impressions of Change	Placebo	32%		--
	3g	47%		0.3075
	6g	52%		0.1368
	9g	80%		0.0002

- In study OMC-GHB-2, a statistically significant greater (compared to placebo) reduction from baseline to endpoint in the total number of cataplexy attacks ($p = 0.0008$) was seen among patients in the 9.0 g/d dosage group compared to placebo-treated group, and a reduction in the number of cataplexy attacks ($p = 0.0529$) also was seen among patients in the 6.0 g/d dosage group.

- A reduction in Epworth Sleepiness Scale from baseline to endpoint was observed in all treatment groups (including placebo) with a dose-response trend similar to that seen for cataplexy; this change reached statistical significance ($p = 0.0001$) in patients in the 9 g/d dosage group compared to placebo.

- The number of inadvertent naps or sleep attacks occurring during a day, an index of excessive daytime sleepiness, was reduced by a statistically significant amount from baseline to endpoint (compared to placebo) in the 6 g/d ($p = 0.0497$) and 9 g/d ($p = 0.0122$) dosage groups.

- The clinical investigator's assessment of change in overall disease severity, the (Clinical Global Impression of change [CGI-c]) shows a clear improvement, with the 80% responder rate in the 9.0 g/d group being significantly different from the 32% responder rate in the placebo group ($p = 0.0002$). Patients in the 3.0 g/d and 6.0 g/d dosage groups showed a dose-response trend in level of improvement.

- No significant differences between treatments were seen in the change from baseline in the median number of hypnagogic hallucinations, sleep paralysis episodes, total amount of sleep, and duration of inadvertent naps/sleep attacks.

- Following cessation of treatment at Visit 6, there was no exacerbation of cataplexy or other adverse events above baseline, suggesting that REM rebound does not occur.

3.1.2 SCRIMA TRIAL

3.1.2.1 Design

The Scrima trial (US) was a Phase II, randomized, double-blind, placebo-controlled, 2-way crossover (balanced for sequence group and gender), single-center trial comparing the efficacy of 50 mg/kg (mean 4.2 g) of sodium oxybate with placebo for the treatment of narcolepsy. The total nightly dose of trial medication was taken in 2 equal doses: at bedtime, and again approximately 3-4 hours later. Each dose was administered orally in Syrup of Orange (25 mL) and distilled water (to 100 mL). The trial design is summarized in Table 3.13.

Table 3.13 Scrima Trial Design

Baseline	Treatment 1	Washout	Treatment 2	Washout
14 Days	29 Days	6 Days	29 Days	6 Days
X	Sodium Oxybate (50 mg/kg)	X	Placebo	X
	Placebo	X	Sodium Oxybate (50 mg/kg)	X

The trial consisted of a screening period during which anticataleptic medications were withdrawn, a 14-day baseline period, two 29-day treatment periods separated by a 6-day washout period, and a washout/follow-up period of at least 5 days. In each of the treatment periods, patients took randomly assigned trial medication (50 mg/kg [mean 4.2 g] sodium oxybate) or a similar volume of diluted Syrup of Orange as placebo. A total of 10 men and 10 women were treated and all completed the trial.

To enter the trial, patients were required to have a history of narcolepsy and cataplexy diagnosed by an accredited clinical polysomnographer, sleep onset REM periods ≥ 2 on the diagnostic Multiple Sleep Latency Test (MSLT), and a sleepiness index* ≥ 75 on the diagnostic MSLT. In addition, to continue into the randomized portion of the trial, following the withdrawal of other anticataplectic medications a patient was required to have a minimum of 10 cataplexy attacks subjectively reported during a 14-day baseline period.

Patients with moderate to severe cataplexy (averaging 20 attacks per week) were enrolled into the trial, and other anti-cataplectic treatment was withdrawn prior to baseline.

3.1.2.2 Objectives

The objectives of the trial were:

- To evaluate as primary variables the average daily number of cataplexy attacks and objective daytime sleepiness (using the sleepiness index determined by the MSLT) in narcolepsy patients during treatment with sodium oxybate as compared to placebo and baseline
- To evaluate as secondary variables the average number of sleep attacks per day, average number of awakenings per night, dosing requirements of methylphenidate, feelings on awakening, mood in the morning and evening, sleep patterns identified on the PSG, and average number of REM onsets determined by the MSLT during treatment with sodium oxybate as compared to placebo and baseline

Safety variables included the incidence of adverse events and changes in laboratory values.

3.1.2.3 Statistical Analysis

Age, weight, age at diagnosis, and the number of sleep and cataplexy attacks were analyzed using a 2-factor ANOVA (analysis of variance). The effects in the model were sequence group, gender, and the interaction of gender and sequence group. The distribution of patients with/without histories of hypnagogic hallucinations or sleep paralysis was tested for independence from gender and sequence group using contingency table methods. All patients enrolled in the study were included. (n = 20). Only patients with baseline data who were included in the post-treatment analysis were analyzed for baseline comparability. A 2-factor ANOVA was performed. The effects in the model were sequence group, gender, and the interaction of gender and sequence group.

Repeated measures ANOVA was performed on the observed data. There were 2 between-patient factors, sequence group and gender, and the 2 within-patient factors,

* Sleepiness Index = 100-(5X total sleep latency minutes/number of naps); abnormal >75, borderline 50-75, normal <50

treatment and week. Since week was frequently significant, either as a main effect or as part of an interaction, further repeated measures analysis for the individual weeks were performed to support the overall analysis. If indicated, supportive analyses on ranks were to be performed.

Only the diary data documented the patient's status prior to treatment in Treatment Period 2. Thus, comparison to the patient's status prior to treatment in Treatment Period 1 and the return to this level was restricted to diary data. A repeated measures ANOVA was performed on the change from baseline data. This analysis was a single within-patient factor, days, and 2 between-patient factors, sequence group and gender. Separate univariate supportive analyses for washout days 1 to 5 were performed, with sequence group, gender, and their interaction as factors. The intercept was tested in each model to identify departure from baseline.

Washout from treatment in Period 1 and 2 (follow-up) was compared for the variables in the diary. A repeated measures ANOVA was performed on the change from baseline data. There were 2 between-patient factors, sequence group and gender, and the 2 within-patient factors, Day 1 to 5 of washout and follow-up.

3.1.2.4 Efficacy Results

Table 3.13a summarized the mean number of cataplexy attacks per day by treatment.

Table 3.13a Mean Number of Cataplexy Attacks Per Day

Treatment Group	Pre-Treatment	Treatment Phase				Overall (SE)	Baseline to Endpoint
	Baseline (SE)	Week 1 (SE)	Week 2 (SE)	Week 3 (SE)	Week 4 (SE)		
GHB	2.9 (0.5)	1.4 (0.2)	1.4 (0.2)	0.9 (0.2)	0.9 (0.2)	1.2 (0.2)	2.9 to 1.2 (p=0.007)
Placebo		1.5 (0.2)	2.0 (0.3)	2.1 (0.4)	1.9 (0.3)	1.9 (0.3)	2.9 to 1.9 (p=0.117)
p-value between treatments	—	n.s.	n.s.	0.005	0.004	0.013	—

n.s. - not significant

During active treatment periods over 4 weeks, a mean of 1.2 cataplexy attacks per day was reported by patients receiving sodium oxybate treatment compared to 1.9 cataplexy attacks per day by patients receiving placebo treatment, representing a mean decrease from baseline of 1.6 for sodium oxybate treatment ($p = 0.007$) and of 1.0 for placebo treatment ($p = 0.117$).

By Week 4, treatment with sodium oxybate was superior to placebo for 84% (16/19) of patients, with a mean of 0.9 cataplexy events per day after treatment with sodium oxybate compared to 1.9 per day after treatment with placebo. No cataplexy events

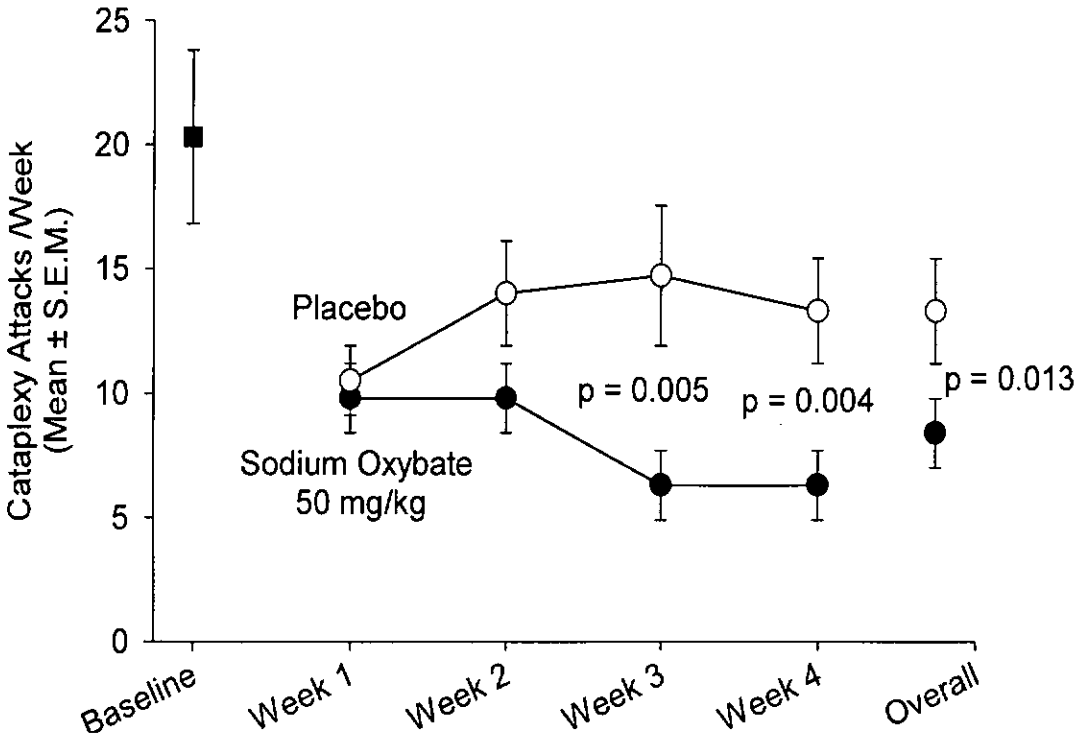
were reported for 21% (4/19) of patients during Week 4 of sodium oxybate treatment compared to 5% (1/19) of patients on placebo. Nine patients (47%) reported an average of at least one fewer cataplexy attacks per day while taking sodium oxybate than while taking placebo (1/19 patients taking placebo averaged at least one less attack than while taking sodium oxybate).

There were also significantly fewer ($p = 0.013$) cataplexy attacks per day during sodium oxybate treatment overall compared to placebo. However, the data suggest an interaction, ie, there was very little difference between treatments at Week 1 ($p = 0.735$, sodium oxybate = 1.4, placebo = 1.5) and a greater difference at Week 2 ($p = 0.073$, sodium oxybate = 1.4, placebo = 2.0). At Weeks 3 and 4, significant differences were detected ($p = 0.005$, sodium oxybate = 0.9, placebo = 2.1; and $p = 0.004$, sodium oxybate = 0.9, placebo = 1.9, respectively). No other significant main effects or interactions were identified, in particular sequence group ($p=0.775$), or treatment x sequence group interaction ($p=0.713$). Thus, no evidence of carryover effect was detected (PLC:GHB-GHB:PLC for PLC-GHB=0.2 with 95% interval-0.9 to 1.3).

The mean number of cataplexy attacks decreased from Week 2 to Week 3 or Week 4 during sodium oxybate treatment and remained lower at Week 4 than Week 1. In contrast, the mean number of a cataplexy attacks increased from Week 1 to Week 2 during placebo treatment and remained higher than Week 1 at Week 4. The crossover design shows no carry-over effect of any variable, indicating that a 5-day washout was sufficient.

The number of cataplexy attacks per week by treatment group for the Scrima trial are presented in Figure 3.11 as mean cataplexy attacks/week ± SEM.

Figure 3.11 Number of Cataplexy Attacks by Treatment Group — Scrima Trial



Data Source: Scrima Trial Report

No significant treatment effects were detected overall for the MSLT sleepiness index [sleepiness index = 100-(5X total sleep latency in minutes/number of naps); abnormal >75, borderline 50-75, normal <50)], although the mean sleepiness index was less during sodium oxybate treatment (87.2) than placebo (90.3).

The mean number of sleep attacks per day during the 4 weeks of treatment decreased significantly from baseline for both sodium oxybate ($p = 0.002$) and placebo ($p = 0.007$), but differences between treatments were not significant. There was no significant difference compared to baseline in the mean number of subjective awakenings at night for either sodium oxybate or placebo, but significantly ($p = 0.042$) fewer awakenings occurred during sodium oxybate treatment versus placebo. There were no significant differences between sodium oxybate or placebo treatments versus baseline or between sodium oxybate and placebo in amount of methylphenidate taken, how patients felt upon awakening, or average morning mood.

For objective PSG studies (Table 3.14), there were statistically significant overall between treatment differences in sleep efficiency ($p = 0.023$), sleep latency ($p = 0.028$),

percentages of Stage 1 and 3 sleep (p = 0.042 and 0.003, respectively), stage shifts (p = 0.006), and number of objective awakenings (p = 0.012), following 50 mg/kg sodium oxybate in the Scrima trial. Hence, the polysomnography data demonstrated that the continuity (increased sleep efficiency and reduced number of awakenings) and depth of sleep (decrease in Stage 1 light sleep and increase in Stage 3 deep sleep) were improved.

Table 3.14 Overnight Sleep in Narcolepsy Patients During GHB vs. Placebo Treatment: Means ± SD for 10 Males and 10 Females

		Placebo		GHB	
	Baseline	Day 1	Day 29	Day 1	Day 29
Sleep measures					
PSG time (min)	475.9 ± 13.5	472.6 ± 29.4	473.9 ± 26.2	474.7 ± 19.3	480.8 ± 3.5
Total sleep (min)	397.4 ± 46.7	413.6 ± 46.5	416.5 ± 41.3	397.2 ± 59.1	409.1 ± 41.7
Stage 0 (min)[a]	78.5 ± 45.5*	58.9 ± 39.2*	57.4 ± 38.6	77.5 ± 50.5	71.6 ± 40.7
No. of wakes[b]	27.2 ± 9.6	25.4 ± 10.2	29.4 ± 11.7	20.6 ± 6.4	23.0 ± 6.2
Sleep efficiency	83.5 ± 9.5*	87.5 ± 8.1*	88.0 ± 7.9	83.5 ± 11.1	85.1 ± 8.5
Sleep stages (%)					
Stage 1[a]	28.8 ± 11.0	26.8 ± 8.7	29.3 ± 10.8	22.4 ± 11.6	24.1 ± 8.4
Stage 2	40.6 ± 8.5*	44.6 ± 8.8*	44.0 ± 10.8	46.4 ± 10.7	44.6 ± 6.3
Stage 3[b]	3.4 ± 3.4	3.1 ± 3.6	2.3 ± 2.6	4.0 ± 4.2	5.8 ± 5.3
Stage 4	4.2 ± 6.6	3.5 ± 6.2	4.4 ± 5.8	5.3 ± 6.7	4.6 ± 4.8
Non-REM	77.0 ± 4.6	77.9 ± 5.1	80.1 ± 5.5	78.1 ± 5.7	79.1 ± 5.3
Delta[a]	7.6 ± 9.5	6.6 ± 9.4	6.8 ± 7.2	9.3 ± 9.3	10.4 ± 9.1
REM sleep	23.0 ± 4.6	22.1 ± 5.1	19.9 ± 5.5	21.9 ± 5.7	20.9 ± 5.3
No. of REM epochs	14.2 ± 6.4	13.6 ± 4.6	12.0 ± 4.7	12.1 ± 5.4	10.8 ± 4.5
Stage shifts[b]	123.4 ± 23.8	127.0 ± 25.6	132.2 ± 32.2	101.9 ± 24.8	114.8 ± 29.2
Latency to					
Sleep[a]	4.2 ± 4.6†	2.4 ± 1.6†	2.4 ± 2.1	3.5 ± 2.9	3.2 ± 2.5
Stage 2	11.0 ± 12.2	10.8 ± 12.4	8.1 ± 12.5	18.0 ± 21.3	11.4 ± 14.1
Delta sleep	39.0 ± 22.3	36.6 ± 17.2	37.7 ± 18.0	67.8 ± 67.4	47.4 ± 52.2
REM sleep	48.5 ± 78.2	31.6 ± 31.1	46.1 ± 47.4	29.8 ± 49.1	23.7 ± 27.5
First 6 h					
Stage 0 (min)	60.0 ± 41.8	44.5 ± 30.9	37.6 ± 25.2	48.0 ± 40.2	42.3 ± 23.5
Sleep efficiency	83.3 ± 11.6	87.6 ± 8.6	89.6 ± 7.0	86.7 ± 11.2	88.3 ± 6.5
Last 2 h					
Stage 0 (min)[a]	18.5 ± 12.7	15.2 ± 12.4	19.9 ± 18.2	29.4 ± 22.0	29.3 ± 23.7
Sleep efficiency	84.1 ± 10.3	87.3 ± 10.2	81.5 ± 15.5	71.7 ± 24.4	75.4 ± 20.4

Repeated-measures ANOVA of treatment differences from baseline: GHB (day 1 and 29) vs. placebo (day 1 and 29): [a]$p < 0.05$, [b]$p < 0.01$.
Baseline vs. placebo day 1: *paired-t: $p < 0.05$, †paired-t: $p < 0.10$.

Source: Scrima L, Hartman PG, Johnson FH, Thomas EE, Hiller FC. The effects of γ-hydroxybutyrate on sleep of narcolepsy patients: a double-blind study. Sleep 1990; 13(6):479-490.

3.1.2.5 Conclusions

Compared to placebo, sodium oxybate, given as a nightly divided dose of 50mg/kg (mean 4.2 g) for 4 weeks, significantly reduced the frequency of cataplexy attacks in a population of chronic narcolepsy patients. The reduction in cataplexy was greater during the last 2 weeks of sodium oxybate treatment than during the first 2 weeks. As assessed by the MLST sleep index, daytime sleepiness was not significantly reduced by this dosage or duration of sodium oxybate treatment. Polysomnography data demonstrated that sodium oxybate significantly enhanced both the continuity and the depth of nocturnal sleep as shown by a reduction in the number of awakenings, a

decrease in the percentage of Stage 1 (light) sleep, and an increase in the percentage of Stage 3 (deep) sleep. Sodium oxybate was generally well-tolerated.

3.1.3 OMC-SXB-21

3.1.3.1 Rationale for OMC-SXB-21

In January 2000, the FDA indicated a requirement for a trial to assess the long-term efficacy of Xyrem in narcoleptic patients. Conventional controlled clinical trial designs to assess long-term efficacy require patients to be randomized into prolonged placebo and active treatment groups. In narcolepsy, a conventional trial would have required patients to withdraw and washout from existing anti-cataplexy medications, [narcoleptics are typically treated with tricyclic antidepressants (TCAs) or serotonin selective reuptake inhibitors (SSRIs)] followed by establishment of baseline levels of cataplexy prior to being randomized into treatment groups. A trial using this conventional design would have presented several difficulties. First, participation would have caused severe hardship for the patients in the placebo group, who would have been without any treatment for cataplexy for the duration of the trial. Second, the potential of not receiving long-term therapy for cataplexy would have resulted in substantial difficulties in the recruitment of sufficient numbers of patients to make the trial statistically robust. These design difficulties necessitated the development of an alternative paradigm for assessing long-term efficacy. The new study paradigm, which became the OMC-SXB-21 protocol, was an adaptation of a design suggested by the Neuropharmacology Division of the FDA. The agency provided extensive input on both study conduct and statistical analysis issues. To assess long-term efficacy, patients in the OMC-SXB-21 trial were removed from stable, long-term, open-label Xyrem therapy in a double-blinded fashion and a return of cataplexy was assessed as the primary efficacy endpoint.

3.1.3.2 Trial Objectives and Design

3.1.3.2.1 Efficacy Objective

OMC-SXB-21 was a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to assess the long-term efficacy of orally administered Xyrem, compared to placebo, for the treatment of narcolepsy. The primary objective of this trial was to provide evidence for the long-term efficacy of Xyrem (sodium oxybate) based on the return of cataplexy symptoms upon cessation of a minimum of 6 months of open-label treatment with sodium oxybate. The measure of efficacy was a comparison between the Xyrem and placebo groups, of the change in the number of cataplexy attacks from baseline (2-week single-blind lead-in active treatment phase) to endpoint (2-week double-blind active or placebo treatment phase).

3.1.3.2.2 Trial Design

The trial design is summarized in Table 3.15 and discussed below.

Table 3.15 OMC-SXB-21 Trial Design

Phase I Screening	**Phase II Lead-In**	**Phase III Double-Blind Treatment**
3 to 5 Days	**14 ± 2 Days (Week 1, Week 2)**	**14 ± 2 Days (Week 1, Week 2)**
Xyrem at established dosage	Single-blind Xyrem at established dosage	Xyrem at established dosage
		Placebo
Stimulant use permitted TCA/SSRI use not permitted		

↑ Visit 1 (Randomization) ↑ Visit 2 ↑ Visit 3 ↑ Visit 4

The trial consisted of 3 phases (4 visits). During Phases I and II, patients continued Xyrem at the same dosage they were taking in OMC-SXB-7 (3, 4.5, 6, 7.5, and 9g per night in divided doses). The period from Visit 1 to Visit 2 served to screen patients for inclusion and exclusion criteria and evaluate hematology and chemistry laboratory results. Patients were randomized immediately following Visit 1. During Phase II (lead-in), patients received single-blind Xyrem for 2 weeks (Visit 2 to Visit 3). In Phase III (double-blind), half the patients received Xyrem at their established dosage, and half received placebo in identical volume to their established Xyrem dose, for 2 weeks (Visit 3 to Visit 4). During Phases II and III, patients kept diaries to record the number of daily cataplexy attacks and adverse events. Patients who received placebo during the double-blind phase were predicted to have a higher incidence of cataplexy attacks than patients who received Xyrem.

3.1.3.2.3 Patient Selection Criteria

Patients were drawn from a pool of patients participating in OMC-SXB-7 (the open-label extension to OMC-GHB-3, OMC-SXB-6, and the Scharf trial). In addition to meeting the entry criteria for participating in the OMC-SXB-7 trial, patients were also required to meet the following criteria for inclusion in OMC-SXB-21:

- Had a history of at least 5 cataplexy attacks per week, confirmed through patient query or medical history, prior to receiving initial treatment (TCAs, SSRIs, and/or Xyrem) for cataplexy.
- Had been treated continuously for the symptoms of narcolepsy with sodium oxybate for a period of 6 months to 3.5 years. The patients must have been previously enrolled in Orphan Medical clinical trials OMC-GHB-3 or OMC-SXB-6.
- Had not been taking TCAs, SSRIs, or any other anti-cataplexy medications, other than Xyrem, within the 30-day period prior to Visit 1 of this trial.
- Stimulant medications were to be maintained at constant levels throughout the trial.

Enrollment of up to 80 patients was planned for this trial. Fifty-five (55) patients were actually treated; all completed the trial.

3.1.3.2.4 Treatments

The Xyrem trial medication was an oral aqueous solution with a concentration of 500 mg/mL of sodium oxybate. Placebo was a sodium citrate solution in equimolar concentration to the sodium in Xyrem oral solution. Placebo was shown to be similar to Xyrem in a blinded taste test (Orphan Medical Protocol OMC-SXB-16).

During the single-blind lead-in phase of the trial, each patient took the same dosage of Xyrem oral solution (3.0, 4.5, 6.0, 7.5, or 9.0 g/d in 2 divided doses) previously taken in the OMC-SXB-7 trial. During the double-blind phase of the trial, patients received either Xyrem at the same dosage as at Visit 2, or placebo at an equivalent volume to the dosage of Xyrem that the patient took during the single-blind phase.

Trial medication was self-administered. Patient compliance was calculated at Visits 2 and 3. Patients were considered non-compliant with trial medication if they missed or exceeded their prescribed doses by 30% or more.

3.1.3.2.5 Randomization and Blinding

Randomization was performed centrally and occurred following the completion of Visit 1. At the request of the FDA, the randomization code was developed to ensure that there was not dose stratification across the placebo and Xyrem treatment groups. Separate randomization code sequences were developed for the existing OMC-SXB-7 treatment doses of 4.5 (3 g/d included in this grouping), 6, 7.5, and 9g/d. Neither the Orphan Medical clinical development representatives nor the clinical site personnel knew the identity of the double-blind medication.

3.1.3.2.6 Efficacy Measurements

Patients were asked to complete a daily diary each night before bedtime during the single-blind and double-blind phases of the trial. The information captured in the diaries was the number of cataplexy attacks the patient had experienced during that day and any AEs or other relevant medical information. A cataplexy attack, episode, or event was defined as a sudden bilateral loss of voluntary muscle tone. To be classified as cataplexy for this trial, the event must have been bilateral, of sudden onset and localized to a specific muscle group(s) or part of the body, and the patient must have been aware of time and place during the event (ie, not a sleep attack or microsleep).

3.1.3.2.7 Statistical Analysis

Efficacy analyses were performed using the Intent-to-Treat Patients population, which included all patients who received 1 or more doses of double-blind trial medication, and had baseline and post-baseline cataplexy measurements.

The primary efficacy variable was the change in the number of cataplexy attacks between baseline (2-week, single-blind lead-in phase) and endpoint (double-blind treatment phase). If fewer or greater than 14 days were available for either treatment phase, then the average number of cataplexy attacks per day was calculated and multiplied by 14.

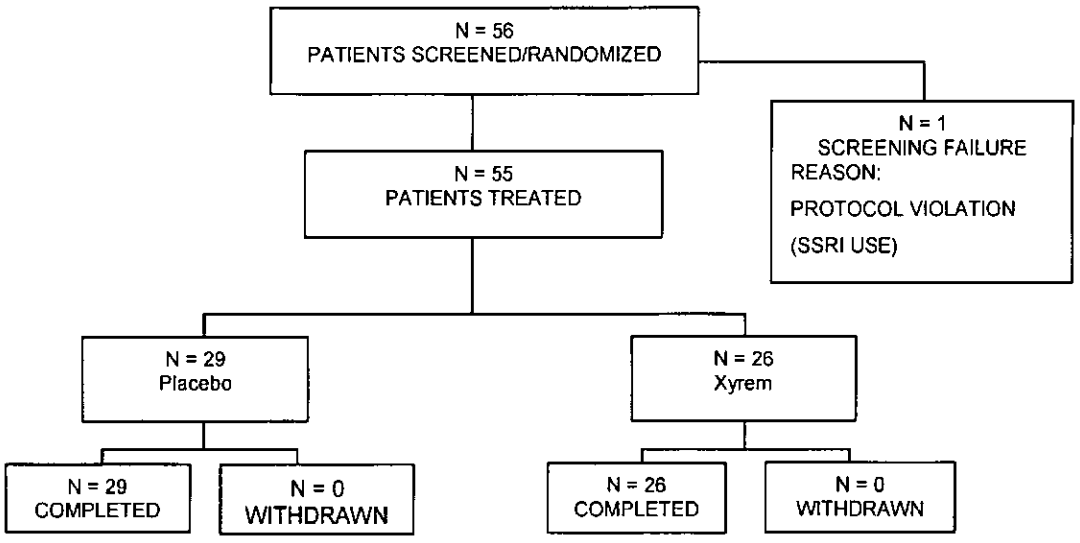
The change in the number of cataplexy attacks was analyzed using a nonparametric analysis of covariance (ANCOVA). Specifically, the baseline number of cataplexy attacks and the change from baseline in the number of cataplexy attacks were replaced by their corresponding ranks, where mean ranks were assigned in case of ties. The rank changes from baseline in the number of cataplexy attacks were analyzed using ANCOVA, including the rank baseline number of cataplexy attacks, treatment group, and baseline-by-treatment group interaction. The overall inference among treatments, placebo versus Xyrem, was presented. Two-sided p-values with a level of significance at 0.05 were used to determine statistical significance.

3.1.3.3 Patient Disposition and Demographics

3.1.3.3.1 Patient Disposition

Figure 3.12 presents the disposition of patients by treatment group. Fifty-six (56) patients were screened and randomized; 1 randomized patient failed screening due to concomitant use of an SSRI and was never treated. A total of 55 patients were treated; all completed the trial.

Figure 3.12 Disposition of Patients



3.1.3.3.2 Patient Demographics

Patient demographic data revealed no significant differences in patient age, gender, weight, height, race, or baseline number of cataplexy attacks between the treatment groups. Table 3.16 summarizes patient demographics and current dosage at screening by treatment group. Prior to trial entry, patients had been taking Xyrem (sodium oxybate) for 7 to 44 (mean = 21) months for the treatment of narcolepsy.

Table 3.16 Demographics and Baseline Characteristics by Treatment Group

Characteristics	Total (N=55)	Treatment Group		p-Value
		Xyrem (N=26)	Placebo (N=29)	
Age (years)				
Mean ± SD	47.7 ± 16.66	47.9 ± 17.06	47.6 ± 16.60	0.955
Range	16.3 – 82.6	19.1 – 82.6	16.3 – 70.0	
Gender (n, %)				
Male	23 (42%)	8 (31%)	15 (52%)	0.172
Female	32 (58%)	18 (69%)	14 (48%)	
Weight (kg)				
Mean ± SD	80.5 ± 20.09	83.8 ± 24.31	77.6 ± 15.22	0.250
Range	54.0 – 142.0	54.0 – 142.0	55.0 – 127.0	
Height (cm)				
Mean ± SD	170.1 ± 10.25	169.6 ± 10.42	170.6 ± 10.24	0.710
Range	152.0 – 188.0	152.0 – 188.0	155.0 – 188.0	
Race (n, %)				
Caucasian	52 (95%)	23 (88%)	29 (100%)	0.099
African-American	2 (4%)	2 (8%)	0	
Asian	0	0	0	
Hispanic	1 (2%)	1 (4%)	0	
Other	0	0	0	
Time on Xyrem (months)				
Mean ± SD	21.22 ± 12.28	23.27 ± 12.36	19.38 ± 12.13	ND
Range	7 – 44	8 – 38	7 – 44	

(continued)

Table 3.16 Demographics and Baseline Characteristics by Treatment Group

Characteristics	Total (N=55)	Treatment Group		p-Value
		Xyrem (N=26)	Placebo (N=29)	
Cataplexy attacks (2-week baseline)				
N	55	26	29	0.436
Mean	12.6	9.0	15.7	
SD	31.75	19.25	39.88	
Median	3.0	1.9	4.0	
Minimum	0.0	0.0	0.0	
Maximum	197.0	86.8	197.0	
Daily Dosage of Xyrem at Screening (n, %)				
3.0 g/d	2 (4%)	1 (4%)	1 (3%)	ND
4.5 g/d	9 (16%)	4 (15%)	5 (17%)	
6.0 g/d	15 (27%)	7 (27%)	8 (28%)	
7.5 g/d	15 (27%)	7 (27%)	8 (28%)	
9.0 g/d	14 (25%)	7 (27%)	7 (24%)	

3.1.3.4 Efficacy Evaluation

3.1.3.4.1 Treatment Compliance

Only 3 (5%) patients (1 placebo, 2 Xyrem) had compliance levels outside the protocol-acceptable range during one or both phases of the trial.

3.1.3.4.2 Efficacy Results

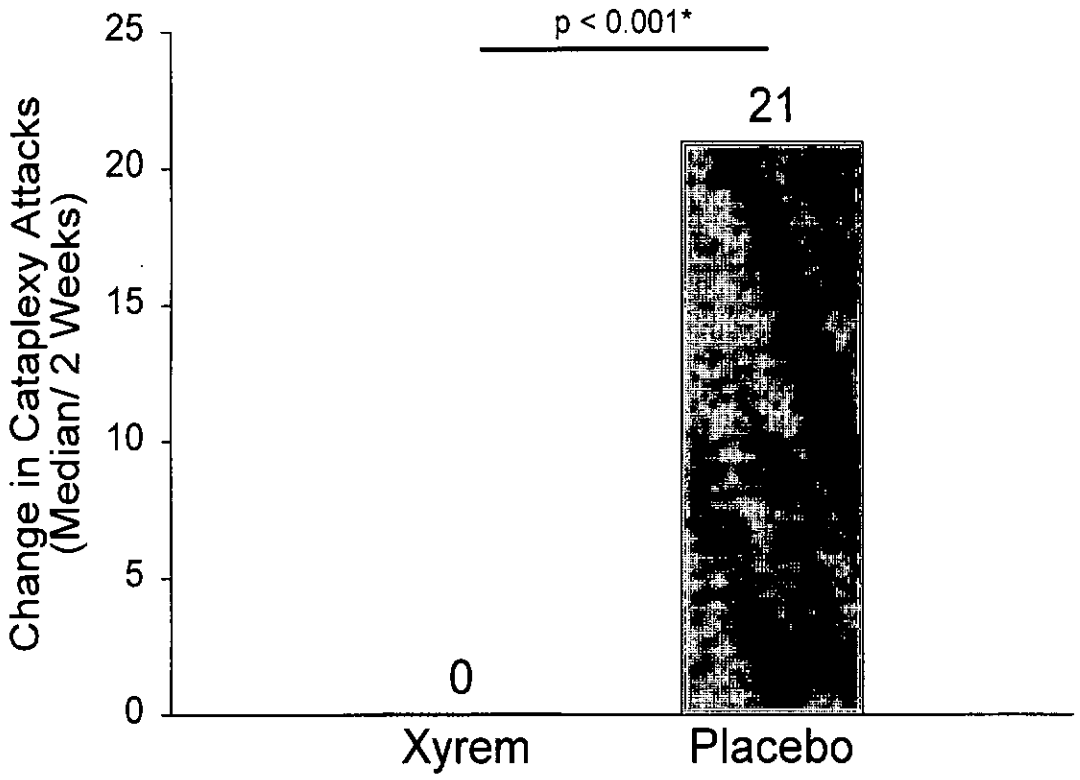
As shown in Table 3.17 and Figure 3.13, there was no change in the number of cataplexy attacks from baseline to endpoint in the Xyrem group (median change 0.0), while cataplexy attacks increased by a median of 21.0 in the placebo group. This difference was statistically significant ($p < 0.001$) when analyzed by an ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction, with a median rank change from baseline of 39.0 for the placebo group and 16.5 for the Xyrem group.

Table 3.17 Change From Baseline in Number of Cataplexy Attacks and Rank Change (Per 2 Weeks) by Treatment Group — Intent-to-Treat Patients

	Xyrem (N=26)			Placebo (N=29)		
	Phase II	Phase III	Change	Phase II[a]	Phase III	Change
Number of cataplexy attacks (per 2 weeks)						
Mean ± SD	9.0 ± 19.25	12.6 ± 30.34	3.6 ± 20.73	15.7 ± 39.88	50.4 ± 81.09	34.6 ± 55.72
Median	1.9	1.1	0.0	4.0	21.0	21.0
Minimum	0.0	0.0	-24.3	0.0	0.0	-15.0
Maximum	86.8	138.3	87.2	197.0	269.2	206.2
Rank change						
Mean ± SD			18.1 ± 12.65			36.9 ± 13.31*
Median			16.5			39.0
Minimum			1.0			3.0
Maximum			52.0			55.0

SD = standard deviation.
[a] Placebo group patients received Xyrem during Phase II.
* $p < 0.001$, from ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction.

Figure 3.13 Median Change from Baseline in Number of Cataplexy Attacks



* p < 0.001, from ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction.

As shown in Table 3.18 and Figure 3.14, change from baseline in the number of cataplexy attacks by week during the double-blind period mirrors the overall change from baseline: no change 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.

Table 3.18 Change from Baseline by Week During the Double-Blind Treatment Period in the Number of Cataplexy Attacks by Treatment Group — Intent-to-Treat Patients

Number of Cataplexy Attacks	Xyrem			Placebo		
	Phase II[a]	Phase III	Change	Phase II[a]	Phase III	Change
Week 1						
Number of Patients	26	26	26	29	29	29
Mean ± SD	4.5 ± 9.62	5.3 ± 11.84	0.8 ± 7.48	7.9 ± 19.94	21.1 ± 35.13	13.2 ± 22.02
Median	0.9	1.0	0.0	2.0	7.0	4.2
Minimum	0.0	0.0	-15.4	0.0	0.0	-7.5
Maximum	43.4	50.8	25.2	98.5	126.0	87.5
Week 2						
Number of Patients	26	26	26	29	29	29
Mean ± SD	4.5 ± 9.62	7.2 ± 18.66	2.7 ± 13.74	7.9 ± 19.94	29.7 ± 47.30	21.8 ± 35.16
Median	0.9	0.5	0.0	2.0	13.0	11.7
Minimum	0.0	0.0	-10.7	0.0	0.0	-7.5
Maximum	43.4	87.5	62.0	98.5	168.0	143.5

[a] Baseline (Phase II) was determined by normalizing the total number of cataplexy attacks during the 2-week Phase II period to 7 days.

Data Source: Appendix Section 14.2.4, Summary Tables 14.2.4.1 and 14.2.4.2.

Figure 3.14 Median Change from Baseline by Week During the Double-Blind Treatment Period in the Number of Cataplexy Attacks — Intent-to-Treat Patients

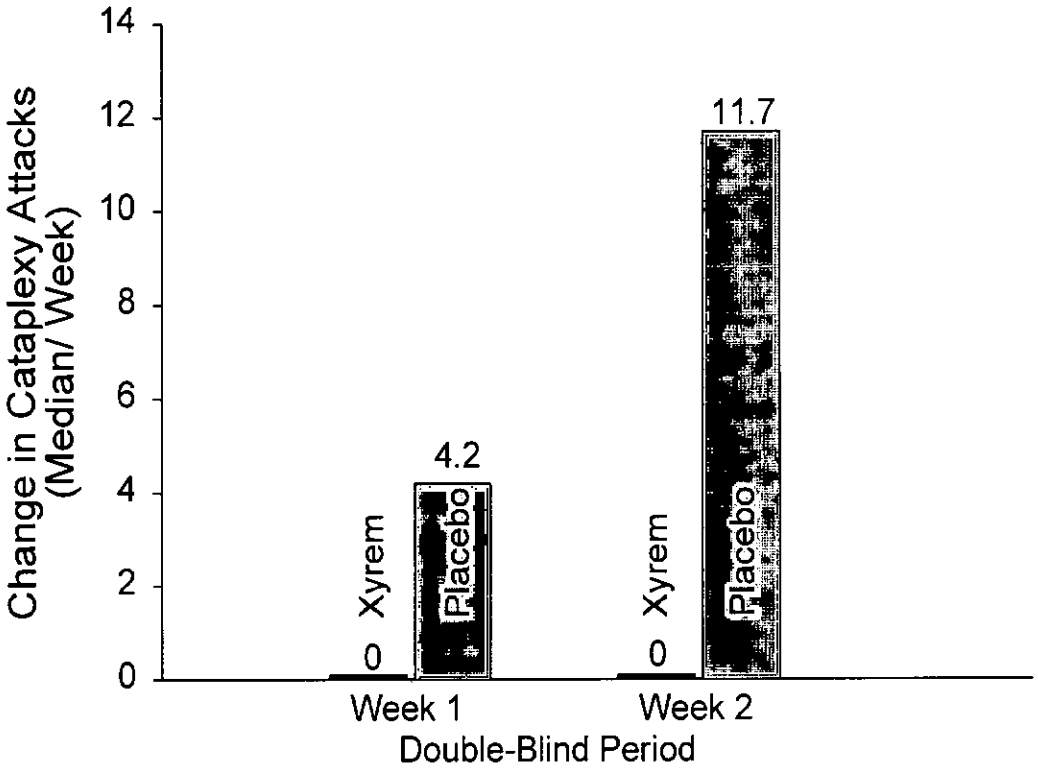
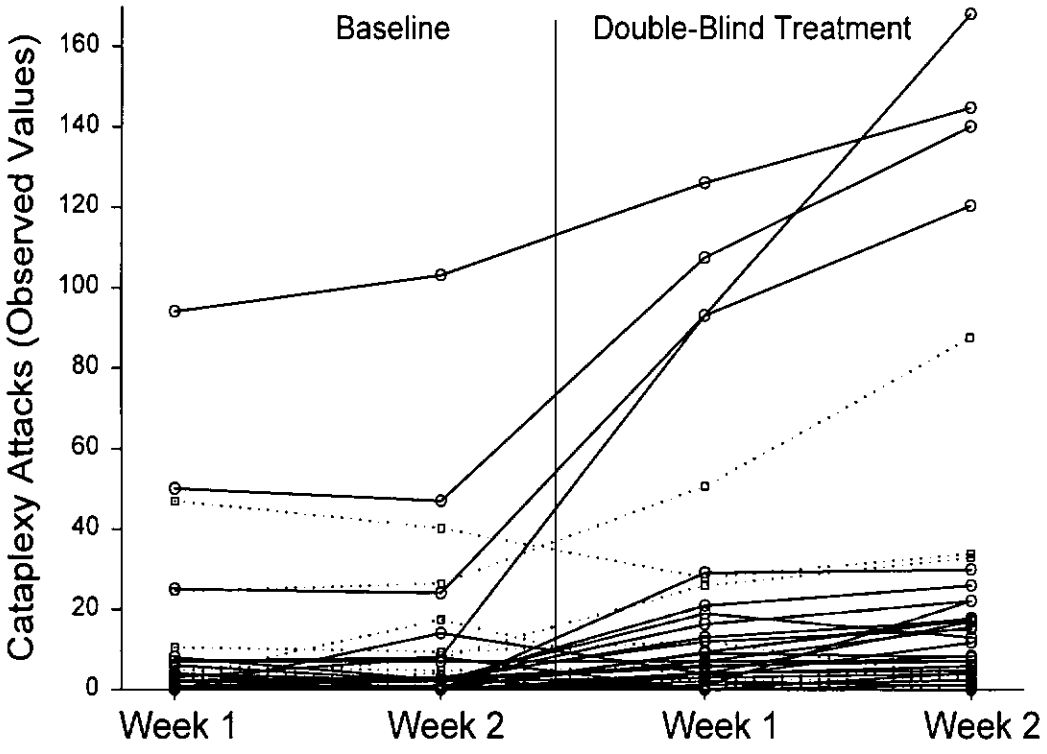


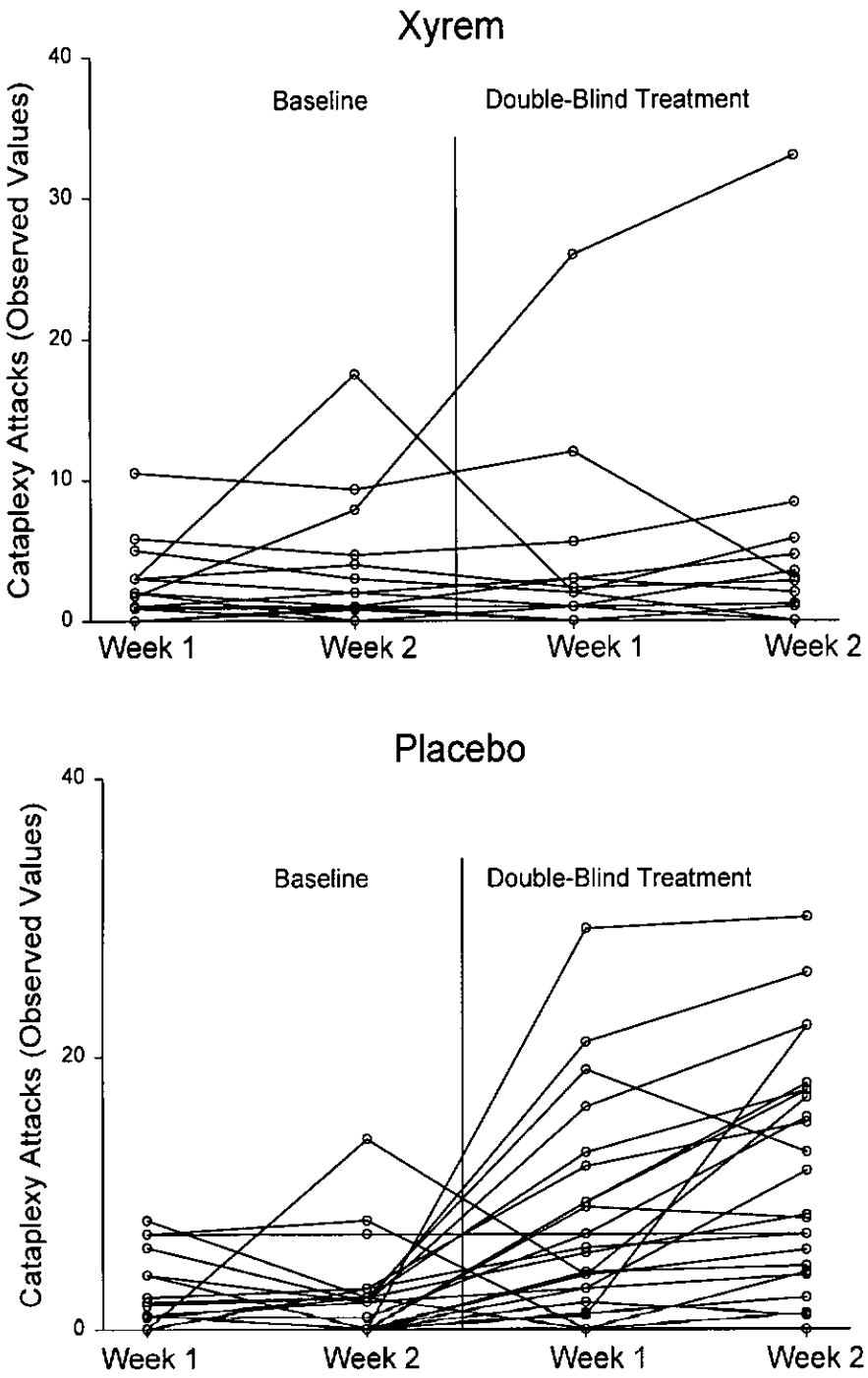
Figure 3.15 is a by-patient display of observed number of cataplexy attacks during Weeks 1 and 2 of the baseline period and during Weeks 1 and 2 of the double-blind treatment period. Solid lines are patients treated with placebo during double-blind treatment; dotted lines are patients treated with Xyrem. Because of the outliers (several patients had over 100 cataplexy attacks per week during Week 2 of the double-blind treatment period), it is difficult to discern a pattern among the data. Figure 3.16 is a by-patient display of observed number of cataplexy attacks over the course of the trial presented by treatment group. In this figure, for clarity, the 6 patients (4 placebo, 2 Xyrem) with values above 40 per week at any time are not displayed. It can be seen that patients who continued to receive Xyrem during double-blind treatment overwhelmingly maintained the low number of cataplexy attacks seen during the baseline period. In contrast, many patients who received placebo during the double-blind treatment phase showed increases at both Weeks 1 and 2, providing visual confirmation of the statistically significant increase (change from baseline) in median number of cataplexy attacks indicated by the summary statistics in Table 3.17 and Figure 3.13.

Figure 3.15 Observed Number of Cataplexy Attacks at Each Visit



Solid lines are patients treated with placebo during double-blind treatment; dotted lines are patients treated with Xyrem.

Figure 3.16 Observed Number of Cataplexy Attacks at Each Visit by Treatment Group



Six patients (4 placebo, 2 Xyrem) with values above 40 per week at any time are not displayed.

3.1.3.4.3 Efficacy Conclusions

OMC-SXB-21 was a randomized, double-blind, placebo-controlled, parallel group, multicenter trial to assess the long-term efficacy of orally administered Xyrem when compared to placebo. Patients entering this trial were using open-label Xyrem for the treatment of narcolepsy for a period of 7 to 44 months (mean = 21 months).

During the lead-in (baseline) phase of the trial, patients continued to take Xyrem in a single-blind fashion at their established effective dosage. The frequency of cataplexy attacks was measured during the 2-week baseline period by patient entries into daily diaries. There was no statistical difference ($p = 0.436$) between treatment groups in the mean number of cataplexy attacks during this period.

Following the baseline period, patients entered the 2-week double-blind treatment phase, where the frequency of cataplexy attacks was captured in daily diaries. Patients given placebo had significantly more cataplexy attacks (median change 21.0) than did patients who continued on active Xyrem treatment (median change 0.0). When the rank change was analyzed, a statistically significant difference was seen ($p < 0.001$), with a median rank change from baseline of 39.0 for the placebo group and 16.5 for the Xyrem group. As shown in Table 3.18 and Figure 3.14, change from baseline in the number of cataplexy attacks by week during the double-blind period mirrors the overall change from baseline: no change 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.

These data strongly indicate that Xyrem is an effective long-term treatment for the control of the narcolepsy symptom of cataplexy.

3.1.4 LAMMERS TRIAL

3.1.4.1 Design

The Lammers trial (The Netherlands) was a prospective, randomized, double-blind, placebo-controlled, 2-way crossover, single-center trial comparing the efficacy of 60 mg/kg (mean 4.7 g) sodium oxybate with placebo for the treatment of narcolepsy. The total nightly dose of trial medication was taken in 2 equal doses: just before going to sleep, and again 4 hours later. Each dose was administered orally in a solution containing sugar, citric acid, crème de cacao essence, and distilled water; placebo also contained trisodium citrate, and sodium chloride. The trial design is summarized in Table 3.19.

Table 3.19 Lammers Trial Design

Baseline 1	Treatment 1	Washout	Baseline 2	Treatment 2
1 Week	4 Weeks	3 Weeks	1 Week	4 Weeks
X	Sodium Oxybate (60 mg/kg)	X	X	Placebo
X	Placebo	X	X	Sodium Oxybate (60 mg/kg)
Continue concomitant treatment for cataplexy and EDS				

The trial consisted of two 5-week periods (1 week baseline observation, 4 weeks treatment) separated by a 3-week washout period. In each of the treatment periods, patients took randomly assigned trial medication (60 mg/kg [mean 4.7 g] sodium oxybate) or a similar placebo) in 2 divided doses at bedtime and 4 hours later as an added medication to existing therapy for narcolepsy. A total of 13 men and 12 women were treated; all completed the trial. One patient (patient 13) failed to keep his diary and was not evaluable.

To enter the trial, patients were required to have had a combination of sleep attacks during the day, and at least 1 of the "REM dissociation phenomena" (cataplexy, hynagogic hallucinations, and sleep paralysis); or, in case of clinical doubt, a positive multiple sleep latency test as recorded with a 24-hour EEG was required.

Patients were allowed to continue taking anti-cataplectic medications (TCAs/SSRIs) they had been using prior to enrollment in the trial; hence, sodium oxybate (or placebo) treatment was taken in addition to the patients' ongoing anti-cataplectic regimen (in contrast to OMC-GHB-2 and the Scrima trial, where anti-cataplectic medication was withdrawn prior to treatment with sodium oxybate). As in the OMC-GHB-2 trial and the Scrima trial, patients were allowed to continue on their stimulant medication for excessive daytime sleepiness at a constant dosage. Patients with cataplexy of relatively mild severity (approximately 5 attacks per week at baseline) were enrolled into the trial.

3.1.4.2 Objectives

Primary efficacy parameters were:

- The opinion of the patients on the benefit of the medication (global therapeutic impression [GTI])
- The opinion of the physician (global clinical impression; [GCI]) was not performed
- The number of cataplexy attacks per day

Secondary efficacy parameters were:

- The number of sleep attacks during the day
- The feeling of sleepiness during the day
- MSLT improvement of the two shortest latencies

- The stability of alertness during the day
- The duration of the nocturnal slow wave sleep on PSG
- The number of stage-shifts at night

The tolerability and safety of the medication was assessed by interviewing the patients. Comments with respect to tolerability were recorded on the patient questionnaires.

3.1.4.3 Statistical Analysis

In the published report (Lammers *et al* [1993]) intragroup differences were analyzed using Wilcoxon's signed-rank test. As a post-hoc reanalysis, an analysis of covariance was used employing a model appropriate for a crossover design. The significance of the covariate was (also) examined. Residuals were analyzed using the Shapiro-Wilk test and non-parametric methods (Wilcoxon).

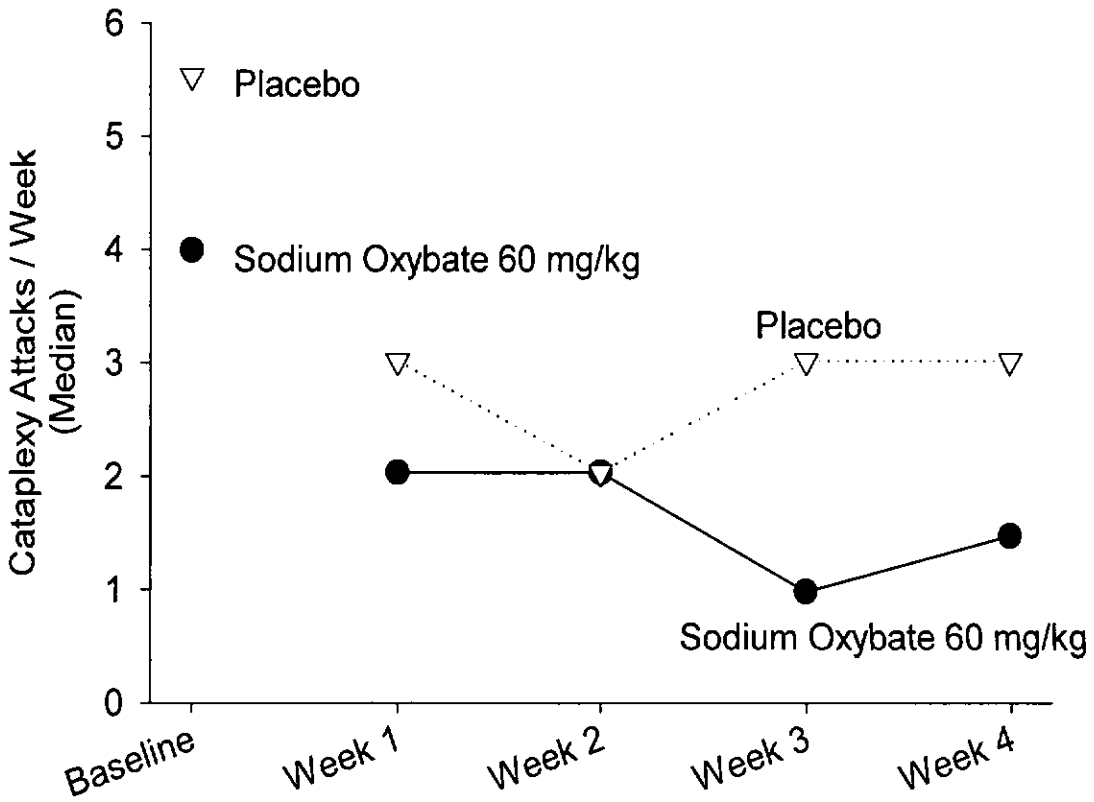
3.1.4.4 Efficacy Results

In the primary efficacy analysis reported in the publication derived from this study (Lammers *et al* [1993]), statistically significant differences between placebo and sodium oxybate-treated groups in the number of cataplexy attacks were not seen. Although the primary endpoint as analyzed according to the original statistical analysis plan did not reach statistical significance, it should be noted that patients enrolled in this trial presented with a much lower rate of cataplexy than seen in either OMC-GHB-2 or the Scrima trial (Lammers patients reported about one-fourth the rate of cataplexy attacks at baseline as did patients in either OMC-GHB-2 or the Scrima trial). In addition to this much lower rate of cataplexy, patients were allowed to continue using anti-cataplectic medication (TCAs/SSRIs) throughout the course of the trial. With such a low severity of disease at baseline, and in the presence of concomitant anti-cataplectic therapy, a robust treatment effect might prove difficult to demonstrate.

In addition, this non-significant p-value (reported in Lammers et al 1993) was obtained using a statistical model that treated each of the two drug administration periods as though they comprised two *independent* samples of patients. When these data were reanalyzed using a statistical model more appropriate for a crossover design (ANCOVA) that included treatment order, patient, period, and baseline cataplexy rate, the difference between placebo and sodium oxybate-treated groups was highly statistically significant ($p = 0.002$).

The number of cataplexy attacks/week by treatment group are presented in Figure 3.17.

Figure 3.17 Number of Cataplexy Attacks by Treatment Group — Lammers Trial



In the Lammers trial (publication), the Global Therapeutic Impression of Change (GTI) as rated by the patients was significantly more often in favor of sodium oxybate; 15/24 (62.5%) patients reported a beneficial effect during sodium oxybate treatment compared to 2/24 (8.3%) patients during placebo treatment ($p =<0.001$).

Marked improvements in excessive daytime sleepiness were evident. Statistically significant between treatment reductions in daytime sleepiness ($p = 0.028$) (based on the patient's assessment of the feeling of sleepiness recorded on a visual analogue scale), inadvertent naps/sleep attacks ($p = 0.001$) (recorded on the patient diary) resulted following 60 mg/kg (mean 4.7 g) sodium oxybate.

Reanalysis of the data using a statistical model more appropriate for a crossover design also revealed a highly significant ($p = 0.002$) reduction in the number of cataplexy attacks.

Among polysomnographic variables, the number of awakenings during REM sleep and the percentage of wakefulness during REM sleep ($p = 0.016$ and 0.007, respectively) were also improved. There were also statistically significant between treatment changes in hypnagogic hallucinations ($p = 0.008$).

3.1.4.5 Conclusions

The Lammers *et al* (1993) publication reported that sodium oxybate is an effective and well-tolerated treatment for symptoms of narcolepsy. Statistically significant between treatment reductions in daytime sleepiness ($p = 0.028$), inadvertent naps/sleep attacks ($p = 0.001$), and the patient GTI ($p<0.001$) following 60 mg/kg (mean 4.7 g) sodium oxybate. The number of awakenings during REM sleep, the percentage of wakefulness during REM sleep, and the frequency of hypnagogic hallucinations were also improved. Reanalysis of the data using a statistical model more appropriate for a crossover design also revealed a highly significant ($p = 0.002$) reduction in the number of cataplexy attacks.

3.2 Uncontrolled Studies

3.2.1 OMC-GHB-3

3.2.1.1 Trial Objectives and Design

3.2.1.1.1 Objectives

OMC-GHB-3 was an open-label, long-term extension of the OMC-GHB-2 double-blind trial. The primary objective of this study was to evaluate the safety of sodium oxybate when used in patients with narcolepsy for up to 24 months at doses of 3g, 4.5g, 6g, 7.5, or 9g daily. The secondary objective of this study was to evaluate the following measures of efficacy:

- Incidence of cataplexy attacks
- Daytime sleepiness as measured by the Epworth Sleepiness Scale and number and duration of inadvertent naps
- Quality of nighttime sleep as measured by the number of awakenings during the night and the total amount of sleep
- Incidence of hypnagogic hallucinations
- Incidence of sleep paralysis
- Clinical Global Impressions of Change in Severity
- Ability to Concentrate
- Quality of Sleep
- Level of Alertness

3.2.1.1.2 Trial Design

Visit 1 occurred concurrently with Visit 7 of OMC-GHB-2. Patients were not randomized to dose. All patients were to begin the study on 6g daily and investigators were required to titrate the patients to the optimum dose (3g, 4.5g, 6g, 7.5g, or 9g sodium oxybate) based on safety and efficacy. Patients made study site visits every 2 weeks during the first month of the trial, (Visits 2 and 3); one month later (Visit 4); then at 2-month

intervals (Visits 5 – 12) for months 4 - 18; then at 3-month intervals (Visits 13 and 14) for months 21 and 24. Primary clinical endpoints were the two week intervals immediately preceding Visits 3, 4, 5, 6, 7, 8 and 9.

Efficacy information was collected using patient diaries through Month 18; for the Month 21 and 24 assessments it was collected via a patient questionnaire completed by the patient during the study site visit.

During these visits the following procedures were performed:

Visit 1

- Administration of Epworth Sleepiness Scale
- Administration of Clinical Global Impressions of Change in Severity

Visits 2 - 12

- Collection and review of all diaries
- Administration of Epworth Sleepiness Scale
- Administration of Clinical Global Impressions of Change in Severity

Visits 13 and 14

- Narcolepsy Symptom Assessment administration

3.2.1.1.3 Patient Selection Criteria

Participation was offered to all patients completing OMC-GHB-2, if they so wished and their physician concurred. They were still required to meet all the same entry criteria with the exception of a minimum incidence of cataplexy of 3 times per week. In addition, patients could not be taking medication for their disease other than a stable dose of stimulant medication.

3.2.1.1.4 Treatments

Patients entering OMC-GHB-3 were to begin the trial with 6g of sodium oxybate nightly. The total nightly dose was divided into 2 equal doses. If indicated, the sodium oxybate dose could be decreased to 3g or 4.5g per night, or increased to 7.5g or 9g per night. After the individualized dose of sodium oxybate was established, patients were to maintain that dose from Visit 2 through the completion of the trial, although dose changes after Visit 2 were permitted if clinically indicated. Patients were considered non-compliant if they missed more than 30% of their expected doses during any period between scheduled visits.

3.2.1.1.5 Efficacy Measurements and Analysis

Patients were instructed to complete diaries on several efficacy measures. These measures included:

- Total number of cataplexy attacks
- Number of complete cataplexy attacks
- Number of partial cataplexy attacks
- Number of inadvertent naps and sleep attacks
- Number of planned naps
- Duration of planned naps
- Number of times patient woke up during the night
- Total amount of sleep
- Number of episodes of hypnagogic hallucinations
- Number of episodes of sleep paralysis
- Ability to Concentrate
- Quality of Sleep
- Level of alertness in morning

Non-diary measures of efficacy included the following:

- Epworth Sleepiness Scale
- Severity of the patient's symptoms as measured by the Clinical Global Impression of Change

The primary efficacy parameter was the change in the total number of cataplexy attacks (TNCA) from baseline (from OMC-GHB-2 trial) to endpoint. Change in TNCA was evaluated based on the weekly average of the TNCA. Since diary entries were not always completed for an assessment period (2 weeks), the completed TCNA data were normalized by calculating the daily average of the endpoint two-week interval and multiplying by 7.

Other efficacy parameters collected during the study were considered secondary measures.

3.2.1.1.6 Statistical and Analytical Plans

The following definitions were used for the planned analyses of this study:

Baseline = the Baseline period in the OMC-GHB-2 trial as defined in the protocol. Baseline for "Overall Ability to Concentrate, Quality of Sleep, and Level of Alertness", was taken from Visit 2 in OMC-GHB-3.

Endpoints = the two week intervals immediately preceding Visits 3, 4, 5, 6, 7, 8 and 9 in the 12-month OMC-GHB-3 trial. The two week intervals immediately preceding Visits 10, 11, and 12 for the 12 month follow-up period.

Statistical analysis was performed on an intent-to-treat population. All patients who received a single dose of study medication during the trial were included. Treatment groups were developed by calculating the average dose used over the course of the study and rounding to the nearest dose category.

The average total number of cataplexy attacks was the primary efficacy measure. Overall treatment group comparison of the log mean change from baseline for TCNA was determined using analysis of covariance (ANCOVA) using the model:

$$\log(TNCA+1) - \text{Baseline } \log(TNCA+1) = \text{Treatment} + \text{Baseline } \text{Log}(TNCA+1)$$

No pairwise comparisons were performed. Within-group and All Patient analyses were performed using Wilcoxon Sign Rank Test.

For the secondary efficacy measures, selected statistical testing was performed. For continuous measures, ANCOVA was used to examine overall treatment effect. Within-group comparisons were performed using paired t-tests. For dichotomous secondary efficacy measures, Fisher's Exact test was utilized to examine overall treatment effect.

3.2.1.2 Patient Disposition and Demographics

3.2.1.2.1 Patient Disposition

By protocol amendment, patients could continue the study for up to 24 months, however, data were analyzed in detail only for the 12-month study duration indicated in the original protocol. Efficacy and safety were analyzed in summary for up to 18 months and 24 months, respectively.

The disposition of patients through 12 months of the study from the combined dose categories is shown in Figure 3.18. Disposition of patients through 24 months is presented in Table 3.20.

Figure 3.18 Disposition of Patients in OMC-GHB-3 Through 12 Months

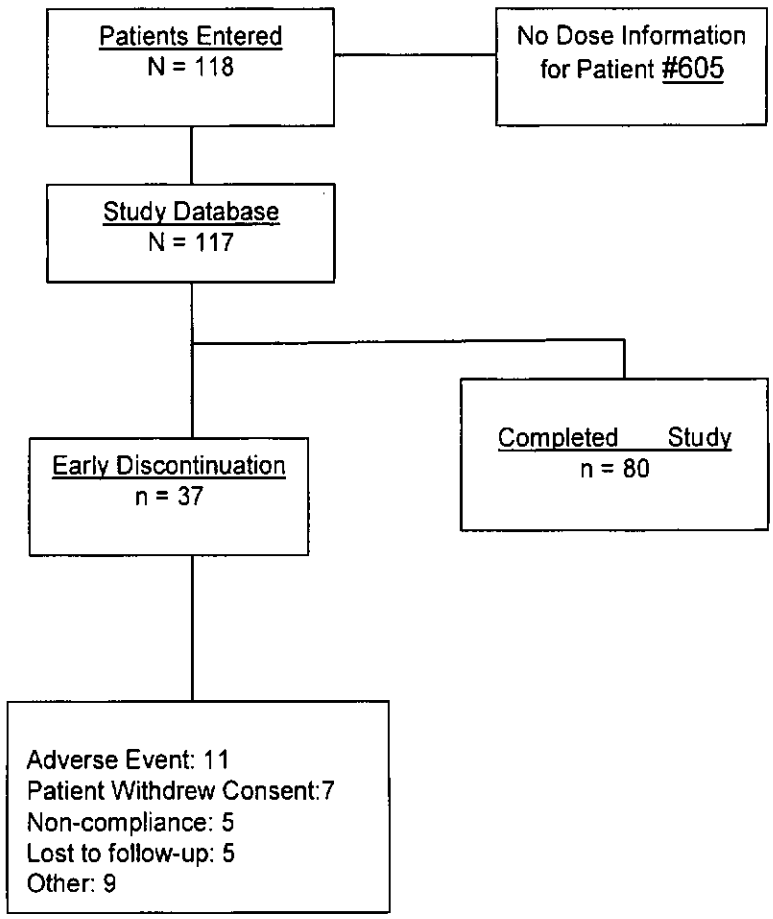


Table 3.20 Disposition of Patients in OMC-GHB-3 Months 12 to 24

	Visit (Month)				
Reason For Withdrawal	9 (12 M)	10 (14 M)	11 (16 M)	12 (18 M)	14 (24 M)
AE	0	1	0	0	0
LOST TO FOLLOW-UP	2	1	0	0	0
NON-COMPLIANCE	2	1	2	2	0
PROTOCOL VIOLATION	0	1	0	0	0
WITHDREW CONSENT	1	1	1	0	2
OTHER	0	1	0	3	1
COMPLETED STUDY	0	2	6	7	39
TOTAL	5	8	9	12	42
Visit	9	10	11	12	14
Active Patients	76	71	63	54	42

3.2.1.2.2 Patient Demographics

The demographic characteristics of the 117 patients who received study medication are summarized in Table 3.21 below.

Table 3.21 Baseline Demographic Characteristics of Study Population (OMC-GHB-3)

Characteristic	All Patients	GHB dose (g) 3	4.5	6	7.5	9	p-value*
	N (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Age (years)							0.262
N	117	15	20	37	25	20	
MEAN	43.4	44.9	48.7	44.3	39.5	40.2	
SD	15.1	14.1	14.7	14.5	17.0	14.1	
MIN	18.0	20.0	25.0	22.0	18.0	24.0	
MAX	79.0	73.0	71.0	67.0	79.0	65.0	
Gender							0.002
Male	51 (43.6)	1 (6.7)	7 (35.0)	15 (40.5)	15 (60.0)	13 (65.0)	
Female	66 (56.4)	14 (93.3)	13 (65.0)	22 (59.5)	10 (40.0)	7 (35.0)	
Race							1.000
Caucasian	108 (92.3)	14 (93.3)	19 (95.0)	33 (89.2)	23 (92.0)	19 (95.0)	
African-American	7 (6.0)	1 (6.7)	1 (5.0)	2 (5.4)	2 (8.0)	1 (5.0)	
Asian	1 (0.9)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	
Other	1 (0.9)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	
Height (cm)							0.017
N	99	12	16	28	24	19	
Mean	172.3	164.9	171.4	172.5	176.2	172.5	
SD	9.4	6.1	10.8	9.9	7.5	9.3	
Weight (kg)							0.003
N	106	13	17	32	24	20	
Mean	83.7	67.0	80.6	85.4	89.5	87.6	
SD	18.0	14.7	16.9	17.1	20.6	12.6	
MIN	48.5	49.4	57.2	48.5	60.8	66.2	
MAX	134.3	93.0	116.1	113.0	134.3	118.0	

*p-value: Age based on ANOVA (GLM);
Sex and Race based on Fisher's Exact Test.
Baseline = the Baseline period in Study OMC-GHB-02.

Statistically significant differences across treatment groups were noted for sex. Additional statistically significant differences across treatment groups were noted for height and weight, consistent with the differences in distribution by sex. The majority of the 3g, 4.5g, and 6g sodium oxybate groups were female, and the majority of the 7.5g and 9g sodium oxybate groups were male.

3.2.1.3 Efficacy Evaluation

3.2.1.3.1 Treatment Compliance

At each study visit through 18 months, the overall patient population was 94% compliant with study medication through 18 months of the study.

3.2.1.3.2 Efficacy Results

By protocol amendment, patients could continue the study for up to 24 months, however, data were analyzed only for the 12-month study duration indicated in the original protocol.

For all efficacy parameters, change from baseline evaluations at specific visits represented comparison to the same measures from the OMC-GHB-2 trial end of baseline period (Visit 4).

Total number of cataplexy attacks. The results presented in Table 3.22, a summary of mean change from baseline to all endpoints for total number of cataplexy attacks per week by visit, show the significant effect produced by all combined dose groups on this primary efficacy parameter. Graphical display for cataplexy attacks per week by visit through 18 months for the median percent change from baseline, are presented in Figure 3.19. Figure 3.19 shows that that majority of the reduction in cataplexy attacks occurred during the first month of sodium oxybate treatment; there was a greater than 75% median reduction in cataplexy attacks at Visit 3 (month 2 from Baseline, month 1 of OMC-GHB-03 study treatment) and an almost 90% median reduction in cataplexy attacks at Visit 4 (month 3 from Baseline, month 2 of OMC-GHB-03 study treatment).

Graphical display for cataplexy attacks per week by dose through 12 months for the median percent change from baseline, are presented in Figure 3.20. Values were calculated from the distribution of change values for each individual. Figure 3.20 displays that there are no dose differences for change in cataplexy attacks with sodium oxybate treatment when patients are titrated to clinical effect. Greater than 90% median reduction was maintained through 18 months of study treatment (19 months from Baseline).

Table 3.22 Change and Percent Change From Baseline to Endpoints for Total Number of Cataplexy Attacks per Week by Visit Through 18 Months (OMC-GHB-3)

	Visit Number (month)									
	3 (1 m)	4 (2 m)	5 (4 m)	6 (6 m)	7 (8 m)	8 (10 m)	9 (12 m)	10 (14 m)	11 (16 m)	12 (18 m)
Change from baseline to Visit										
N[1]	103	102	93	89	83	77	75	71	62	52
Mean[2]	-23.65	-27.50	-30.91	-32.24	-34.70	-34.51	-35.48	-36.79	-35.47	-36.14
SD	33.04	36.89	41.92	42.73	43.22	43.68	43.49	45.92	39.27	43.18
Median	-15.08	-18.25	-18.67	-19.00	-22.56	-22.17	-23.00	-23.60	-25.08	-20.08
1st Quart.	-27.00	-32.17	-34.35	-35.00	-37.83	-38.00	-38.00	-41.46	-41.00	-44.49
3rd Quart.	-5.50	-7.39	-10.00	-9.13	-11.00	-11.00	-10.50	-10.84	-11.81	-11.07
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
% Change from baseline to Visit										
Mean[2]	-61.09	-72.24	-77.93	-81.89	-86.40	-73.12	-80.05	-84.03	-85.38	-83.19
SD	60.02	46.63	35.53	29.75	25.14	79.29	42.04	30.92	22.91	25.40
Median	-76.67	-88.24	-89.53	-92.50	-96.96	-92.19	-93.08	-94.35	-95.28	-92.68
1st Quart	-93.91	-98.37	-98.00	-100.00	-100.00	-100.00	-99.73	-100.00	-100.00	-99.60
3rd Quart	-50.39	-68.07	-77.42	-80.96	-84.87	-79.03	-77.78	-83.20	-79.76	-78.61
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[1]N reflects all patients with available data for number of cataplexy attacks at that visit.
[2]Weekly average total number of cataplexy attacks (TNCA) assessed as: (Daily average of the endpoint two week interval)*7
*p-value(Within Group) based on Wilcoxon Sign Rank test for change from baseline.

Figure 3.19 Median Percent Change from Baseline for Total Number of Cataplexy Attacks Per Week through 18 Months (OMC-GHB-3)

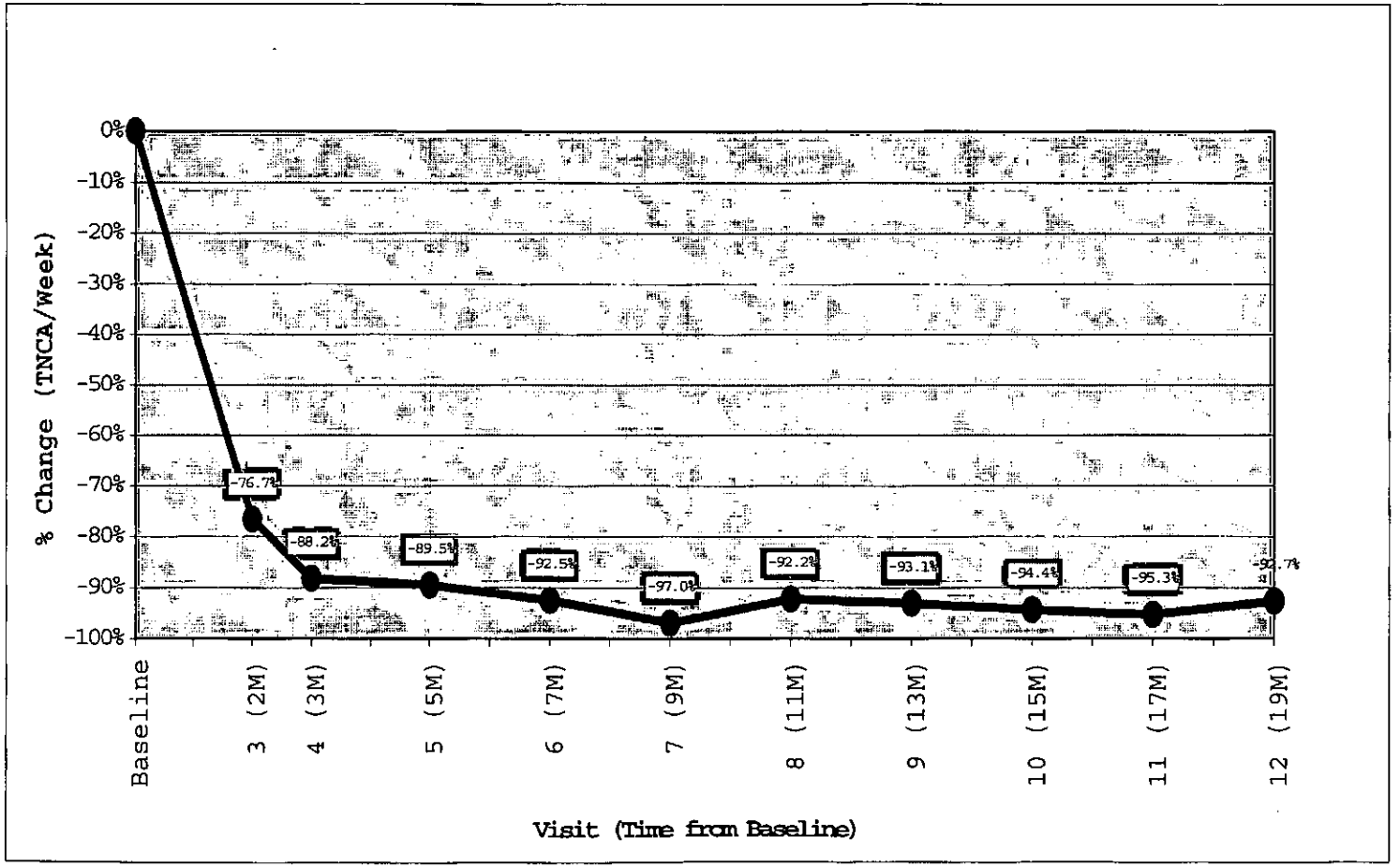
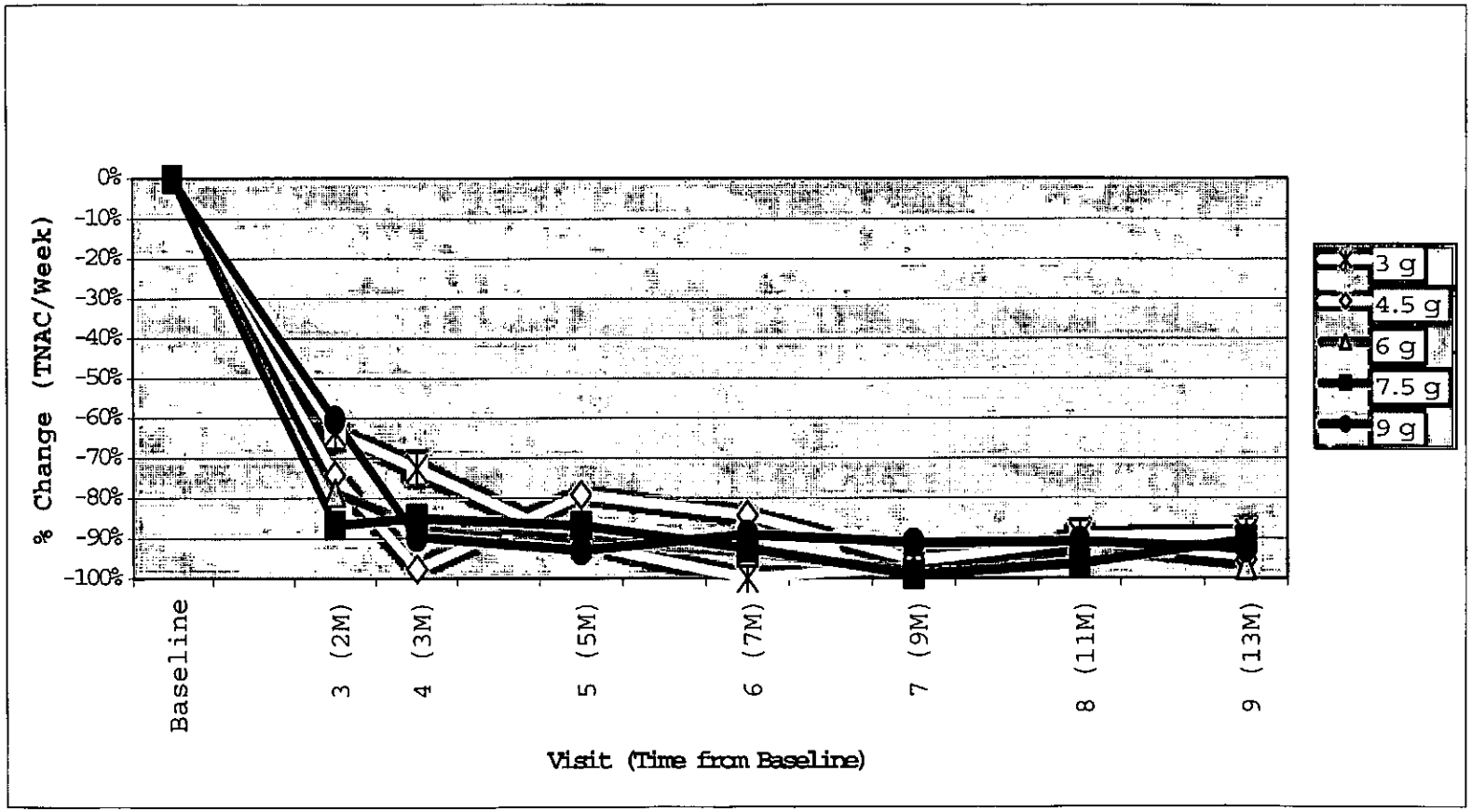


Figure 3.20 Median Percent Change from Baseline for Total Number of Cataplexy Attacks Per Week by Dose through 12 Months (OMC-GHB-3)



Daytime Sleepiness. The results presented in Table 3.23, a summary (through 12 months of the study) of change from baseline to overall endpoints in daytime sleepiness by visit as measured by the Epworth Sleepiness Scale (ESS), show the significant effect produced by the combined dose groups on this secondary efficacy parameter. There was statistically significant improvement observed at all visits, but there was little or no change in the daytime Epworth Sleepiness Scale values with successive visits. The overall mean change from baseline was -4.47 (SD = 5.05) at Visit 3 (1 month) and -5.30 (SD = 4.57) at Visit 9 (12 months). The mean change from baseline in Epworth Daytime Sleepiness was statistically significant ($p<0.001$) at all study visits.

Table 3.23 Change from Baseline to Endpoints in Daytime Sleepiness as Measured by the Epworth Sleepiness Scale by Visit

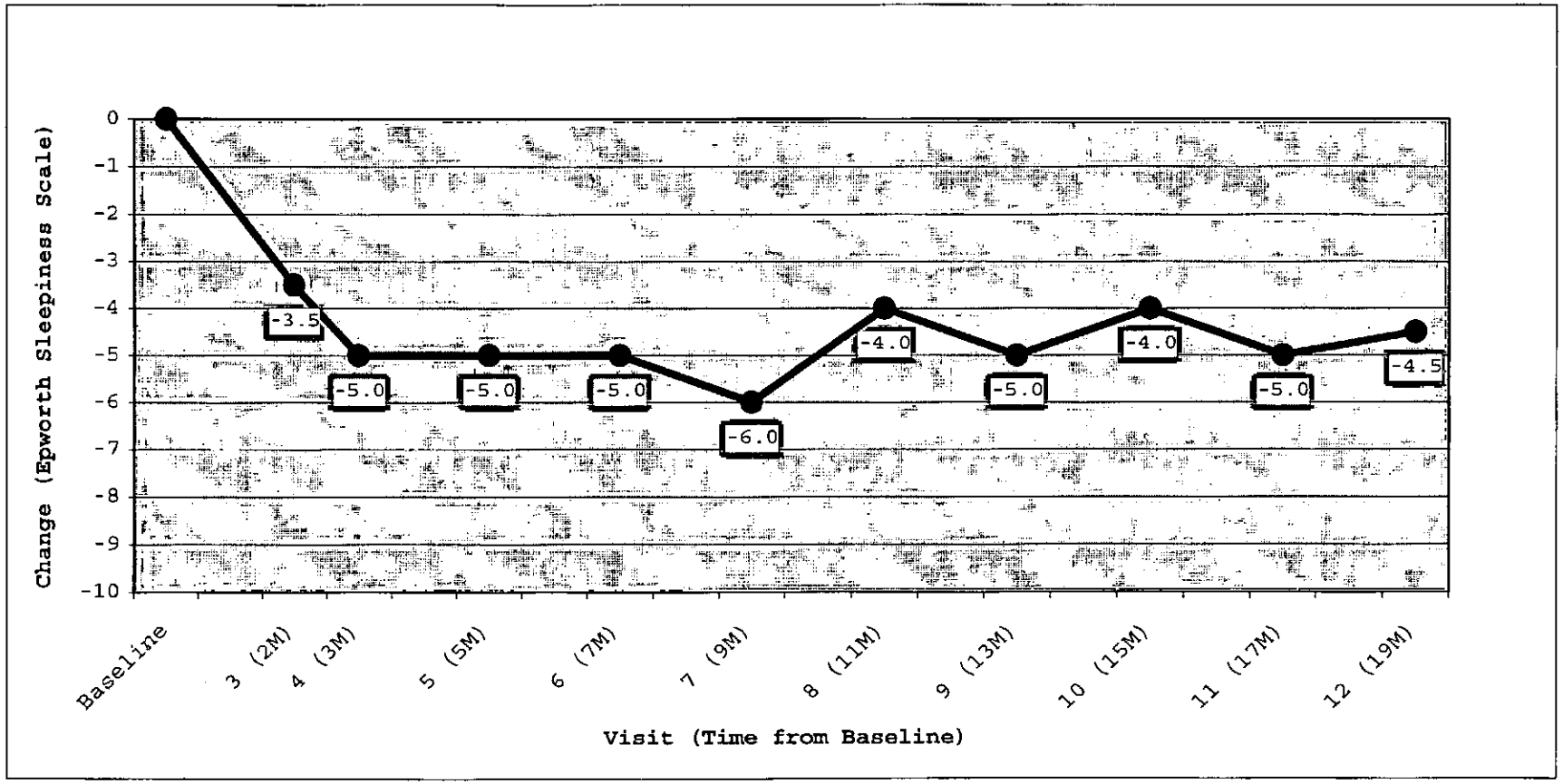
	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline* to Visit							
N[1]	106	99	91	87	83	75	74
Mean	-4.47	-5.56	-6.02	-5.76	-6.30	-5.23	-5.30
SD	5.05	5.44	5.53	4.82	5.05	4.81	4.57
Median	-3.50	-5.00	-5.00	-5.00	-6.00	-4.00	-5.00

[1]N reflects all patients with available data for Epworth Sleepiness scale at that visit.
*Baseline taken from OMC-GHB-2.

Graphical display for daytime sleepiness by visit through 18 months for the median change from baseline is presented in Figure 3.21. Visit times (months) for Figure 3.21 time intervals are measured from the Baseline (Baseline, taken from OMC-GHB-02, was 1 month prior to Visit 1 of OMC-GHB-03) rather than time since Visit 1, and, therefore, do not reflect the exact amount of time in study OMC-GHB-3. These values were calculated from the distribution of change values for each individual. The maximum effect was achieved by Visit 4 (month 3 from Baseline, month 2 of OMC-GHB-03 study treatment). The maximum decrease in daytime sleepiness was an approximate 35% median decrease in the Epworth Sleepiness scale. Clinical benefit in diminished daytime sleepiness appeared to be maintained through 18 months of study treatment (19 months from Baseline). Statistical assessment across treatment groups (3, 4.5, 6, 7.5, and 9 g/d) demonstrated that there were no significant dose differences for change in the Epworth Sleepiness Scale values.

It is important to note that the changes in EDS in response to Xyrem treatment show an identical temporal response as was seen in cataplexy, with maximum change occurring in about 8 weeks from start of treatment, and then maintained response over the remainder of the 12 months.

Figure 3.21 Median Change from Baseline in Daytime Sleepiness (Epworth Sleepiness Scale) through 18 Months (OMC-GHB-3)



Inadvertent Naps/Sleep Attacks. Table 3.24 presents change from baseline to endpoints in total number and duration of inadvertent naps and sleep attacks/day by visit. These data demonstrate a slight decline (increased negative change from baseline) in the number of inadvertent naps and a general trend towards continued decline (increased negative change from baseline) in the duration of inadvertent naps with successive visits. There was no statistically significant Xyrem effect on this parameter.

Table 3.24 Change from Baseline to Endpoints in Total Number and Duration of Inadvertent Naps (Sleep Attacks/day) by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline to Visit							
Total number of inadvertent naps (sleep attacks) (N/day)							
N[1]	103	102	93	89	83	77	75
Mean	-0.77	-0.84	-0.91	-1.03	-1.04	-0.93	-1.03
SD	1.28	1.41	1.36	1.36	1.39	1.36	1.29
Median	-0.64	-0.63	-0.71	-0.85	-0.84	-0.85	-0.60
Total duration of inadvertent naps and sleep attacks (min)							
N[1]	102	101	92	88	82	77	75
Mean	-20.27	-24.29	-25.59	-26.27	-26.05	-28.35	-29.64
SD	39.00	42.45	40.60	44.32	52.21	46.26	47.74
Median	-9.96	-12.31	-11.36	-11.69	-14.32	-14.87	-10.86

[1]Patients with non-missing assessments.

Number and Duration of Planned Naps. Table 3.25 presents change from baseline to endpoints in total number and duration of planned naps by visit. These data demonstrate a decrease from baseline to Visit 3 in the number of planned naps with no change at subsequent visits and a decrease in the duration of planned naps at Visit 3 with continued improvement at successive visits. There was no statistically significant Xyrem effect on this parameter.

Table 3.25 Change From Baseline to Endpoints in Total Number and Duration of Planned Naps by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline to Visit							
Total number of planned naps (N/day)							
N[1]	102	101	93	88	82	76	74
Mean	-0.21	-0.23	-0.24	-0.29	-0.24	-0.20	-0.25
SD	0.50	0.56	0.68	0.68	0.74	0.83	0.74
Median	-0.14	-0.14	-0.10	-0.14	-0.12	-0.16	-0.15
Total duration of planned naps (min)							
N[1]	100	100	92	87	81	76	74
Mean	-12.63	-13.26	-14.94	-16.96	-15.60	-14.49	-17.17
SD	34.41	40.64	44.81	46.01	51.50	53.57	52.63
Median	-5.45	-7.77	-7.28	-12.77	-7.47	-9.74	-10.14

[1]Patients with non-missing assessments.

Nighttime sleep. Improvement in nighttime sleep was measured by collecting the number of reported awakenings during each night and the total amount of sleep each night preceding the visit to the research center. Improvement in nighttime sleep recorded in the patient diaries was evaluated and compared to the same measures from the OMC-GHB-2 trial end of baseline visit (Visit 4).

The results for the number of awakenings and total amount of sleep are shown in Table 3.26. These data demonstrate improvement from baseline at successive visits for number of awakenings per night and improvement from baseline in the total duration of sleep per night. There was little change at successive visits in the total duration of sleep per night.

Table 3.26 Change From Baseline to Endpoints for the Number of Awakenings Each Evening and the Total Amount of Sleep by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline to Visit for:							
Number of awakenings (N/night)							
N[1]	103	102	93	89	83	77	75
Mean	-0.64	-0.71	-0.82	-0.95	-0.86	-0.95	-0.92
SD	1.51	1.62	1.66	1.59	1.58	1.65	1.60
Median	-0.48	-0.64	-0.57	-0.79	-0.71	-0.67	-0.54
Total amount of sleep (min)							
N[1]	102	101	92	88	81	76	75
Mean	18.45	14.09	21.97	18.32	26.33	22.86	19.60
SD	68.80	66.97	73.08	75.14	76.33	97.45	80.68
Median	16.39	9.75	15.31	17.50	24.07	13.60	13.72

[1]Patients with non-missing assessments.

Hypnagogic hallucinations and Sleep paralysis. Not all patients with narcolepsy report either hypnagogic hallucinations or sleep paralysis. However, in this study, 102 patients (87.2%) and 103 patients (88.0%), reported hypnagogic hallucinations or sleep paralysis symptoms, respectively, at Visit 3. The number of occurrences of these symptoms as recorded in the patient diaries were evaluated and compared to the same measures from the
OMC-GHB-2 trial end of baseline visit (GHB-2 Visit 4).

The results for the number of hypnagogic hallucinations and number of episodes of sleep paralysis are summarized in Table 3.27. A trend towards diminished symptoms was evident, at Visit 3 compared to Baseline and at subsequent visits.

Table 3.27 Change From Baseline to Endpoints for the Number of Hypnagogic Hallucinations and Number of Episodes of Sleep Paralysis by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline to Visit for:							
Number of hypnagogic hallucinations (N/day)							
N[1]	102	101	93	88	82	76	74
Mean	-0.48	-0.58	-0.64	-0.71	-0.71	-0.78	-0.78
SD	1.83	1.89	2.07	2.17	2.23	2.36	2.38
Median	-0.18	-0.22	-0.23	-0.30	-0.28	-0.30	-0.29
Number of episodes of sleep paralysis (N/day)							
N[1]	103	102	93	89	83	77	75
Mean	-0.38	-0.43	-0.44	-0.48	-0.49	-0.54	-0.51
SD	0.95	1.11	1.16	1.21	1.23	1.30	1.29
Median	-0.07	-0.08	-0.08	-0.09	-0.14	-0.14	-0.12

[1]Patients with non-missing assessments.

Clinical Global Impression of Change (CGI-c). Table 3.28 displays the results for the CGI-c assessments for each visit by individual treatment group. For the purposes of this report, patients are categorized as "responders" or "non-responders". Approximately 80% of all patients were categorized as responders at Visit 3, however, there appeared to be a trend towards continued improvement (increased percentage of responders) at successive visits.

The response was relatively uniform across doses; there was a statistically significant difference across treatment groups at Visits 4 (p=0.017) and 6 (p=0.016) only. This difference by dose was most probably due to the variability inherent in any group with a relatively small number of patients (n = 14 for the 3g sodium oxybate dose group at Visit 4 and n = 15 for the 4.5g sodium oxybate dose group at Visit 6) and not a true reflection of a real dose-effect.

Table 3.28 Change from Baseline to Endpoints for Clinical Global Impression of Change (CGI-c) by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
N[1] Total Patients	108	101	95	89	83	77	74
Change from baseline to Visit							
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Very much improved	36 (33.3)	38 (37.6)	40 (42.1)	40 (44.9)	40 (48.2)	35 (45.5)	34 (45.9)
Much improved	48 (44.4)	50 (49.5)	41 (43.2)	44 (49.4)	40 (48.2)	38 (49.4)	33 (44.6)
Minimally improved	15 (13.9)	9 (8.9)	7 (7.4)	3 (3.4)	2 (2.4)	3 (3.9)	6 (8.1)
No change	3 (2.8)	1 (1.0)	4 (4.2)	1 (1.1)	1 (1.2)	1 (1.3)	0 (0.0)
Minimally changed	5 (4.6)	3 (3.0)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Much worse	1 (0.9)	0 (0.0)	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Responder*	84 (77.8)	88 (87.1)	81 (85.3)	84 (94.4)	80 (96.4)	73 (94.8)	67 (90.5)
Non-responder	24 (22.2)	13 (12.9)	14 (14.7)	5 (5.6)	3 (3.6)	4 (5.2)	7 (9.5)

[1]N reflects all patients with available data for CGI-c scores at that visit.

*Responder = "Very much improved" or "Much improved" on CGI-c scale. Non-responder = all other categories except "Not assessed".

Ability to Concentrate, Quality of Sleep, and Level of Alertness. The efficacy measures of ability to concentrate, quality of sleep, and level of alertness are summarized in Table 3.29. The Baseline for Ability to Concentrate was Visit 2 of the OMC-GHB-3 Study; for other variables Baseline was the Baseline (Visit 4) of the OMC-GHB-2 Study. At Visit 3 all dose groups provided statistically significant improvement in the three efficacy parameters. The only exceptions were in Quality of Sleep (p=0.056) and Level of Alertness (p=0.068), both in the 4.5g treatment group. Similar statistical significance was observed for the three efficacy parameters at Visit 9. The only exception was in Level of Alertness (p=0.055), in the 3g sodium oxybate treatment group. These p-values, just above the level of statistical significance, were probably due to variability inherent in the small number of patients (n=6) in the 4.5g group, and did not reflect a true treatment failure. There were no statistically significant values across-treatments.

Table 3.29 Change from Baseline to Endpoints for the Overall Ability to Concentrate, Quality of Sleep, and Level of Alertness by Treatment Group

	All Patients	GHB dose (g)					p-value*
		3	4.5	6	7.5	9	
Measure[1] of change from baseline[2] to **visit 3**							
Ability to Concentrate							
N[3]	104	14	6	55	8	21	0.719
Mean	0.66	0.81	0.56	0.66	0.76	0.56	
SD	0.59	0.69	0.37	0.58	0.58	0.61	
Median	0.69	0.93	0.41	0.69	0.79	0.44	
p-value**	<0.001	0.001	0.013	<0.001	0.007	<0.001	
Quality of Sleep							
N[3]	105	14	6	55	9	21	0.720
Mean	0.76	0.74	0.48	0.80	0.84	0.74	
SD	0.56	0.46	0.48	0.59	0.59	0.57	
Median	0.79	0.94	0.43	0.78	0.87	0.86	
p-value**	<0.001	<0.001	0.056	<0.001	0.003	<0.001	
Level of Alertness							
N[3]	105	14	6	55	9	21	0.463
Mean	0.65	0.67	0.37	0.70	0.74	0.53	
SD	0.58	0.49	0.39	0.63	0.67	0.48	
Median	0.65	0.56	0.33	0.67	0.81	0.52	
p-value**	<0.001	<0.001	0.068	<0.001	0.011	<0.001	

[1]Weighted Average of Measure (WAM) = $(1xN_{POOR} + 2xN_{FAIR} + 3xN_{GOOD} + 4xN_{EXCEL})/N$, where N_{POOR}, N_{FAIR}, N_{GOOD}, N_{EXCEL} = number of days with poor, fair, good, and excellent level of measure, respectively. $N = N_{POOR} + N_{FAIR} + N_{GOOD} + N_{EXCEL}$ = total number of days reported.

[2]Baseline for Ability to Concentrate was the Visit 2 of Study OMC-GHB-3; for other measures, Baseline was the Baseline period in Study OMC-GHB-2.

[3]Patients with non-missing assessments.

*p-value for overall treatment group based on ANOVA (GLM)

**p-value within treatment group based on paired t-test for change from baseline.

3.2.1.4 Conclusions

Eighty-six patients (73.5%) reached dose stabilization in this open-label, long-term study. For all patients who reached dose stabilization, the mean was 3.38 weeks. As displayed in Table 3.30, there was an increased distribution of patients in the higher dose groups by last reported dose.

Table 3.30 Distribution of Patients by the Last Reported Dose (OMC-GHB-3)

	GHB dose (g)				
All Patients	**3**	**4.5**	**6**	**7.5**	**9**
	n	n	n	n	n
	(%)	(%)	(%)	(%)	(%)
117	16	11	42	13	35
	(13.7)	(9.4)	(35.9)	(11.1)	(29.9)

Overall clinical improvement, assessed as change from baseline, was evident at the earliest endpoint (Visit 3), and was maintained at all endpoints throughout the study. Patients were titrated to achieve maximum clinical benefit. In general, there appeared to be no compelling evidence of enhanced benefit with increasing dose. The data from this 12-month, open-label study demonstrate that 3g to 9g doses of sodium oxybate taken in divided doses before bedtime and 2.5-4 hours later produced significant and long-term clinical improvement in the symptoms of narcolepsy.

For the overall population, there was highly statistically significant improvement from baseline at all visits for the primary efficacy parameter, number of cataplexy attacks. There appeared to be continued improvement at successive visits; the mean change from baseline for overall treatment was a decrease of 23.65 cataplexy attacks at Visit 3 and a decrease of 35.48 cataplexy attacks at Visit 9.

Except for the 3g and 4.5g sodium oxybate dose groups at Visit 3 (p=0.122 and p=0.074, respectively), the change from baseline in number of cataplexy events was highly statistically significant for all dose groups at all visits. Statistical assessment across treatment groups demonstrated that there was no significant dose differences for change in this primary efficacy parameter. It is important to note that patients in study OMC-GHB-3 began the study on 6g daily and investigators were required to titrate the patients to an individualized dose (3g, 4.5g, 6g, 7.5g, or 9g sodium oxybate) based on safety and efficacy. Therefore, p-values for comparisons across dose groups were not expected to show statistical significance as doses represented the patients' average dose throughout the study and were not randomized groups.

Except for the 4.5g sodium oxybate dose group at Visit 3 (p=0.104) and Visit 6 (p=0.087), the decrease from baseline in daytime sleepiness as measured by the

Epworth Sleepiness Scale was statistically significant for all dose groups at all visits. There was little or no additional improvement, however, beyond Visit 3.

A trend towards diminished symptoms was evident for all secondary efficacy parameters including: frequency and duration of inadvertent naps and sleep attacks; frequency and duration of planned naps; frequency of awakenings that occurred during the night; and frequency of hypnagogic hallucinations and episodes of sleep paralysis. However, the statistical design did not provide definitive statistical support for the clinical benefit of sodium oxybate for these secondary efficacy parameters.

For all patients the overall response to treatment, as assessed by the Clinical Global Impression of Change, was clear and positive. Responders ranged from 78.5% at Visit 3 to 96.4% at Visit 7. There was a slight trend towards a dose relationship in the CGI-c at the earlier visits, and there was no statistically significant difference across treatment groups.

3.2.2 OMC-SXB-20

3.2.2.1 Rationale

Nocturnal polysomnography provides an objective means to determine the neurological and physiological changes in response to treatment, and would provide an opportunity to obtain a broader understanding of the overall effects of Xyrem on sleep. Previous polysomnographic studies of the effects of sodium oxybate have been published in normal subjects (Lapierre 1990), non-narcoleptic depressive patients (Mamelak 1977) and in surgical patients with intravenous infusion to produce sedation (Entholzner 1995), all indicating that sodium oxybate increased delta wave sleep.

Medications used for cataplexy (TCAs and SSRIs) and for improved sleep (hypnotics and barbiturates) are known to cause a decrease in REM sleep. For example, the reductions in REM sleep have been noted for, but are not limited to, the benzodiazepine hypnotics flunitrazepam, flurazepam, and triazolam (Borbely 1985), fluvoxamine and other SSRIs (Wilson 2000, Oberndorfer 2000), the TCA imipramine (Kupfer 1989), and the imidazopyridine hypnotic Zolpidem (Brunner 1991). Since sodium oxybate has been described to produce improvement of sleep and cataplexy symptoms, it was of interest for this NDA to characterize the effects of this drug on narcoleptic sleep architecture in relation to dose.

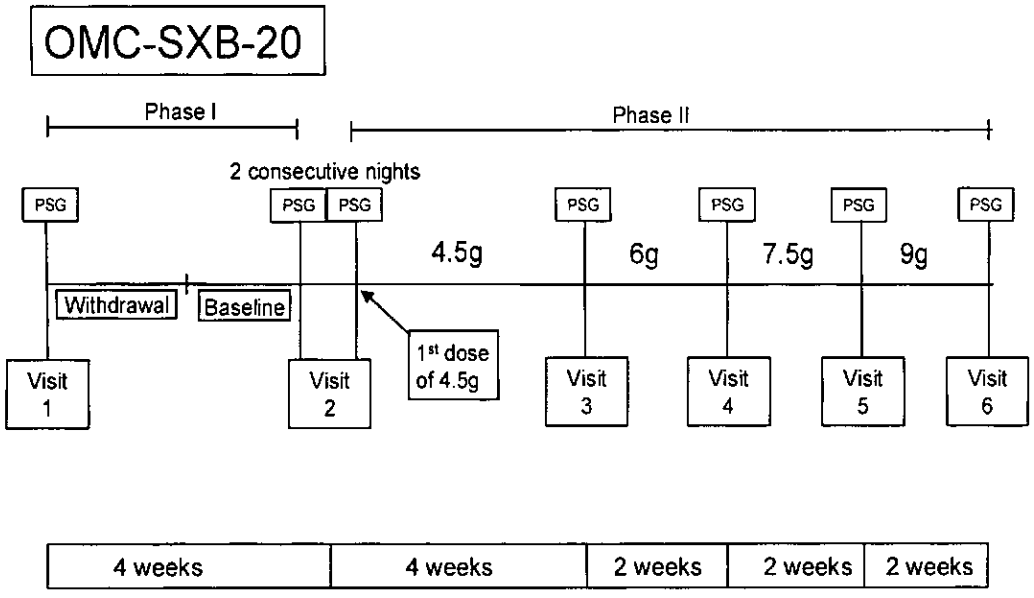
The effects of sodium oxybate on objective measures of nocturnal sleep in narcoleptic patients have been studied in six previous clinical studies (Broughton and Mamelak 1976,1980; Scharf 1985; Bedard 1989; Scrima 1990; Lammers 1993). These six studies have examined the non-comparative effects of doses of sodium oxybate ranging from 2.25 g up to 6.75 g. In general, these previous PSG studies demonstrated that sodium oxybate produces a modest decrease in Stage 1 sleep, no changes in Stage 2 sleep, a marked increase in Stages 3 and 4 sleep (delta sleep or slow wave sleep), and a decrease in the number of awakenings. Several of the trials also documented a decrease in the number of stage shifts and a decrease in REM latency. No change in

REM stage sleep duration was reported. Since the dosing regimen of sodium oxybate in these studies was different from Xyrem, it was of interest for this NDA to characterize the effects of Xyrem on the sleep architecture profile of narcoleptic patients across the doses proposed in the therapeutic regime.

3.2.2.2 Trial Objectives/Design

The primary objective of this trial design (Figure 3.22) was to characterize the polysomnographic (PSG) sleep architecture in narcoleptic patients at four escalating doses (4.5 g, 6.0 g, 7.5 g, and 9.0 g) of Xyrem, encompassing a 10-week exposure to Xyrem. In addition, parameters relating to daytime function were also evaluated for possible corresponding relationship to PSG effects.

Figure 3.22 OMC-SXB-20 Trial Design



The OMC-SXB-20 clinical trial was designed as an open-label trial using patients diagnosed with narcolepsy and with a history of cataplexy. The patients were required to be currently treated with TCAs or SSRIs, so as to be able to determine the profile of the effects of removal of these anti-cataplectic medications. The first phase of the trial was the withdrawal and washout from pre-existing medications of stable TCAs, SSRIs, and hypnotics. In the last two weeks of this phase, all patients were free of TCAs, SSRIs, and hypnotics. At the beginning of the first phase, an overnight PSG was performed to assess PSG status resulting from TCA, SSRI, and/or hypnotic therapy and again at the end of phase I (baseline, prior to first dose of Xyrem) as a baseline measure. Stimulant medication was maintained at constant dose throughout all phases of the trial.

The second phase of the trial began with the patient receiving the first night dosing of 4.5 g Xyrem (sodium oxybate) and ended after a 10-week escalation to a final 9 g dose. An overnight PSG was performed on the night of the first dose of 4.5g Xyrem to measure any acute changes in the PSG produced by Xyrem. Each patient remained on a stable 4.5 g dose of Xyrem for 4 weeks. After the 4-week stable dosing period, another PSG was performed, and Xyrem was increased to 6.0 g, 7.5 g, and 9.0 g in successive two-week intervals (see Figure 3.22). An overnight PSG was performed on the last night of each dose of Xyrem to measure the effects of each dose of Xyrem on the PSG, and to define any dose-response on sleep architecture for each patient. For all PSG nights, Xyrem dose was administered in divided dosing just prior to lights out and again 4.0 hours later.

Subjective determinations of the effects of Xyrem on daytime sleepiness were measured by the Epworth Sleepiness Scale (ESS), and changes in common symptoms of narcolepsy were assessed by the Narcolepsy Symptoms Assessment (NSA). In addition to these subjective measures, an objective measure of the effects of Xyrem on daytime sleepiness were evaluated by the well-established procedure, the Maintenance of Wakefulness Test (MWT). The ESS Questionnaire and the NSA were administered at each visit. The Maintenance of Wakefulness Test (MWT) was administered four times: while still on TCA, SSRI, and/or hypnotics (Visit 1), after washout of these medications (Visit 2; baseline), after 4 weeks at 4.5 g Xyrem (Visit 3), and after 2 weeks at 9 g Xyrem (Visit 6).

3.2.2.2.1 Primary Measures

The primary measures consisted of a set of objective clinical PSG parameters in relation to dose of Xyrem, recorded overnight in a sleep laboratory setting. The set of objective PSG parameters for each study night included the following:

- Total Sleep Time (TST) in minutes following the first and second dose of Xyrem and a summation. Total Sleep Time is the duration of time during which the patient was recorded to be in any of the sleep stages. (Total time in bed for this trial was 8.0 hours.)
- Sleep latency in minutes following the first and second dose of Xyrem. Sleep latency is the period of time in minutes between the epoch when the lights were turned off in the room where the nocturnal PSG was being performed and the first epoch that was scored as Stage 1, 2, 3, 4 or REM.
- Stage 1 sleep time in minutes following the first and second dose of Xyrem and a summation. Stage 1 sleep time is the duration of time in minutes in which the EEG recording was scored as Stage 1 sleep. Stage 1 sleep is defined as a relatively low voltage, mixed frequency EEG without rapid eye movements (REMs).
- Stage 2 sleep time in minutes following the first and second dose of Xyrem and a summation. Stage 2 sleep time is the duration of time in minutes in which the EEG recording is scored as Stage 2 sleep. Stage 2 sleep time is defined as 12 to 14 cycles per second (cps) sleep spindles and K-complexes on a background of relatively low voltage, mixed frequency EEG activity. Sleep spindles are a spindle-shaped cluster of waves.

- Stage 3 & 4 sleep time in minutes following the first and second dose of Xyrem and a summation. Stage 3 and 4 sleep time is the duration of time in minutes in which the EEG recording was scored as Stage 3 or Stage 4 sleep. Stage 3 sleep is defined as a form of slow wave sleep, and is used when between 20 to 50 percent of the epoch (30 seconds) is occupied by delta waves of peak-to-trough voltage equal to or greater than 75 microvolts. Stage 4 sleep is the slow wave sleep during which at least 50 percent of the epoch is occupied by delta waves of peak-to-trough voltage equal to or greater than 75 microvolts. Stage 3 and 4 sleep thus represents the slow wave sleep during which at least 20 percent of the epoch is occupied by delta waves of peak-to-trough voltage equal to or greater than 75 microvolts (Rechschaffen and Kales 1968).
- Delta power in microvolts^2/Hz following the first and second dose of Xyrem and an average. Delta power is the accumulated index of EEG signal power for frequencies between 0.5 to 4.0 Hz that occur during sleep stages 1, 2, 3, or 4 all divided by the number of fast Fourier transforms (FFTs) performed in those stages and 3.5 Hz (Guilleminault 1998).
- Rapid Eye Movement (REM) Sleep time in minutes following the first and second dose of Xyrem and a summation. REM Sleep time is the duration of time in minutes in which the EEG recording was scored as Stage REM. Stage REM sleep is defined as rapid eye movement sleep, a relatively low voltage, mixed frequency EEG in conjunction with episodic REMs and low amplitude electromyogram.
- REM sleep latency in minutes following the first and second dose of Xyrem and a summary. REM sleep latency is the duration of time in minutes between the first epoch of sleep and the first epoch scored as REM.
- Wake After Sleep Onset (WASO) in minutes following the first and second dose of Xyrem and a summation. WASO is the duration of time in minutes that the patient was wakeful (Stage W) after sleep onset had initially occurred; sleep onset was defined as the time after which a 30 second epoch scored as Stage 1, 2, 3, 4, or REM occurred. This is defined as the duration of time that is staged as awake that occurs between sleep onset and "Lights On" at the end of the sleep period.
- Stage shifts per hour following the first and second dose of Xyrem and an average. Stage shifts per hour is the number of times that an epoch (30 seconds) was scored as having a different EEG sleep stage than the previous epoch all divided by the total time between lights out and lights on.
- Total awakenings following the first and second dose of Xyrem and a summation. Awakenings is a term defined by the number of occurrences of wake epochs immediately following a sleep epoch.

3.2.2.2.2 Secondary Measures

Secondary measures consisted of both subjective and objective tools to ascertain the effects of Xyrem on daytime symptoms of narcolepsy. The set of parameters included:

- The ESS Questionnaire (Johns 1991) was used as an indication of daytime sleepiness. It was performed at each visit prior to the overnight PSG. The ESS Questionnaire instructed patients to rate their "chance of dozing" on a scale of 0-3 (never, slight, moderate, and high chance of dozing) in each of eight standard possible situations.

- The initial NSA, at Visit 1, asked the patients to historically rate their common narcolepsy symptoms for the week prior to starting the clinical trial, while the follow-up NSA evaluations (Visits 2 – 6) rated qualitative changes in narcolepsy symptoms for the previous week in comparison to the time before entry into the trial.
- The MWT is a standardized 40-minute EEG to determine the patient's daytime wakefulness under specified soporific conditions (quiet, darkened room and semi-recumbent position) at four times during the day, spaced two hours apart (Mitler 1982, 1998). The MWT trials were used to assess average sleep latency time and to determine whether or not a sleep-onset REM Period (SOREMP) had occurred. For the MWT trials, the patient was instructed to keep to the same schedule of stimulant medications for the day of each of the MWT tests during the trial, as well as caffeine and nicotine consumption. MWT sleep latency was defined as the duration of time in minutes (up to 40-minutes) between the time when the room where the EEG was being performed was darkened and either the first epoch that was scored as Stage 2, 3, 4, or REM, or the first of 3 consecutive stages of Stage 1 sleep. For the MWT, determination of sleep latency required 10 minutes of subsequent sleep whether continuous or intermittent. The individual trial was stopped once sleep onset had been determined, or after 40 minutes if no sleep occurred.

Baseline and endpoints are defined as follows:

- Baseline consisted of the data collected on Visit 2a for PSG, ESS, and MWT; the baseline for the NSA was Visit 1. Visit 2a represents the period when patients had discontinued TCAs, continued stimulants, and was just prior to Xyrem dosing.
- Endpoints for this trial consisted of Visit 1, the first night of Xyrem administration (Visit 2b), and subsequent visits (Visit 3, 4, 5, 6)

3.2.2.3 Patient Demographics

Twenty-seven narcoleptic patients were enrolled into the trial; twenty-five patients were treated at four investigative sites; and 21 patients completed the trial. In the patient population, there was a trend towards older (average 52.6 years old),female (72%), overweight (average 84.2 kg), and Caucasian (92%) patients. It is known that age of the patient population will have an impact on sleep architecture, specifically a reduction in Stages 3 and 4 sleep are seen with increasing age. Recent literature indicates that older males exhibit markedly reduced levels of slow-wave sleep (Stage 3 and 4) (Van Cauter, 2000).

During the withdrawal period, patients withdrew from pre-existing medications of TCAs, SSRIs, and hypnotics. In the last two weeks of this phase, all patients were free of TCAs, SSRIs, and hypnotics. Stimulant medications were continued at stable dosing throughout the trial. Eighty-eight percent (88%) of patients took TCAs, SSRIs, or hypnotics prior to the start of treatment. The most frequently used medications were venlafaxine, taken by 24% of patients, fluoxetine, taken by 20% of patients, and sertraline, taken by 16% of patients.

3.2.2.4 Efficacy Evaluation

3.2.2.4.1 Primary Variables

The primary efficacy analysis — Polysomnography Variables – (Table 3.31) provides an overall summary of total sleep time (TST), sleep latency, time in Stage 1, time in Stage 2, time in Stage 3 and 4 (also see Figure 3.23), REM sleep time, delta power, REM sleep latency, wake time after sleep onset (WASO), number of stage shifts per hour, and number of total awakenings.

Table 3.31 Overall Summary of Changes from Baseline in Nocturnal Polysomnography Variables by Dosage — Intent-to-Treat Patients

Visit	1	2a	2b	3	4	5	6
Variable	Anti-Cataplexy Medications	Baseline[a]	1st dose 4.5 g	4.5 g	6.0 g	7.5 g	9.0 g
N	20	21	18	20	21	20	20
Stage 1 Time (min)							
Sum							
Mean (SD)	13.3 (27.63)	74.8 (31.43)	-19.8 (23.56)	-2.5 (31.61)	-6.7 (27.02)	-5.4 (39.12)	-12.2 (32.04)
P-value from baseline[b]	0.044	-	0.002	0.733	0.268	0.544	0.106
Stage 2 Time (min)							
Sum							
Mean (SD)	-1.8 (62.17)	217.8 (45.45)	-4.3 (37.40)	-0.9 (51.46)	-0.9 (62.67)	6.3 (54.05)	20.2 (58.11)
P-value from baseline[b]	0.898	-	0.636	0.938	0.947	0.607	0.137
Stage 3 and 4 Time (min)							
Sum							
Mean (SD)	0.6 (13.29)	3.5 (8.38)	5.0 (17.08)	0.6 (8.71)	5.4 (20.16)	10.7 (21.02)	23.2 (39.80)
P-value from baseline[c]	0.636	-	0.296	0.771	0.296	0.056	0.012
Delta Power (microvolts^2/Hz)							
Average							
Mean (SD)	3417.3 (31189.26)	69708.6 (19296.87)	12482.3 (10438.58)	4771.3 (13806.55)	12598.9 (25627.51)	22208.8 (17940.01)	32629.3 (27165.27)
P-value from baseline[b]	0.630	-	<0.001	0.139	0.036	<0.001	<0.001

(continued)

Table 3.31 Overall Summary of Changes from Baseline in Nocturnal Polysomnography Variables by Dosage — Intent-to-Treat Patients

Visit	1	2a	2b	3	4	5	6
Variable	Anti-Cataplexy Medications	Baseline[a]	1st dose 4.5 g	4.5 g	6.0 g	7.5 g	9.0 g
N	20	21	18	20	21	20	20
REM Sleep Time (min)							
Sum							
Mean (SD)	-37.5 (43.21)	87.2 (28.93)	16.6 (32.66)	-15.8 (30.43)	-18.1 (29.16)	-21.0 (34.07)	-33.8 (36.23)
P-value from baseline[b]	0.001	-	0.046	0.032	0.010	0.013	<0.001
REM Sleep Latency (min)							
1st half							
Mean (SD)	60.5 (98.32)	44.0 (52.21)	-18.1 (62.32)	-0.5 (70.04)	2.6 (60.69)	7.0 (83.35)	33.6 (91.71)
P-value from baseline[c]	0.010	-	0.424	0.668	0.545	0.776	0.057
2nd half							
Mean (SD)	39.3 (82.38)	47.3 (47.69)	-6.3 (40.89)	-1.2 (80.02)	-18.8 (52.36)	13.0 (75.07)	-3.3 (72.98)
P-value from baseline[c]	0.070	-	0.640	0.735	0.162	0.568	0.791
WASO (min)							
Sum							
Mean (SD)	19.2 (45.89)	79.0 (28.37)	-0.3 (34.61)	12.4 (30.70)	7.8 (42.02)	-4.4 (41.96)	-5.2 (36.79)
P-value from baseline[b]	0.078	-	0.973	0.088	0.406	0.644	0.533
TST (min)							
Sum							
Mean (SD)	-25.4 (58.19)	383.4 (29.15)	-2.5 (42.04)	-18.6 (37.79)	-20.4 (55.05)	-9.3 (51.58)	-2.6 (42.84)
P-value from baseline[b]	0.066	-	0.804	0.041	0.105	0.430	0.789

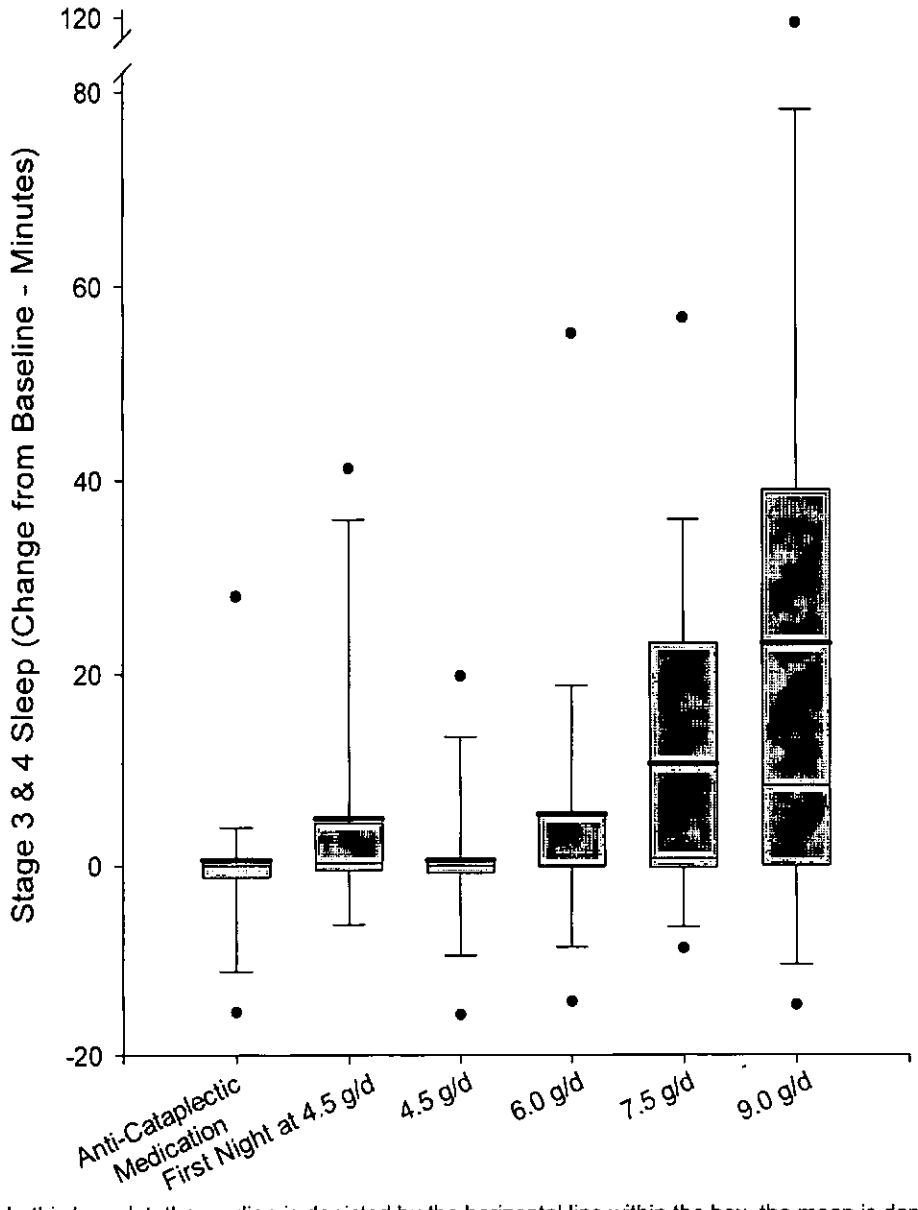
(continued)

Table 3.31 Overall Summary of Changes from Baseline in Nocturnal Polysomnography Variables by Dosage — Intent-to-Treat Patients

Visit	1	2a	2b	3	4	5	6
Variable	Anti-Cataplexy Medications	Baseline[a]	1st dose 4.5 g	4.5 g	6.0 g	7.5 g	9.0 g
N	20	21	18	20	21	20	20
Sleep Latency (min)							
1st half							
Mean (SD)	3.4 (6.39)	2.2 (2.16)	0.1 (1.89)	1.4 (2.48)	4.1 (10.76)	2.6 (3.79)	3.9 (5.35)
P-value from baseline[c]	0.022	-	0.693	0.048	0.042	0.005	0.003
2nd half							
Mean (SD)	2.7 (5.33)	2.5 (2.84)	2.4 (5.46)	3.8 (7.12)	3.8 (6.95)	6.1 (9.85)	3.9 (5.54)
P-value from baseline[c]	0.053	-	0.058	0.020	0.012	0.005	0.005
Stage Shifts Per Hour							
Average							
Mean (SD)	1.5 (5.22)	21.0 (5.28)	-3.2 (3.72)	0.3 (4.59)	-0.8 (3.92)	-3.1 (4.00)	-1.5 (4.86)
P-value from baseline[b]	0.217	-	0.002	0.792	0.364	0.002	0.185
Total Awakenings							
Sum							
Mean (SD)	4.5 (16.04)	50.2 (13.67)	-9.1 (14.22)	-0.2 (14.83)	-5.1 (14.82)	-12.9 (13.21)	-12.4 (16.34)
P-value from baseline[b]	0.230	-	0.015	0.964	0.131	<0.001	0.003

[a] Visit 2a (Baseline) is the actual value, all other visits are changes from baseline.
[b] Within treatment p-values:t-test
[c] Within treatment p-values:Wilcoxon signed rank test

Figure 3.23 Changes in Stage 3 and 4 Sleep (From Baseline) — Intent-to-Treat Patients



In this box plot, the median is depicted by the horizontal line within the box, the mean is depicted by the bold horizontal line, the limits of the box are the 1st and 3rd quartiles, the whiskers are the 10th and 90th percentiles, and the upper and lower circular symbols denote the 95th and 5th percentiles, respectively.

3.2.2.4.2 Secondary Variables

The secondary efficacy analysis are presented in the accompanying tables, and provides a complete, overall summary of the results from Epworth Sleepiness Score, Narcolepsy Symptoms Assessment, and Maintenance of Wakefulness Test.

Epworth Sleepiness Score (Table 3.32)
There were marked dose-related decreases in the mean ESS across all doses, incremental beyond the continued stable dosing of stimulants. These mean decreases in the ESS, a subjective measure of daytime sleepiness, also support changes seen in previous Xyrem studies (OMC-GHB-2; OMC-GHB-3). Changes in the ESS seen in the SXB-20 study are comparable to results of recent placebo-controlled stimulant studies with modafinil, a well-established stimulant for narcoleptics, in which mean ESS scores decreased 4 to 5 points in the modafinil group. A minimal decrease was observed in the placebo control (US Modafinil in Narcolepsy Study Group, 2000), indicating that ESS scores on narcoleptics in an open-label trial, such as OMC-SXB-20, may constitute real changes, as opposed to perceived changes.

Narcolepsy Symptom Assessment (Table 3.33)
There were improvements in narcolepsy symptoms of cataplexy attacks, hypnagogic hallucinations, number of sleep paralysis episodes, number of inadvertent naps/sleep attacks during the day, number of awakenings at night, and the severity of daytime sleepiness beginning with Visit 3, after 4 weeks on the 4.5 g dosage. Greater reductions in narcolepsy symptoms were seen with increasing Xyrem dosage. Quality of sleep at night, ability to concentrate, and overall condition also improved beginning with Visit 3, after 4 weeks on the 4.5 g dosage. In general, improvement in symptoms was observed with increasing doses of Xyrem, relative to the condition of the patient prior to starting the trial (when on TCA/SSRI/hypnotics).

Table 3.32 Summary of Changes from Baseline in the Epworth Sleepiness Scale by Dosage — Intent-to-Treat Patients

Visit Condition	1 Anti-Cataplexy Medica-tions	2a Baseline	2b 1st dose 4.5 g	3 4.5 g	4 6.0 g	5 7.5 g	6 9.0 g
N	21	21	21	21	21	20	21
Mean	-1.9	19.8	0.5	-2.4	-3.8	-4.8	-5.8
SD	1.92	2.66	2.11	2.75	3.62	4.02	4.55
Median	-2.0	20.0	0.0	-2.0	-3.0	-4.0	-7.0
Minimum	-6.0	12.0	-3.0	-9.0	-12.0	-13.0	-14.0
Maximum	3.0	24.0	5.0	2.0	0.0	1.0	2.0
P-value from baseline	<0.001	-	0.341	<0.001	<0.001	<0.001	<0.001
Inference with 4.5 g	-	-	-	-	0.042	<0.001	<0.001
Inference with 6.0 g	-	-	-	-	-	0.076	0.006
Inference with 7.5 g	-	-	-	-	-	-	0.317

Visit 2a (baseline) is the actual value, all other visits are changes from baseline.
Within treatment p-values: Wilcoxon signed rank test. Between treatment p-values: ANOVA on rank changes from baseline.

Table 3.33 Summary of Follow-up Narcolepsy Symptoms Assessment by Dosage — Intent-to-Treat Patients

Visit Condition	2a Pre-treatment	3 4.5 g	4 6.0 g	5 7.5 g	6 9.0 g
Number of Patients	**21**	**21**	**21**	**21**	**21**
Number of Cataplexy Attacks	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	13 (62%)	3 (14%)	0	0	0
Decreased	0	11 (52%)	17 (81%)	18 (86%)	18 (86%)
About the same	8 (38%)	7 (33%)	4 (19%)	2 (10%)	3 (14%)
Number of Hypnagogic Hallucinations	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	8 (38%)	3 (14%)	1(5%)	0	0
Decreased	0	6 (29%)	10(48%)	15 (71%)	16 (76%)
About the same	13 (62%)	12 (57%)	10(48%)	5 (24%)	5 (24%)
Number of Sleep Paralysis Episodes	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	8 (38%)	1(5%)	0	0	0
Decreased	0	8 (38%)	14 (67%)	15 (71%)	16 (76%)
About the same	13 (62%)	12 (57%)	7 (33%)	5 (24%)	5 (24%)
Number of Inadvertent Naps/Sleep Attacks During the Day	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	13 (62%)	1(5%)	0	0	0
Decreased	0	11 (52%)	16 (76%)	16 (76%)	16 (76%)
About the same	8 (38%)	9 (43%)	5 (24%)	4 (19%)	5 (24%)
Number of Awakenings at Night	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	8 (38%)	2 (10%)	1(5%)	0	3 (14%)
Decreased	3 (14%)	11 (52%)	11 (52%)	13 (62%)	12 (57%)
About the same	10(48%)	8 (38%)	9 (43%)	7 (33%)	6 (29%)

(continued)

Table 3.33 Summary of Follow-up Narcolepsy Symptoms Assessment by Dosage — Intent-to-Treat Patients

Visit Condition	2a Pre-treatment	3 4.5 g	4 6.0 g	5 7.5 g	6 9.0 g
Number of Patients	**21**	**21**	**21**	**21**	**21**
Severity of Daytime Sleepiness	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	12 (57%)	1(5%)	1(5%)	0	0
Decreased	0	14 (67%)	14 (67%)	14 (67%)	16 (76%)
About the same	9 (43%)	6 (29%)	6 (29%)	6 (29%)	5 (24%)
Quality of Sleep at Night	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Much improved	0	4 (19%)	5 (24%)	5 (24%)	5 (24%)
Somewhat improved	3 (14%)	12 (57%)	14 (67%)	13 (62%)	12 (57%)
Unchanged	9 (43%)	4 (19%)	2 (10%)	2 (10%)	2 (10%)
Somewhat worse	4 (19%)	1(5%)	0	0	2 (10%)
Much worse	5 (24%)	0	0	0	0
Ability to Concentrate	21(100%)	21(100%)	21(100%)	21(100%)	21(100%)
Much improved	0	0	3 (14%)	3 (14%)	1 (5%)
Somewhat improved	0	9 (43%)	10 (48%)	11 (52%)	13 (62%)
Unchanged	11 (52%)	9 (43%)	7 (33%)	6 (29%)	7 (33%)
Somewhat worse	9 (43%)	3 (14%)	1 (5%)	0	0
Much worse	1 (5%)	0	0	0	0
Overall Condition	21(100%)	21(100%)	21(100%)	21(100%)	21(100%)
Much improved	0	1 (5%)	5 (24%)	7 (33%)	9 (43%)
Somewhat improved	0	16 (76%)	12 (57%)	12 (57%)	8 (38%)
Unchanged	5 (24%)	3 (14%)	4 (19%)	1 (5%)	3 (14%)
Somewhat worse	8 (38%)	1 (5%)	0	0	1 (5%)
Much worse	8 (38%)	0	0	0	0

The number of patients reported does not equal the total patients treated if data was missing.

Maintenance of Wakefulness Test (Table 3.34)

Polysomnographic measurement of daytime wakefulness indicated a dose related increase in sleep latency. Mean (SD) sleep latency time in minutes was 4.5 (6.01) minutes at Visit 2a (baseline). Mean (SD) change at Visit 3 on 4.5 g Xyrem was 3.7 (7.68) minutes and mean change (SD) at Visit 6 on 9.0 g Xyrem was 6.1 (6.82) minutes. There were statistically significant changes from baseline at Visit 3 ($p = 0.038$), and Visit 6 ($p<0.001$).

These increases in sleep latency were incremental beyond current stimulant therapy. The magnitude of these changes for the 9 g Xyrem dose group (6.1 min) was larger than that shown for all dosages of Modafinil in recent controlled studies compared to placebo, a well-established stimulant medication for daytime sleepiness in narcoleptics. In one study, changes from baseline were only 2.1 min for 200 mg modafinil and 1.9 min for 400 mg modafinil (US Modafinil in Narcolepsy Study Group, 2000) and, in another study, changes from placebo were 4.5 min for 200 mg modafinil and 6.0 min for 400 mg modafinil (Broughton 1997).

There was a dose-related decrease in the percentage of patients with one or more sleep-onset REM period (SOREMP). At Visit 2a (baseline), 18 of 21 patients (86%) had SOREMP. At Visit 3 on 4.5 g Xyrem, 13 of 21 patients (62%) had SOREMP, and 6 of 20 patients (30%) on 9.0 g Xyrem had SOREMP. Patients on anti-cataplexy medications (Visit 1 in Table 3.34) also had decreases in SOREMPs, but not as profound as those on 9.0 g Xyrem. Prior research has shown that decreases in SOREMPs are positively associated with a reduction in cataplexy attacks (Amira 1985; Hishikawa 1995).

Table 3.34 Summary of Maintenance of Wakefulness Test by Visit — Intent-to-Treat Patients

Visit	1	2a	3	6
	Anti-Cataplexy Medica-tions	Baseline	4.5 g	9.0 g
Number of Patients	**21**	**21**	**21**	**20**
Sleep Latency (minutes)				
N	21	21	21	20
Mean	1.0	4.5	3.7	6.1
SD	5.69	6.01	7.68	6.82
Median	0.6	2.3	1.0	3.3
Minimum	-10.8	0.5	-8.0	-5.0
Maximum	16.6	27.1	30.2	21.9
p-value from baseline	0.441	—	0.038	<0.001
Inference with Visit 3	—	—	—	0.286
SOREMP				
Yes	11 (52%)	18 (86%)	13 (62%)	6 (30%)
No	10 (48%)	3 (14%)	8 (38%)	14 (70%)

SOREMP = Sleep-onset rapid eye movement period.
Visit 2a (baseline) is the actual visit, all other visits are changes from baseline.
Within treatment p-values: t-test. Between treatment p-values: ANOVA on rank changes from baseline.
For SOREMP: Frequencies are actual counts at each visit.

3.2.2.5 Conclusions and Discussion

3.2.2.5.1 Conclusions

With respect to the effect of four dosages of Xyrem on overnight polysomnography (PSG) recordings in narcoleptic patients, the following conclusions can be derived from the present data:

1. Xyrem treatment resulted in a dose related increase in slow wave sleep (SWS, delta sleep, Stage 3 & 4) across all 4 doses reaching significance at the 9.0 g/night regimen.
2. Delta power, a derived index of all slow wave signals, showed a dose related increase that was highly significant on the first night following 4.5 g as well as after 2 weeks of dosing at 6.0 g, 7.5 g and 9.0 g/night.
3. 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.
4. Across doses a non-significant decrease in Stage 1 sleep was observed, while the amount of Stage 2 sleep remained unchanged.
5. An acute increase in REM sleep was demonstrated with the initial 4.5 g treatment, with subsequent dose related significant decreases in total REM sleep duration at all 4 doses.
6. No significant change in REM latency was observed among the 4 doses studied.
7. No dose related change in total sleep time (TST) was observed; however, a significant decrease in TST was found following 4.5 g/night dosing for 4 weeks.
8. The number of shifts in sleep stage demonstrated a decreasing trend at doses greater than 4.5 g/night but a significant decrease was recorded only following 7.5 g/ night Xyrem.
9. The total time spent awake after the onset of sleep (WASO) was not significantly altered by any of the Xyrem doses.
10. A significant dose-dependent increase in sleep latency was observed across all 4 doses.

Consistent with the objective PSG findings, the subjective report by the patients on the Narcolepsy Symptom Assessment indicated a dose related improvement in the overall quality of sleep and the perceived number of nighttime awakenings as compared to the patient's self assessment at study entry while still on their anti-cataplectic and stimulant medications. The nocturnal symptoms of hypnogogic hallucinations and sleep paralysis likewise were decreased appreciably in 16 of 21 (76%) patients.

The following are the conclusions derived from the objective and subjective measures of daytime sleepiness:

1. The administration of Xyrem produced a significant increase in sleep latency as measured by the MWT. This dose-dependant increase averaged 3.7 minutes ($p = 0.038$) after 4 weeks of 4.5 g nightly that further increased to a mean improvement of 6.1 minutes ($p < 0.001$) following the nightly 9.0 g dose. This measured response is additive to that produced by concomitant stimulant dosing.

2. The presence of SOREMPs during MWT, which occurred in of 18 of 21 patients (86%) at baseline, decreased to 13 of 21 (62%) following 4 weeks of 4.5 g Xyrem nightly. SOREMPs further decreased to 6 of 20 patients (30%) following the 9.0 g dose.
3. The ESS total score significantly decreased in a dose-dependent manner by the nightly administration of Xyrem. The median total score of 20 at baseline improved by 2 points following the 4.5 g dose regimen ($p < 0.001$) and by 7 points after the 9.0 g dose ($p < 0.001$).
4. The patients in the current trial reported substantial improvements in subjectively determined (by NSA recording of) daytime narcolepsy symptoms including the incidence of cataplexy attacks, the number of inadvertent naps as well as decreased daytime sleepiness, and increased the ability to concentrate and a perception of overall improvement in their narcolepsy while taking nightly doses of Xyrem.

3.2.2.5.2 Discussion

This study was designed to allow descriptive comparison of standard parameters of sleep architecture in a group of narcoleptic patients initially on stimulant and anti-cataplectic medications (TCAs, SSRIs, and hypnotics) and to assess changes when these anti-cataplectic medications were discontinued (down-titration over two weeks, followed by two weeks of no medication) to provide a baseline recording with only stimulant medications continued. This allowed measurement of the PSG effects attributed to these medications and a proximate comparison with sodium oxybate effects. Dosing with Xyrem in an escalating dose regimen provided the basis for assessment of both the acute PSG effects (during first night of dosing at 4.5 g) and across the dose range from 4.5 to 9.0 g/night, representing the principal dosing regimens for Xyrem in the treatment of narcolepsy. Collection of the parameters representative of daytime sleepiness by objective (MWT) and subjective (ESS, NSA) measures allowed consideration of the relationship between nighttime sleep characteristics, Xyrem dose (or time-on-drug), and daytime clinical effect.

3.2.2.5.2.1 Stage 3 and 4 Sleep

The most important finding of this report is that of the dose-dependent increase in the restorative Stage 3 and 4 sleep time (delta sleep, slow wave sleep) following treatment with Xyrem (sodium oxybate). The increase in slow wave sleep following treatment with sodium oxybate has been repeatedly reported in the literature (Broughton 1976, 1980; Scharf 1985; Bedard 1989; Scrima 1990; Lammers 1993). The relatively small amount of slow-wave sleep recorded across the entire trial (e.g. 3.5 minutes at baseline) was attributed to the presence of strict scoring criteria which required that the slow-wave EEG amplitude be at least 75 micro-volts (peak-to-trough) (Rechtschaffen 1968), a voltage that would be expected to be low in this trial due to the high average age of the patient population (Van Cauter 2000). Slow-wave sleep for the initial polysomnograph when the patients were on TCAs, SSRIs, or hypnotics was not significantly different from baseline, confirming that these medications lack the ability to increase slow wave sleep (Borbely 1985, Kupfer 1994, Wilson 2000, Oberndorfer 2000).

3.2.2.5.2.2 Delta Power

This increase in slow wave sleep is coincident with an increase in delta power. Delta power was determined by spectral analysis (using fast Fourier transformation) of the digital EEG signals from electronic PSG recordings so as to determine the index of all slow waves occurring during non-REM sleep between 0.5 and 4 Hz (Guilleminault 1998, Pivik 1993). As dose increases, the corresponding increase in delta power supports the increase in Stage 3 and 4 sleep. Stage 3 and 4 sleep only represents those sleep epochs containing greater than 20% and 50%, respectively, of slow waves with amplitudes of 75 microvolts or higher. Delta power differs in that it measures the total EEG signal in the delta wave range during all stages of NREM sleep. Slow wave sleep and delta wave signals in general (delta power) constitute that component of sleep that has been found to have restorative properties as demonstrated by correlation with measures of daytime performance and alertness (Jurado 1989, Schneider-Helmert 1987, Crenshaw 1999, Edinger 2000, Takahashi 1994).

3.2.2.5.2.3 REM Sleep

The effects on REM sleep time in this study were particularly interesting, and not entirely in keeping with the published literature. The expected decrease in REM sleep that was associated with TCA/SSRI/hypnotic treatment was supported by these data, with a highly significant (p=0.001) mean reduction of 37.5 minutes from the baseline mean total REM sleep time of 87.2 minutes. The acute pharmacologic response to Xyrem dosing at 4.5 g on the first night was a significant increase in total REM sleep time (p=0.046), which was followed by dose-dependent significant reductions in total REM sleep time across the 4.5, 6.0, 7.5, and 9.0 g dose groups. Previous literature had reported either no change in the proportion of REM sleep (Scrima 1990, Bedard 1989, Lammers 1993, Scharf 1985, Mamelak 1981) in narcoleptics, or a marked increase in REM sleep in the patients with depression (Broughton 1976). Further consideration of REM efficiency and REM density measures could be usefully applied to these recordings to assist in the interpretation of this unexpected data. There is a suggestion of a reciprocal relationship between REM and non-REM (NREM) sleep in humans (Merica 1998, Toussaint 1997, Uchida 1992, Takahashi 1994) and in rats (Benington 1994, Borbely 1984). Thus, the subsequent reduction in total REM sleep time beyond the pharmacologic increase produced by the initial dose of 4.5 g Xyrem may be an outcome of the drug-mediated increase in slow wave sleep.

3.2.2.5.2.4 REM Latency

Although often associated with decreases in REM latency in narcoleptics at lower doses of sodium oxybate (Broughton 1976, 1980; Scharf 1985; Bedard 1989; Scrima 1990; Lammers 1993), REM latency in the patient population in OMC-SXB-20 has not shown a decrease in REM latency, nor any dose effects. In contrast, the chronic dosing of TCA/SSRI/hypnotic medication present at the start of the trial lead to a marked increase in REM latency, relative to that recorded after their withdrawal and washout (baseline). Based on the distinctly different effects on REM latency between TCA/SSRI/hypnotic

medications at the start of the trial and escalating Xyrem dosing, the difference in effects could represent different neuropharmacological mechanisms.

As this is a small, open-label study, definitive conclusions cannot be established from any of these independent measures. However, the uniform changes in all subjective assessments and the objective measure as provided by the MWT in daytime sleepiness provides strong support for the therapeutic response to Xyrem treatment across the range of doses studied. This provides further consistent support for the previously submitted subjective data from the OMC-GHB-2 and OMC-GHB-3 studies.

In this single-arm trial, there is a confounding of effects between time-on-drug and dose-escalation. In all findings that exhibit an increase in extent of effect across the study, a definite statement regarding the dose-dependency of these effects must be qualified by the fact that these increases in extents of effects may be caused in part by the duration of time on drug (10 weeks of exposure while escalating dose up to 9 g at Visit 6). This is an unmitigatable feature of the trial. However, the source of the effect (time and/or dose level) does not diminish the impact of the drug on PSG parameters and narcolepsy symptoms.

3.2.2.5.2.5 Maintenance of Wakefulness Test (MWT)

The incremental improvement in sleep latency for the MWT, over-and-above that which was already present with current stimulant treatment, provides an opportunity to strongly suggest that Xyrem improved daytime alertness by a large magnitude.

3.3 Efficacy Summary

Based on the results of two adequate and well-controlled studies (OMC-GHB-2 and the Scrima trial), a supporting controlled study (Lammers trial) and supportive data from 2 uncontrolled studies (OMC-GHB-3 and OMC-SXB-6), dosages of between 3 g/d and 9 g/d of sodium oxybate are effective in the treatment of narcolepsy (reducing the frequency of cataplexy attacks and excessive daytime sleepiness [reduction in the Epworth Sleepiness Scale and the number of inadvertent naps or sleep attacks] associated with narcolepsy).

The findings of OMC-GHB-2 and OMC-GHB-3 taken together support the conclusion that, while the therapeutic benefit of sodium oxybate is clearly evident within 4 weeks of nightly therapy, the full benefit is not achieved until the patient has been treated for 2 to 3 months.

A blinded, randomized trial, OMC-SXB-21, provided evidence for the long-term efficacy of Xyrem. In this trial, patients abruptly discontinued from long-term (7 to 44 months) Xyrem therapy, had a recurrence of cataplexy.

Results of the long-term open-label dose-titration studies (OMC-GHB-3 and OMC-SXB-6) also shows long-term effectiveness of dosages from 3 g/d to 9 g/d when titrated to optimal clinical effectiveness for individual patients.

Overall, clinical improvement and benefit of sodium oxybate in the treatment of patients with narcolepsy is documented by both the physician-based (CGIc) and patient-based (Global Therapeutic Impression of Benefit) assessments.

Evidence (OMC-SXB-6) suggests that patients can safely decrease or discontinue other anti-cataplectic therapy (TCAs/SSRIs) once treatment with sodium oxybate is initiated, with continuing clinically satisfactory reduction in frequency of cataplectic attacks. There is no evidence of rebound cataplexy or other withdrawal effects (other than a return of narcolepsy symptoms) when patients are removed from sodium oxybate after 4 weeks of therapy at dosages up to 9 g/d.

In addition, sodium oxybate further improves daytime sleepiness when used adjunctively in narcoleptic patients already maintained on stimulant medications to treat their daytime sleepiness.

OMC-SXB-20 was an open-label pharmacological study that evaluated the effect of Xyrem on sleep architecture using objectively-measured nocturnal polysomnography at four escalating doses (4.5 g, 6 g, 7.5 g, 9 g) over a 10-week dosing period. The most important finding of this study is that of the increase in slow-wave sleep across all four doses of Xyrem compared to baseline in narcoleptic patients, with statistically significant increases in Stage 3&4 sleep reached at the 9.0 g per night dose as well as statistically significant increases in Delta Power at all four doses. Another important finding was the dose-related improvement in daytime sleepiness, as measured by the Maintenance of Wakefulness Test (MWT), which objectively quantifies the sleep latency of patients who are trying to remain awake while experiencing defined, soporific conditions. The increase in MWT sleep latency, relative to baseline, averaged 3.7 minutes ($p = 0.038$) after 4 weeks of 4.5 g per night of Xyrem that further increased to a mean improvement of 6.1 minutes ($p < 0.001$) following the nightly 9.0 g Xyrem dose. This vigorous response is additive to that already produced by concomitant stimulant dosing, supporting the reasons to conclude that Xyrem can be used to markedly improve daytime sleepiness in narcoleptics.

SECTION 4
SAFETY

4.0 SAFETY

4.1 Overview of Sodium Oxybate Trials

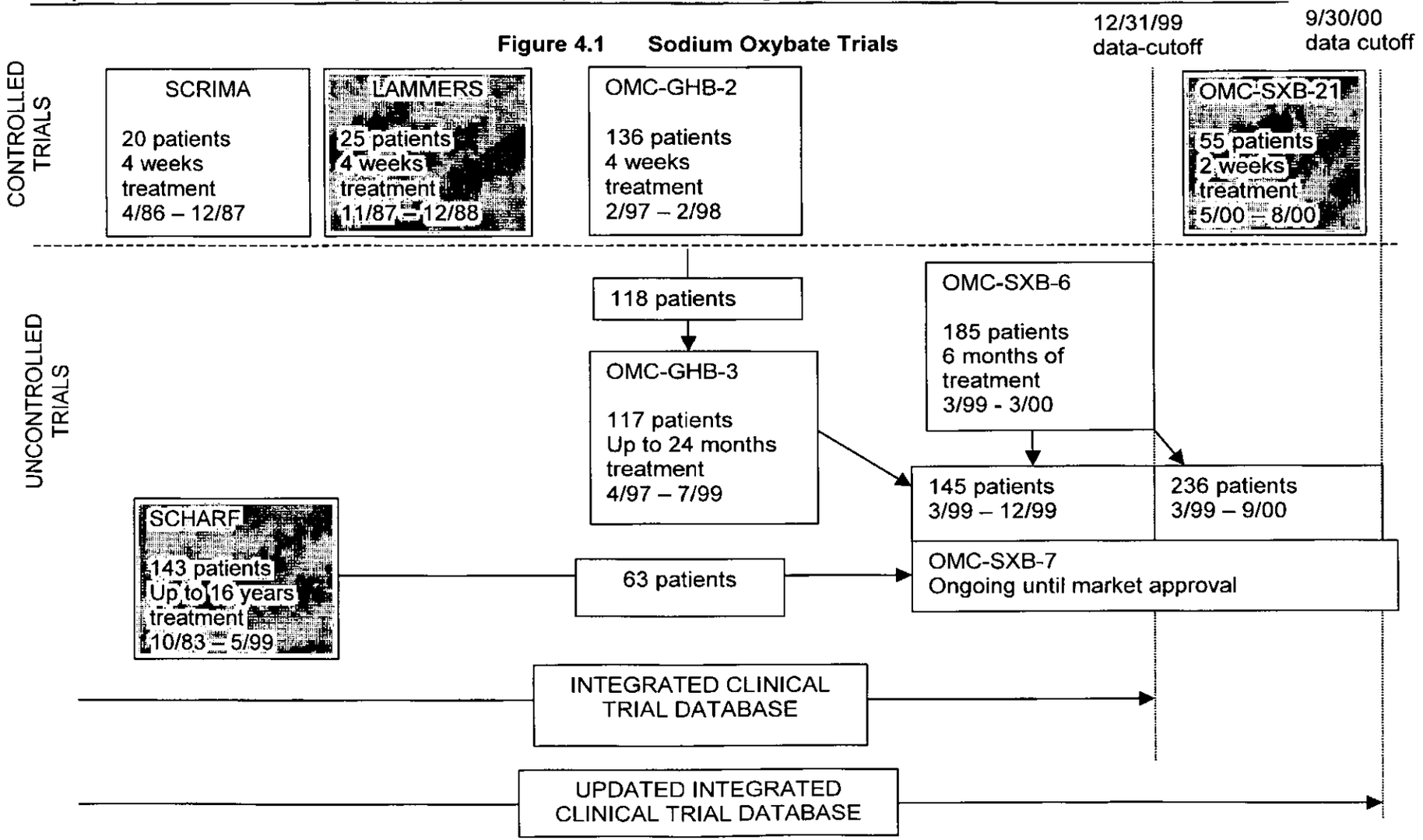
The following represents a summary of all available safety information for Xyrem (sodium oxybate). The safety data were carefully collected and reported by independent investigators conducting the clinical trials that make up the safety database in the Xyrem New Drug Application. The comprehensive database was reviewed by medical experts and summarized in individual clinical trial reports and in an Integrated Summary of Safety (submitted to FDA October 2, 2000). Safety data submitted subsequently included the Clinical Trial Report for controlled trial OMC-SXB-21 (submitted December 16, 2000) and a 4-Month Safety Update for the ongoing open-label trial (OMC-SXB-7, submitted February 2, 2001).

Four databases were used in compiling this analysis of safety:

- The updated integrated clinical trial database – this was a merge of the original integrated clinical trial database used for the Integrated Summary of Safety in the NDA and the 4-Month Safety Update database
  - The original integrated clinical trial database included two 4-week, placebo-controlled trials (Scrima and OMC-GHB-2) and 3 open-label, long-term trials (OMC-GHB-3, OMC-SXB-6, and OMC-SXB-7, the last through December 31, 1999), with a total of 402 patients, 148 of whom participated in more than 1 trial.
  - The 4-Month Safety Update database included 236 patients in the OMC-SXB-7 trial (with an additional 51 patients that transferred from OMC-SXB-6 to OMC-SXB-7 after the December 31, 1999 data cut-off).
- The Lammers trial, a 4-week, placebo-controlled trial, which was also included in the Integrated Summary of Safety as a separate database (this was not integrated in the statistical database due to its simplified method of data collection), with 25 patients
- The Scharf trial, an open-label, long-term trial, which was also included in the Integrated Summary of Safety as a separate database (this was not integrated in the statistical database due to the trial design and its history), with 143 patients, 63 of whom also participated in OMC-SXB-7 and are therefore included in the updated integrated clinical trial database
- The OMC-SXB-21 trial, a 4-week, placebo-controlled trial with 55 patients, all of whom also participated in OMC-SXB-7 (however, their safety data during OMC-SXB-21 are not included in the updated integrated clinical trial database; they were reported in the OMC-SXB-21 clinical trial report)

Figure 4.1 shows the trials included in this safety analysis. Shaded boxes represent the 3 trials (Lammers, Scharf, and OMC-SXB-21) not included in the updated integrated clinical trial database.

Figure 4.1 Sodium Oxybate Trials



Only Adverse Events (AEs) occurring during treatment were included in the analysis of the updated integrated clinical trial database and the Scharf trial.

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 clinical trial (Scharf). Related AEs were seen for 247(61%) of the 402 patients in the updated integrated clinical trial database. Severe AEs were seen for 82 (20%) of the 402 patients In the Scharf trial, severe AEs were seen for 21 (15%) of the 143 patients during the first 6 months on sodium oxybate.

Serious Adverse Events (SAEs) were experienced by 27 (7%) of the 402 patients in the updated integrated clinical trial database and 54 (38%) of the 143 patients in the Scharf trial. Two (<1%) deaths were reported in the updated integrated clinical trial database (both in the OMC-SXB-7 trial, including patient 0936, who died 5 months after the September 30, 2000, data cutoff), and 11 (8%) deaths were reported in the Scharf trial over 16 years. None of these deaths was considered related to trial medication. Fifty-three patients (13%) discontinued due to 1 or more AEs in the updated integrated clinical trial database, and 23 (16%) patients did so in the long-term (Scharf) trial. Of the discontinued patients, 42 (10%) in the updated integrated clinical trial database and 6 (4%) in the Scharf trial discontinued due to AEs considered to be related to trial medication.

For purposes of analysis, patients who had Xyrem oral solution dosages other than the protocol specified dosages were assigned a dosage according to the algorithm shown in Table 4.1.

Table 4.1 Algorithm for Assigning Dosages Other Than Those Specified by Protocol

Dosage (g/d)	Dosage Assignment(g/d)
≤ 0.00	Missing
> 0.00 to < 3.75	3.0
≥ 3.75 to < 5.25	4.5
≥ 5.25 to < 6.75	6.0
≥ 6.75 to < 8.25	7.5
≥ 8.25	9.0

4.2 Drug Exposure

In 4 of the clinical trials, patients were treated with sodium oxybate for 6 months or longer, including OMC-SXB-6 (6-month trial), OMC-GHB-3 (2-year trial), OMC-SXB-7 (2-year trial [amended to 30 months] and ongoing), and Scharf (16-year trial).

Table 4.2 provides an overview of duration of exposure for the 399 patients who received sodium oxybate in the updated integrated clinical trial database (up to September 30, 2000). Three patients received placebo in OMC-GHB-2, and did not

continue into an open-label trial; they are therefore not included in this table. The overall patient exposure was 296 patients with ≥ 6 months, 223 patients with ≥ 1 year, and 48 patients with an exposure of ≥ 2 years.

Table 4.2 Updated Integrated Clinical Trial Database — Cumulative Duration of Sodium Oxybate Exposure, by Patient Dosage

Duration of Exposure[b]	Total	Sodium Oxybate Patient Dosage[a] (g/d)				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
≥ 6 mo (168 d)	296 (74%)	9 (9%)	50 (19%)	115 (40%)	59 (44%)	62 (48%)
≥ 1 y (336 d)	223 (56%)	5 (5%)	27 (10%)	60 (21%)	26 (20%)	34 (26%)
≥ 2 y (672 d)	48 (12%)	2 (2%)	4 (1%)	13 (4%)	9 (7%)	13 (10%)

[a] Patient Dosage: the number of patients who took the specified dosage at any time during the trial. Patients could be counted for more than 1 dosage; alternatively, patients may not have taken any 1 dosage for the specified time period but did take sodium oxybate overall for that period. Therefore, the sum of patients exposed to specific dosages does not equal the total number of patients.

[b] Duration was calculated based on a 28-day month. Duration of exposure was not calculated for the 3 patients who received placebo only.

Table 4.3 provides the duration of exposure for the 479 patients in the combined experience from the updated integrated clinical trial database and the Scharf trial. With the experience from the long-term Scharf trial included, the overall patient exposure was 360 patients with ≥ 6 months, 286 patients with ≥ 1 year, and 150 patients with an exposure of ≥ 2 years.

Table 4.3 Updated Integrated Clinical Trial Database Plus Scharf Trial — Cumulative Duration of Sodium Oxybate Exposure, by Patient Dosage

Duration of Exposure[b]	Total	Sodium Oxybate Patient Dosage[a] (g/d)				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	**479 (100%)**	**198 (100%)**	**377 (100%)**	**383 (100%)**	**184 (100%)**	**159 (100%)**
≥ 6 mo (168 d)	360 (75%)	25 (13%)	87 (23%)	171 (45%)	83 (45%)	70 (44%)
≥ 1 y (336 d)	286 (60%)	12 (6%)	55 (15%)	114 (30%)	50 (27%)	42 (26%)
≥ 2 y (672 d)	150 (31%)	6 (3%)	26 (7%)	66 (17%)	34 (18%)	23 (14%)

[a] Patient Dosage: the number of patients who took the specified dosage at any time during the trial. Patients could be counted for more than 1 dosage; alternatively, patients may not have taken any 1 dosage for the specified time period but did take sodium oxybate overall for that period. Therefore, the sum of patients exposed to specific dosages does not equal the total number of patients.

[b] Duration was calculated based on a 28-day month. Duration of exposure was not calculated for the 3 patients who received placebo only.

Both with and without the experience from the Scharf trial, the most frequently administered dosage for all 3 durations of exposure (≥ 6 months, ≥ 1 year, and ≥ 2 years) was 6.0 g/d.

Total exposure to sodium oxybate (calculated based on twelve 28-day months) was 330 patient-years in the updated integrated clinical trial database, 2 patient-years in the Lammers trial, and 996 patient-years in the Scharf trial, or a total of 1,328 patient-years.

4.3 Updated Integrated Clinical Trials

The updated integrated clinical trial database is composed of a merge of the original integrated clinical trial database used for the Integrated Summary of Safety in the NDA and the 4-Month Safety Update database.

In the OMC-GHB-3 trial, 34 patients received placebo and all but 3 of these continued into open-label trials with sodium oxybate. Since all data in the updated integrated clinical trial database are presented by last dosage, only the 3 patients who did not go on to treatment with sodium oxybate are included in the placebo group. Since the 20 patients in the Scrima trial received both placebo and sodium oxybate, they are included in the sodium oxybate group.

As shown in Table 4.4, a majority of patients in the updated integrated clinical trial database had completed treatment (48/402, 12%) or were still enrolled in OMC-SXB-7 as of the September 30, 2000, data cutoff (210/402, 52%). Of the 144 patients who discontinued treatment, 52 (13%) did so due to AEs.

Table 4.4 Patient Disposition — Updated Integrated Clinical Trial Database

Patient Disposition	Total	Placebo	Sodium Oxybate
Patients treated	402 (100%)	3 (100%)	399 (100%)
Completed treatment	48 (12%)	2 (67%)	46 (12%)
Ongoing treatment	210 (52%)	0	210 (52%)
Discontinued treatment	144 (36%)	1 (33%)	143 (36%)
AE[a]	53 (13%)	1 (33%)	52 (13%)
Patient request/withdrew consent	34 (8%)	0	34 (9%)
Patient non-compliance	19 (5%)	0	19 (5%)
Other	18 (4%)	0	18 (5%)
Lost to follow-up	11 (3%)	0	11 (3%)
Lack of efficacy	5 (1%)	0	5 (1%)
Protocol deviation/violation	4 (<1%)	0	4 (<1%)
Death[a]	2 (<1%)	0	2 (<1%)

[a] Count includes patient 0936, who died on 2/24/01, 5 months after data cutoff, but is included here for completeness.

4.3.1 INCIDENCE OF ADVERSE EVENTS

Table 4.5 summarizes the AEs by sodium oxybate dosage at onset for the updated integrated clinical trial database.

- The majority of the 402 patients (331, 82%) experienced at least 1 AE.
- Approximately half of the patients (247, 61%) experienced related AEs.
- Severe AEs were reported for 82 patients (20%).
- Only 24 patients (6%) experienced SAEs.
- 53 patients (13%) discontinued due to AEs.
- There were 2 deaths (1%).

A higher incidence of AEs was seen with the 9.0 g/d sodium oxybate group compared with the other 4 dosage groups. 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 groups)
- Patients with SAEs (6% for 9.0 g/d, vs. 1% to 3% for the other 4 dosage groups)
- Patients with related AEs (55% for 9.0 g/d, vs. 28% to 40% for the other 4 dosage groups)
- Patients with severe AEs (16% for 9.0 g/d, vs. 3% to 12% for the other 4 dosage groups)
- Discontinuations due to AEs (14% for 9.0 g/d, vs. 3% to 6% for the other 4 dosage groups)

However, the incidence for each category was lower for 7.5 g/d than for 6.0 g/d, making it difficult to infer a true dose-response relationship. Interestingly, the incidence for the placebo group was similar to that for the 9.0 g/d group for patients with at least 1 AE (70%) and patients with related AEs (50%).

Table 4.5 AEs by Dosage at Onset — Updated Integrated Clinical Trial Database

	Total[a]	Place-bo	Sodium Oxybate Dosage at Onset (g/d)					
			Total[a]	3.0	4.5	6.0	7.5	9.0
Number of patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
At least 1 AE	331 (82%)	38 (70%)	326 (82%)	58 (60%)	138 (51%)	181 (62%)	72 (54%)	101 (78%)
SAEs	27 (7%)	0	27 (7%)	0	5 (2%)	11 (4%)	3 (2%)	10 (8%)
Related AEs	247 (61%)	27 (50%)	241 (60%)	37 (38%)	92 (34%)	115 (40%)	37 (28%)	71 (55%)
Severe AEs	82 (20%)	3 (6%)	80 (20%)	3 (3%)	25 (9%)	35 (12%)	6 (5%)	20 (16%)
Discontinu-ations due to AEs	53 (13%)	1 (2%)	52 (13%)	5 (5%)	15 (6%)	14 (5%)	4 (3%)	18 (14%)
Deaths	2 (1%)	0	2 (1%)	0	0	2 (1%)	0	0

[a] Patients are counted only once in each category. However, patients could have had more than 1 AE with different dosages at onset, so the sum of the patients in the dosage at onset groups may exceed the total number of patients in each event category.

Table 4.6 summarizes the incidence of AEs occurring in ≥ 5% of patients in the updated integrated clinical trial database. The most frequently reported AEs included headache (116 patients, 29%), nausea (94 patients, 23%), dizziness (76 patients, 19%), and pain (71 patients, 18%). The most frequently affected body systems were body as a whole (225 patients, 56%) and the nervous system (206 patients, 51%). 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.

Approximately half of the patients (247, 61%) experienced a related AE. The great majority of these patients reported AEs that were mild (99 patients, 40% of those with related AEs, 25% of the total population) or moderate (112 patients, 45% of those with related AEs, 28% of the total population). Severe related AEs were experienced by 36 patients (15% of those with related AEs, 9% of the total population). A higher incidence of both moderate and severe AEs overall was seen in the 9.0 g/d group. Moderate AEs were seen in 28% of the 9.0 g/d group, compared with 11% for placebo and 13% to 15% for the other 4 sodium oxybate groups; severe AEs were seen in 8% of the 9.0 g/d group, vs. 2% for placebo and 1% to 4% for the other 4 sodium oxybate groups. The incidence of severe related AEs for the most frequently reported AEs listed above was 1% (5/402) for headache, 1% (3/402) for nausea, 1% (4/402) for dizziness,

and 0 for pain. A higher incidence of mild headache was seen for placebo (11%), compared with 2% to 6% for the 5 sodium oxybate groups. No apparent differences were seen in the other AEs among the 6 groups, including placebo and the 5 sodium oxybate dosage at onset groups.

Table 4.6 AEs Occurring in ≥ 5% of Any Group, by Body System, COSTART Preferred Term, and Dosage at Onset — Updated Integrated Clinical Trial Database

Body System COSTART Preferred Term	Total[a]	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total[a]	3.0	4.5	6.0	7.5	9.0
Number of patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
Body as a Whole	225 (56%)	25 (46%)	221 (55%)	39 (40%)	81 (30%)	106 (37%)	41 (31%)	57 (44%)
Abdominal pain	25 (6%)	1 (2%)	24 (6%)	4 (4%)	6 (2%)	9 (3%)	3 (2%)	4 (3%)
Accidental injury	38 (9%)	0	38 (10%)	4 (4%)	6 (2%)	17 (6%)	6 (5%)	9 (7%)
Asthenia	36 (9%)	1 (2%)	35 (9%)	5 (5%)	6 (2%)	17 (6%)	5 (4%)	9 (7%)
Back pain	28 (7%)	2 (4%)	27 (7%)	2 (2%)	4 (1%)	13 (4%)	6 (5%)	8 (6%)
Chest pain	21 (5%)	0	21 (5%)	2 (2%)	4 (1%)	9 (3%)	5 (4%)	4 (3%)
Flu syndrome	41 (10%)	2 (4%)	39 (10%)	6 (6%)	7 (3%)	14 (5%)	10 (8%)	7 (5%)
Headache	116 (29%)	12 (22%)	112 (28%)	19 (20%)	40 (15%)	42 (14%)	13 (10%)	25 (19%)
Infection	42 (10%)	1 (2%)	41 (10%)	5 (5%)	2 (1%)	19 (7%)	7 (5%)	8 (6%)
Malaise	10 (2%)	3 (6%)	9 (2%)	1 (1%)	1 (<1%)	1 (<1%)	4 (3%)	3 (2%)
Pain	71 (18%)	4 (7%)	70 (18%)	12 (12%)	18 (7%)	33 (11%)	8 (6%)	16 (12%)
Viral infection	40 (10%)	0	40 (10%)	2 (2%)	6 (2%)	18 (6%)	5 (4%)	12 (9%)
Cardiovascular System	47 (12%)	2 (4%)	45 (11%)	6 (6%)	5 (2%)	17 (6%)	8 (6%)	11 (9%)
Digestive System	157 (39%)	9 (17%)	150 (38%)	23 (24%)	43 (16%)	62 (21%)	21 (16%)	42 (33%)
Diarrhea	38 (9%)	1 (2%)	37 (9%)	4 (4%)	6 (2%)	15 (5%)	7 (5%)	9 (7%)
Dyspepsia	32 (8%)	5 (9%)	27 (7%)	7 (7%)	8 (3%)	7 (2%)	2 (2%)	7 (5%)
Nausea	94 (23%)	4 (7%)	90 (23%)	9 (9%)	21 (8%)	31 (11%)	13 (10%)	30 (23%)
Vomiting	34 (8%)	1 (2%)	33 (8%)	1 (1%)	6 (2%)	14 (5%)	3 (2%)	10 (8%)
Metabolic and Nutritional System	53 (13%)	2 (4%)	53 (13%)	6 (6%)	8 (3%)	19 (7%)	14 (11%)	14 (11%)
Weight loss	12 (3%)	0	12 (3%)	0	0	4 (1%)	3 (2%)	6 (5%)

(continued)

Table 4.6 AEs Occurring in ≥ 5% of Any Group, by Body System, COSTART Preferred Term, and Dosage at Onset — Updated Integrated Clinical Trial Database

Body System COSTART Preferred Term	Total[a]	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total[a]	3.0	4.5	6.0	7.5	9.0
Number of patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
Musculoskeletal System	74 (18%)	2 (4%)	72 (18%)	8 (8%)	19 (7%)	33 (11%)	9 (7%)	12 (9%)
	21(5%)	2(4%)	19(5%)	2(2%)	7(3%)	10(3%)	1(1%)	2(2%)
Nervous System	206 (51%)	17 (31%)	201 (50%)	31 (32%)	66 (25%)	98 (34%)	31 (23%)	63 (49%)
Abnormal dreams	20 (5%)	0	20 (5%)	2 (2%)	8 (3%)	7 (2%)	4 (3%)	1 (1%)
Confusion	30 (7%)	1 (2%)	29 (7%)	4 (4%)	6 (2%)	11 (4%)	6 (5%)	10 (8%)
Depression	28 (7%)	1 (2%)	27 (7%)	5 (5%)	2 (1%)	12 (4%)	4 (3%)	6 (5%)
Dizziness	76 (19%)	2 (4%)	74 (19%)	16 (16%)	15 (6%)	34 (12%)	9 (7%)	22 (17%)
Emotional lability	13 (3%)	3 (6%)	10 (3%)	2 (2%)	2 (1%)	2 (1%)	1 (1%)	3 (2%)
Insomnia	25 (6%)	1 (2%)	24 (6%)	1 (1%)	8 (3%)	11 (4%)	3 (2%)	3 (2%)
Nervousness	35 (9%)	6 (11%)	31 (8%)	3 (3%)	9 (3%)	14 (5%)	3 (2%)	8 (6%)
Sleep disorder	47 (12%)	2 (4%)	45 (11%)	4 (4%)	15 (6%)	21 (7%)	5 (4%)	12 (9%)
Somnolence	60 (15%)	8 (15%)	55 (14%)	11 (11%)	14 (5%)	23 (8%)	5 (4%)	14 (11%)
Respiratory System	127 (32%)	6 (11%)	125 (31%)	16 (16%)	34 (13%)	61 (21%)	20 (15%)	18 (14%)
Cough increased	24 (6%)	2 (4%)	22 (6%)	5 (5%)	6 (2%)	10 (3%)	2 (2%)	1 (1%)
Pharyngitis	48 (12%)	3 (6%)	47 (12%)	5 (5%)	8 (3%)	23 (8%)	10 (8%)	2 (2%)
Rhinitis	36 (9%)	1 (2%)	35 (9%)	4 (4%)	12 (4%)	11 (4%)	7 (5%)	5 (4%)
Sinusitis	32 (8%)	0	32 (8%)	5 (5%)	6 (2%)	16 (6%)	4 (3%)	4 (3%)
Skin	61 (15%)	4 (7%)	58 (15%)	4 (4%)	9 (3%)	27 (9%)	5 (4%)	19 (15%)
Sweating	18 (4%)	0	18 (5%)	2 (2%)	2 (1%)	6 (2%)	1 (1%)	10 (8%)
Special Senses	52 (13%)	3 (6%)	49 (12%)	8 (8%)	10 (4%)	16 (6%)	7 (5%)	12 (9%)

(continued)

Table 4.6 AEs Occurring in ≥ 5% of Any Group, by Body System, COSTART Preferred Term, and Dosage at Onset — Updated Integrated Clinical Trial Database

Body System COSTART Preferred Term	Total[a]	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total[a]	3.0	4.5	6.0	7.5	9.0
Number of patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
Urogenital System	94 (23%)	6 (11%)	90 (23%)	7 (7%)	18 (7%)	43 (15%)	10 (8%)	25 (19%)
Incontinence urine	8 (2%)	0	8 (2%)	0	0	2 (1%)	0	6 (5%)
Urinary incontinence	28 (7%)	0	28 (7%)	2 (2%)	8 (3%)	9 (3%)	6 (5%)	6 (5%)

[a] Patients are counted only once in each category. However, patients could have had more than 1 instance of the same AE with different dosages at onset, so the sum of the patients in the dosage at onset groups may exceed the total number of patients in each event category or body system summary.

4.3.2 SERIOUS ADVERSE EVENTS

SAEs during treatment were experienced by 27 (7%) of the 402 patients in the updated integrated clinical trial database. Sodium oxybate dosage at onset was 3g for 1 patient 4.5 g/d for 5 patients, 6.0 g/d for 13 patients, 7.5 g/d for 2 patients, and 9.0 g/d for 8 patients (2 patients [1433 and 1630] had SAEs with different dosages at onset, and are counted twice).

Treatment-related SAEs were seen in only 11 of the 27 patients (1 in OMC-GHB-2, 1 in OMC-GHB-3, 3 in OMC-SXB-6, and 6 in OMC-SXB-7), resulting in an overall incidence of 3% (11 of 402) of SAEs possibly, probably, or definitely related to sodium oxybate treatment in the updated integrated clinical trial database.

Nine of the 11 treatment-related SAEs noted in the database resulted in inpatient hospitalization (1 SAE [23230] was originally classified as definitely related by the Investigator and upon further evaluation was determined to be not related: Therefore there are 10 treatment related SAEs.

- Patient 0207 (OMC-GHB-2) experienced confusion (severe, probably related) on Day 7 at a sodium oxybate dosage of 6.0 g/d, and was permanently discontinued from the trial. The patient recovered normal mental status following initial treatment with Haldol on the day of hospital admission. There have been no recurrences since study discontinuation.

- Patient 0232 (OMC-SXB-7) experienced acute paranoid delusional psychosis (severe, probably related) on Day 476 at a sodium oxybate dosage of 9.0 g/d, and was permanently discontinued from the trial. The SAE resolved approximately 2 months after discontinuing trial medication.

- Patient 0238 (OMC-SXB-6) fell and struck his head, proceeding to apnea, thinking abnormal, and coma (severe, probably related) on Day 170 at a sodium oxybate dosage of 4.5 g/d, and was permanently discontinued from the trial. The event resolved with no sequelae or recurrence following removal from trial medication.

- Patient 1131 (OMC-SXB-7) intentionally overdosed with Xyrem (approximately 150 g) (severe, definitely related to study medicine) on Day 280 while on a sodium oxybate maintenance dosage of 9.0 g/d, and was permanently discontinued from the trial. The patient had a history of treatment for depression and a previous suicide attempt. The patient was given psychiatric and medical referrals.

- Patient 1305 (OMC-GHB-3) experienced agitation (severe, possibly related) on Day 678 at a sodium oxybate dosage of 9.0 g/d, and trial medication was temporarily stopped. The patient later experienced an AE of "movement disorder" (Periodic Leg Movement in Sleep) and was discontinued from the trial on day 982.

- Patient 1735 (OMC-SXB-6) experienced abortion (mild, possibly related) on Day 108, previously at a sodium oxybate dosage of 6.0 g/d; however, she had been

permanently discontinued from the trial on Day 66 when she became pregnant (protocol violation, failing the inclusion criteria).

- Patient 2030 (OMC-SXB-7) began experiencing intermittent brief reactive psychosis (severe, possibly related) on Day 207 at a sodium oxybate dosage of 9.0 g/d, and was permanently discontinued from the trial. The patient was treated with Zyprexa and Trazadone and the event resolved with no recurring psychosis.

- Patient 23230 (OMC-SXB-7) began experiencing intermittent chest pain (originally severe, and definitely related, later determined to be not related) on Day 119. The patient was hospitalized for atypical chest pain, was treated and was discharged with the diagnosis of esophageal spasms. Patient participation is ongoing in trial OMC-SXB-7.

- Patient 2536 (OMC-SXB-7) fractured her ankle (severe, possibly related) on Day 228 at a sodium oxybate dosage of 9.0 g/d, and was permanently discontinued from the trial. The patient was discharged from the hospital on day 235 and referred to the rehabilitation clinic.

The remaining 2 treatment-related SAEs did not require inpatient hospitalization:

- Patient 0231 (OMC-SXB-6) experienced dizziness, confusion, nausea, vomiting, vertigo, and asthenia (all severe, possibly related) on Day 119 at a sodium oxybate dosage of 9.0 g/d, and was permanently discontinued from the trial. All events resolved within 24 hours of occurrence.

- Patient 14043 (OMC-SXB-7) attempted suicide by buspirone overdose (severe, possibly related) on Day 216 at a sodium oxybate dosage of 7.5 g/d, and was permanently discontinued from the trial. In current follow-up, patient's family state that the patient is doing well since her release from psychiatric treatment.

4.3.3 DISCONTINUATIONS AND OTHER SIGNIFICANT ADVERSE EVENTS

Fifty-three patients in the updated integrated clinical trial database withdrew due to 1 or more AEs, including 52 patients receiving sodium oxybate and 1 patient receiving placebo (0818).

Sodium oxybate dosage at onset was 3.0 g/d for 5 patients, 4.5 g/d for 15 patients, 6.0 g/d for 14 patients, 7.5 g/d for 4 patients, and 9.0 g/d for 18 patients.

Of the 53 patients discontinued due to AEs, 42 experienced AEs considered related to trial medication by the investigator (Table 4.7).

Table 4.7 Related AEs Causing Discontinuation — Updated Integrated Clinical Trial Database

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[a]		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0204	OMC-GHB-3	6.0	33	51	Insomnia	Insomnia	No	Moderate
0207	OMC-GHB-2	6.0	7	9	Acute confusional state	Confusion	Yes	Severe
0213	OMC-GHB-3	9.0	90	135	Depressed mood	Depression	No	Moderate
		9.0	90	135	Excessive tiredness	Asthenia	No	Moderate
0221	OMC-GHB-2	9.0	13	15	Dizzy	Dizziness	No	Moderate
		9.0	13	15	Increased sleepiness	Somnolence	No	Moderate
		9.0	13	15	Nauseated	Nausea	No	Moderate
		9.0	13	15	Weakness (had trouble standing)	Asthenia	No	Moderate
	OMC-GHB-3	3.0	30	108	Lethargic all day	Somnolence	No	Mild
0231	OMC-SXB-6	9.0	119	119	Dizziness	Dizziness	Yes	Severe
		9.0	119	119	Confusion	Confusion	Yes	Severe
		9.0	119	119	Nausea	Nausea	Yes	Severe
		9.0	119	119	Vomiting	Vomiting	Yes	Severe
		9.0	119	119	Vertigo	Vertigo	Yes	Severe
		9.0	119	119	Weakness	Asthenia	Yes	Severe
0232	OMC-SXB-7	9.0	476	489	Acute paranoid delusional psychosis	Paranoid reaction	Yes	Severe
0238	OMC-SXB-6	4.5	170	170	Respiratory failure	Apnea	Yes	Severe
		4.5	170	170	Non-responsive	Coma	Yes	Severe
0409	OMC-GHB-3	9.0	61		Weight loss	Weight loss	No	Mild
0509	OMC-GHB-2	6.0	1	2	Restless leg syndrome increased	Hyperkinesia	No	Severe
0533	OMC-SXB-6	4.5	10		Swelling in legs	Peripheral edema	No	Severe

(continued)

Table 4.7 Related AEs Causing Discontinuation — Updated Integrated Clinical Trial Database

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[a]		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0605	OMC-GHB-2	9.0	9	12	Daytime sedation feeling; "drugged feeling"	Somnolence	No	Mild
		9.0	9	12	Poor concentration	Thinking abnormal	No	Mild
0637	OMC-SXB-6	7.5	93[b]		Restless legs	Hyperkinesia	No	Moderate
		7.5	93[b]		Anxiety	Anxiety	No	Moderate
0701	OMC-GHB-3	6.0[c]	32		Decreased sexual libido	Libido decreased	No	Moderate
		6.0[c]	32		Decreased initiative to start any activity by gradual progression	Apathy	No	Mild
0702	OMC-GHB-2	9.0	20	25	Confusion	Confusion	No	Moderate
		9.0	20	25	Forgetfulness	Amnesia	No	Moderate
		9.0	20	23	Hallucinations	Hallucinations	No	Moderate
		9.0	21	21	Nausea	Nausea	No	Mild
		9.0	22	24	Paranoia	Paranoid reaction	No	Mild
0801	OMC-GHB-3	9.0	147	178	Chest pain, patient on drug, no hospitalization, no concomitant medication	Chest pain	No	Moderate
0802	OMC-GHB-3	9.0	49	55	Nervousness	Nervousness	No	Moderate
		9.0	49	51	Metallic taste	Taste perversion	No	Mild
		9.0	49	51	Upset stomach	Dyspepsia	No	Moderate
0809	OMC-GHB-3	3.0	332	332	Inability to control body 1 hr after taking medicine	Incoordination	No	Mild
0818	OMC-GHB-2	Placebo	23		Insomnia	Insomnia	No	Moderate
0821	OMC-GHB-3	6.0	39	51	Headaches	Headache	No	Moderate
		6.0	40	51	Irritable	Nervousness	No	Moderate

(continued)

Table 4.7 Related AEs Causing Discontinuation — Updated Integrated Clinical Trial Database

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[a]		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0824	OMC-GHB-2	9.0[c]	5	5	Difficulty breathing	Dyspnea	No	Severe
	OMC-GHB-3	3.0	25	29	Difficulty breathing	Dyspnea	No	Moderate
0836	OMC-SXB-6	4.5	1		Headache	Headache	No	Moderate
0844	OMC-SXB-6	4.5	1	42	Nausea	Nausea	No	Moderate
		4.5	1	42	Vomiting	Vomiting	No	Moderate
		4.5	1	42	Headaches	Headache	No	Severe
0901	OMC-GHB-2	3.0	2	18	Lethargy	Somnolence	No	Mild
		3.0	2	18	Nausea	Nausea	No	Moderate
		3.0	3	18	Chest pressure	Chest pain	No	Mild
1131	OMC-SXB-7	9.0	280	280	Conscious overdose	Intentional overdose	Yes	Severe
1134	OMC-SXB-6	4.5	3		Urinary incontinence	Urinary incontinence	No	Moderate
1142	OMC-SXB-6	7.5	31	34	Left eye exposure keratitis	Keratitis	No	Mild
1201	OMC-GHB-2	9.0	5	5	Patient lost bowel control while asleep	Incontinence, fecal	No	Moderate
14043	OMC-SXB-7	7.5	216	216	Attempted suicide	Suicide attempt	Yes	Severe
1504	OMC-GHB-2	9.0	2	2	Nausea	Nausea	No	Severe
		9.0	2	2	Vertigo	Vertigo	No	Severe
		9.0	2	2	Vomiting	Vomiting	No	Severe
1631	OMC-SXB-6	6.0	23	59	Sleepwalking	Sleep disorder	No	Moderate
		4.5	44	59	Fragmented sleep	Sleep disorder	No	Severe
		4.5	44	60	Involuntary limb movements in sleep	Sleep disorder	No	Moderate
1735	OMC-SXB-6	6.0	108[d]	108[d]	Miscarriage	Abortion	Yes	Mild
2030	OMC-SXB-7	9.0	207	214	Brief reactive psychosis	Psychosis	Yes	Severe

(continued)

Table 4.7 Related AEs Causing Discontinuation — Updated Integrated Clinical Trial Database

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[a]		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
2532	OMC-SXB-6	4.5	16	43	Sleepwalking	Sleep disorder	No	Mild
		4.5	16	43	Dizziness	Dizziness	No	Mild
		4.5	39	43	Arms and legs numb	Paresthesia	No	Mild
2533	OMC-SXB-6	4.5	25	81	Nausea	Nausea	No	Moderate
		6.0	74	81	Morning grogginess	Somnolence	No	Moderate
2536	OMC-SXB-7	9.0	228	228	Fractured ankle	Fractured ankle	Yes	Severe
2537	OMC-SXB-6	4.5	12		Increased headaches	Headache	No	Moderate
2633	OMC-SXB-6	4.5	2	4	Increased awakenings	Sleep disorder	No	Mild
		4.5	2	4	Tongue paresthesia	Paresthesia	No	Mild
2933	OMC-SXB-6	4.5	29		"Phlegm/knot" in throat	Pharyngitis	No	Moderate
3231	OMC-SXB-6	6.0	56		Exacerbation of colitis (Crohn's disease)	Colitis	No	Moderate
3830	OMC-SXB-6	7.5	52	62	Nausea	Nausea	No	Moderate
		7.5	58	58	Vomiting	Vomiting	No	Moderate
3831	OMC-SXB-6	3.0	12	24	Itching and swelling of extremities	Pruritus	No	Moderate
		3.0	12	24	Itching and swelling of extremities	Edema	No	Moderate
3930	OMC-SXB-6	4.5	2	3	Sleep paralysis	Sleep disorder	No	Moderate

[a] Day relative to start of treatment.
[b] Whole or partial data imputed from start of trial medication.
[c] Dosage carried forward.
[d] Patient discontinued study drug on study day 66, and the event of miscarriage occurred on day 108.

4.3.4 DEATHS

Two deaths, both suicides (0531 and 0936), were recorded among the 402 patients in the updated integrated clinical trial database. One (0531, coded as death) was due to multiple drug toxicity that included toxic levels of 6 psychotropic drugs other than sodium oxybate. The second patient (0936) had a history of depression and a subsequent suggested diagnosis of bipolar disease. This event was officially ruled as a death due to cardiovascular disease (without autopsy by the Medical Examiner), but later evidence pointed to a possible overdose that included lithium, Paxil, and Percocet as well as sodium oxybate. This event occurred on 2/24/01, which was 5 months after the data cutoff (9/30/00), but is included here for completeness. Both deaths were considered unrelated to study drug.

4.3.5 LABORATORY RESULTS

Laboratory evaluations for the original integrated clinical trial database (laboratory results were not analyzed for the 4-Month Safety Update for OMC-SXB-7) included blood chemistry, hematology, and urinalysis. Mean changes from baseline to last observation were small and similar across all 6 groups (placebo and 5 sodium oxybate last dosage groups) for all parameters.

4.3.5.1 Blood Chemistry

Shifts in ≥ 10% of the patients were only seen for calcium and total bilirubin. A shift from normal to low calcium was seen in 14 of 132 patients (11%) in the OMC-GHB-2 and OMC-GHB-3 trials (duration of up to two years); this ranged from 0 in the placebo group (for a 4 week treatment period) and the 7.5 g/d sodium oxybate last dosage group to 25% in the 3.0 g/d sodium oxybate last dosage group (treatment duration of up to two years). A shift from normal to low total bilirubin was seen in 32 of 314 patients (10%); this ranged from 4% in the 7.5 g/d sodium oxybate last dosage group (duration of up to two years) to 33% in the placebo group (4-week treatment period).

4.3.5.2 Hematology

Shifts in ≥ 10% of the patients were only seen for basophils, with a shift from high to normal in 30 of 310 patients (10%); this ranged from 0 in the placebo group (4-week treatment period) to 20% in the 3.0 g/d sodium oxybate last dosage group (duration of up to two years).

4.3.5.3 Urinalysis

Shifts in ≥ 10% of the patients were only seen for protein, with a shift from positive to negative in 42 of 307 patients (14%); this ranged from 6% in the 4.5 g/d sodium oxybate last dosage group (duration of up to two years) to 33% in the placebo group (4-week treatment period).

4.3.6 VITAL SIGNS AND ECG

Vital signs (pulse, respiration, blood pressure, body temperature, body weight) and ECG were analyzed for the original integrated clinical trial database (vital signs and ECG were not analyzed for the 4-Month Safety Update for OMC-SXB-7). Mean changes for all vital sign parameters were small, and were similar across all 6 groups (placebo group and 5 sodium oxybate last dosage groups).

Shifts from baseline to last observation in ECG results were analyzed. No shifts in ≥ 10% of the patients were seen overall or in any patient group for either abnormal to within normal limits or within normal limits to abnormal.

4.3.7 SAFETY SUMMARY – UPDATED INTEGRATED CLINICAL TRIALS

In dosages between 3 and 9g nightly in divided doses, sodium oxybate was generally well tolerated in the 5 trials comprising the Updated Integrated Clinical Trials. The side effects were usually mild in severity and most frequently included nausea, dizziness, and headache, and less frequently urinary incontinence (enuresis) and somnambulism (sleepwalking).

In the Updated Integrated Clinical Trials, a total of 296 patients have taken sodium oxybate for at least 6 months; of these, 223 patients have taken sodium oxybate for at least 1 year and 48 patients have taken sodium oxybate for at least 2 years. Total exposure to sodium oxybate was 329.89 patient years.

Of the 402 narcolepsy patients in this data base, 331 (82%) reported at least 1 AE. Adverse events considered to be possibly, probably, or definitely related to treatment with sodium oxybate were reported in 247 (61%) patients. Severe AEs were reported in 82 (20%) of the patients. Serious AEs were reported for a total of 27 (7%) patients, 10 whom had SAEs that were considered related to trial medication. Two deaths were reported (both suicides and both unrelated to trial medication).

Laboratory evaluations included blood chemistry, hematology, and urinalysis. The only potentially significant laboratory abnormality was hypocalcemia, which was present in 23 (17%) of 132 patients. It was a variable measure in 15 of these patients, with a return to normal during sodium oxybate treatment. In all cases, the reduction in calcium levels was minor and deemed not of clinical significance.

4.4 Lammers Trial

The Lammers trial was a double-blind, placebo-controlled, crossover trial in 25 patients to assess the effects of 60 mg/kg sodium oxybate or placebo in narcolepsy.

Sodium oxybate was well tolerated. AEs during the Lammers trial were few and mild, and were experienced by 6 (24%) of the 25 patients, as follows:

- 2 patients during the washout period (1 patient with frequent headache, and 1 patient with severe dreaming)
- 1 patient on placebo (kidney problems, urination problems/stranguria)
- 3 patients on sodium oxybate:
  - 1 patient with severe perspiration, influenza/common cold, sore throat, headache, and frequent micturition
  - 1 patient with bladder infection, sore throat, and flickering in the eyes
  - 1 patient with terrible dreaming, dry mouth, paralysis in legs and arms, anxious, and insecure

No SAEs or deaths were reported during the trial, and no patient withdrew due to an AE.

4.5 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 open-label trial. Table 4.8 summarizes the disposition of the 143 patients in the Scharf trial. As of the NDA cutoff date of May 31, 1999, 63 of these patients transferred into the Orphan Medical Treatment IND protocol OMC-SXB-7. Of the remaining 80 patients, 8 continued to participate in the Scharf open-label trial, and 71 patients had discontinued from the Scharf open-label trial prior to the cutoff date. The reasons for discontinuation were: non-compliance (24); adverse events (23); cost of study participation (13); patient request (5); lack of efficacy (4); protocol deviation and other (1 each). The patient listed as "other" for reason for discontinuation, entered Dr. Scharf's GHB fibromyalgia trial. One patient was a screen failure.

Table 4.8 Summary of Patient Disposition in Scharf Clinical Trial

Patient Disposition	Number of Patients
Patients screened	143
Patients treated	142
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[a]
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.

This open-label, long-term (up to 16 years) clinical trial was developed under the investigator's IND following consultation with the FDA in 1983. These data were collected by Dr. Scharf more as a matter of clinical record than for drug development research and, hence, there are some differences from the other trials (eg, laboratory results were generated from many different laboratories, dose titration extended to dosages as high as 12.5 g/d). These data, do, however, provide experience in long-term treatment exposure. A total of 143 patients were enrolled in this trial, with 85% (121/143), 73% (104/143), 52% (74/143), and 32% (46/143) receiving sodium oxybate for > 6 months, > 1 year, > 5 years, and > 10 years, respectively.

The FDA and Orphan Medical, Inc agreed to a compilation of the Scharf data on the premise that it would potentially provide a profile of long-term clinical experience with sodium oxybate. Orphan Medical performed a retrospective compilation of the data for all 143 patients treated for up to 16 years.

4.5.1 INCIDENCE OF ADVERSE EVENTS – SCHARF TRIAL

In the Scharf trial, Adverse Events were recorded retrospectively on CRFs from information reported by patients in daily diaries (sleep logs) and from investigator-maintained medical records. These data included any untoward events noted by the patients, including possible side effects and effects of concomitant medications, as well as intercurrent illnesses, injuries, or accidents.

The majority of the 143 patients (136, 95.1%) experienced at least 1 AE. This is to be expected, given the unusually long duration of the trial (16 years, with 32% of patients on sodium oxybate for > 10 years). For this reason, it is difficult to compare these results with those given for the updated integrated clinical trial database, the Lammers trial, and the OMC-SXB-21 trial. To provide an easier basis for comparison, AEs over the first 6 months were analyzed for OMC-SXB-6, OMB-GHB-3, and Scharf.

Over the course of the Scharf trial, AEs reported by only 1 or 2 patients accounted for 44% of the AEs, which does not support a strong association with sodium oxybate.

Severe AEs were reported by 21 patients (14.7%) during their first 6 months in the trial. Over the course of the trial, one third of the patients (54, 37.8%) experienced SAEs, and 23 patients (16.1%) discontinued due to AEs. Eleven deaths (7.7%) were reported. No apparent differences were seen among the 5 sodium oxybate dosage of longest duration groups.

The most frequently reported AEs (nearly all of which were to 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%), dyspepsia (25.2%) and enuresis (23%).

Many of the most frequently reported AEs were considered not related to trial medication. During the first 6 months of treatment, the proportion of the reported AEs that were related to trial medication was 100% for sleep disorder (sleepwalking) and urinary incontinence, 48% for dizziness, 24.2% for nausea, 10.8% for pain, 7.7% for dyspepsia, and 5.9% for abdominal pain. No related AEs were seen for accidental injury, diarrhea, fever, flu syndrome, increased cough, pharyngitis, rhinitis, or sinusitis.

The frequency of cardiovascular AEs (arrhythmias and ventricular extrasystoles) appeared to be higher in the Scharf trial (26%) than in the other 2 trials (1% for OMC-SXB-6, 15% for OMC-GHB-3). This higher incidence probably reflects the higher incidence (approximately 20%) of prior history of cardiovascular disease in the Scharf trial population at baseline, and the expected age-related progression and presentation of cardiovascular morbidities in this long-term trial. Consistent with this observation is the fact that 5 of the 11 deaths in the Scharf trial were from cardiovascular causes and were unrelated to sodium oxybate treatment (as were the other 6 deaths).

4.5.1.1 Adverse Events Over the First 6 Months

To more easily compare the results from the Scharf trial with those from the other clinical trials, the incidence of AEs over the first 6 months of treatment with sodium oxybate was compared in the OMC-SXB-6, OMC-GHB-3, and Scharf trials.

The incidence of frequently occurring AEs including headache, nausea, pain, dizziness, and pharyngitis was similar in all 3 studies, except for pain (9% in OMC-SXB-6, 20% in

OMC-GHB-3, and 26% in Scharf). The incidence of patients reporting 1 or more AEs was similar in the 3 trials (78% for OMC-SXB-6, 91% for OMC-GHB-3, and 87% for Scharf).

4.5.2 SERIOUS ADVERSE EVENTS – SCHARF TRIAL

A total of 205 SAEs were reported for 54 of the 143 patients (37.8%) in the Scharf trial. Sodium oxybate dosage at onset was 3.0 g/d for 1 patient, 4.5 g/d for 17 patients, 6.0 g/d for 21 patients, 7.5 g/d for 7 patients, and 9.0 g/d for 5 patients. Dosage at onset was unknown for 3 patients.

Only 6 of the 54 patients had SAEs considered to be related to trial medication. In addition, relationship to trial medication was missing for 7 patients with SAEs: patient 012 (disorientation, stupor, weakness), patient 047 (ulcerated colon), patient 054 (skin cancer), patient 070 (back pain), patient 241 (severe headaches), patient 273 (tumors in neck-parotid glands), and patient 277 (hospital readmission after uvulopalatopharyngoplasty surgery).

Table 4.9 Patients with Serious Adverse Events Judged Related to the Study Medication

Patient Number	Age Sex	COSTART Term	Verbatim Term	Unexpected/ Expected	Dose[1]	Time on Drug (yr)
017[2]	68, M	Overdose	Overdose	Unexpected	18g	1.6
017	68, M	Coma	Comatose	Unexpected	18g	1.6
017	68, M	Stupor	Unresponsive	Unexpected	18g	1.6
019[3]	41, M	Suicide Attempt	Suicide Attempt	Unexpected	UNK	2.0
048[2]	27, F	Convulsion	Convulsive-like seizure	Unexpected	8.3g	5.3
048	27, F	Incontinence Urine	Urinary Incontinence	Expected	8.3g	5.3
257[2]	32, M	Reaction Unevaluable	Potential overdose	Unexpected	12g	2.6
257	32, M	Apnea	Hypoxemia	Unexpected	11.3g	8.0
267[3]	61, F	Overdose	Overdose	Unexpected	UNK	4.6
281[2]	59, M	Injury Accidental	Contusion from fall (over right eye)	Unexpected	7.5g	1.0
281	59, M	Injury Accidental	Contusion from fall (right arm)	Unexpected	7.5g	1.0
281	59, M	Injury Accidental	Head injury from fall	Unexpected	7.5g	1.0

[1]The dose listed is the dose associated with the SAE, not the patient's most common dose during the study.
[2]Patients who had more than one SAE as part of a single event except for patient 257 which represents two events.
[3]Patient reported to have taken an overdose of sodium oxybate although the exact dose is not known.

A relationship between higher dosages of trial medication and SAEs was found in this trial, although not in any other trial. Possible contributory factors affecting the frequency of SAEs include the length of the trial (16 years), the individual patients' increased age during the course of the trial (from a mean age of 45.3 years at entry to approximately 61 years at last observation), the SAEs that would be expected to occur in patients with narcolepsy, the baseline rate of cardiovascular abnormalities, and, for some patients, the continued use of TCAs.

4.5.3 DISCONTINUATIONS AND OTHER SIGNIFICANT ADVERSE EVENTS

Twenty-three patients withdrew from the Scharf trial because of AEs. Sodium oxybate last dosage was 3.0 g/d for 5 patients, 4.5 g/d for 2 patients, 6.0 g/d for 9 patients, 7.5 g/d for 5 patients, and 9.0 g/d for 2 patients. Eight of these patients subsequently died; the reasons for discontinuation in these 8 patients were the same as the causes of death with the exception of patient 243, who withdrew from the trial because of weight loss, and died 4 months later because of a heart attack.

AEs leading to withdrawal were considered to be related to trial medication in 6 of the 23 patients:

- Patient 019 was hospitalized following a suicide attempt (SAE) using an overdose of sodium oxybate on an unspecified date. This SAE was believed to be definitely related to treatment (intentional overdose) with sodium oxybate, and the patient was discontinued from the trial. The patient was started on sodium oxybate 5.3 g/d on July 12, 1987; his last recorded dosage of sodium oxybate (9.0 g/d) was July 30, 1989.

- Patient 259 discontinued sodium oxybate due to AEs of "feeling like a zombie," stiffness in legs and chest, and excessive crying (COSTART terms delirium, hypertonia, and emotional lability). These AEs, which were considered to be probably related to trial medication, were first reported on June 6, 1987 (sodium oxybate was begun June 3,1987at a dose of 5.3g/d), at which time the dosage of sodium oxybate was decreased to 3.0 g/d. The dosage was further reduced over the next 11 days to 0.8 g/d. The problem did not resolve, and the patient was discontinued on July 15, 1987.

- Patient 271 began taking sodium oxybate (5.3 g/d) in October 1994. He reported an AE of swollen ankles and feet (COSTART term edema) on January 18, 1995. This AE was considered to be possibly related to trial medication. Initial action was to reduce salt intake, with no change in sodium oxybate dosage. The event did not resolve, and the patient discontinued the trial on April 30, 1995. The last recorded dosage of sodium oxybate was 4.3 g/d.

- Patient 066 began taking sodium oxybate on March 25, 1985. She was discontinued from 7.5g sodium oxybate treatment on 4/20/91 due to possible drug-induced lupus. The patient presented rheumatoid-like symptoms accompanied by a series of sustained high anti-nuclear antibody (ANA) titers over a period of five months preceding her discontinuation. Titers for ANA continued to be elevated for the 6 months following the discontinuation of sodium oxybate. Anti-histone antibody titer reported on 10/5/92 was negative. No symptoms consistent with lupus accompanied the elevated ANA titers and no diagnosis of drug-induced lupus or systemic lupus erythematosus was made.

- Patient 244 began taking sodium oxybate on June 21, 1988. The patient was discontinued due to high ANA titer (possible drug-induced lupus) on May 3, 1989.

The dose at discontinuation was 2.3g. No symptoms consistent with lupus accompanied the elevated ANA titers and no diagnosis of drug-induced lupus or systemic lupus erythematosus was made. Follow-up notes of November 1992 indicated that the patient was negative for both ANA and anti-histone antibodies. The patient also informed the site that she was participating in a sodium oxybate trial under Dr. Scrima's IND. Dr. Scrima reported that the patient participated in his trial until termination in 2000 with good efficacy and no symptoms of lupus.

- Patient 254 began taking sodium oxybate on May 2, 1988. The patient discontinued due to a serious adverse event of pulmonary interstitial infiltrate, possible pulmonary toxicity on June 26, 1989. The sodium oxybate dose at discontinuation was 4.5g. The event resulted in in-patient hospitalization. The SAE report notes that the event was not related to trial medication, but source documents note that the event was "possibly related to the GHB or even the sodium load associated with GHB use". Follow-up efforts with the patient to determine if the event resolved with trial medication discontinuation were unsuccessful.

4.5.4 DEATHS – SCHARF TRIAL

Eleven patients died in the Scharf trial, including 5 deaths from cardiovascular-related causes, 5 deaths from cancer (3 lung, 1 colon, and 1 bladder), and 1 death related to a boating accident. None of the deaths was considered related to trial medication.

A significant prior history of contributory disease was present in all 5 cardiovascular-related deaths. In 2 of the 5 deaths from cancer, there was significant past history of malignancy. The medical history for 1 of the patients who developed lung cancer included persistent cold symptoms. No significant factors prior to diagnosis were identified for the remaining 2 cancer deaths.

The deaths occurred following 1.2 to 10.4 years of treatment with sodium oxybate. Of the 11 deaths reported to FDA, in only 5 cases did the date of death occur within 30 days of the last reported dose of sodium oxybate. In 4 of these cases, there was significant past medical history of disease; in the fifth case there was a history of persistent respiratory symptoms prior to the diagnosis of lung cancer.

This analysis does not reveal a pattern that could be viewed as causally related to sodium oxybate.

4.6 OMC-SXB-21 Trial

The OMC-SXB-21 clinical trial was a randomized, double blind, placebo-controlled, multicenter trial in 55 patients to assess the long-term efficacy of sodium oxybate compared with placebo. This trial was specifically designed to provide evidence of long-term efficacy of sodium oxybate based on the return of cataplexy symptoms upon cessation of a minimum of 6 months of open-label sodium oxybate treatment. A 2-week lead-in period with single-blind treatment with Xyrem at the patient's established dosage was followed by a 2-week period of double-blind treatment with either Xyrem or placebo.

Patients randomized to placebo experienced abrupt cessation of treatment and a return of cataplexy as the definitive endpoint measure. A total of 17 patients (31%, 17/55) – 7 of 26 (27%) Xyrem patients and 10 of 29 (34%) placebo patients – experienced at least 1 AE during the trial. In the double-blind period, there were no statistically significant differences between the Xyrem and placebo groups in the incidence of patients with an AE (12% for Xyrem, 31% for placebo; p = 0.108), related AEs (4% for Xyrem, 14% for placebo; p = 0.355), or severe AEs (0 for Xyrem, 3% for placebo; p = 1.000). No deaths, discontinuations, or serious AEs occurred during the trial. The incidence and severity of AEs were low. The majority were considered to be unrelated to trial medication. During the double-blind treatment period, patients on placebo did not experience a statistically significant change in vital signs or laboratory values.

Recent literature reports (Friedman 1996, Galloway 1997) indicate that abrupt discontinuation of high-dose, chronic sodium oxybate has resulted in withdrawal symptoms, which consistently include insomnia, anxiety, and tremors. Of these, insomnia, which generally resolved within 3 days, was the most consistently described symptom. Hallucinations (Hernandez 1998) have also been reported. In the OMC-SXB-21 placebo patients, these withdrawal symptoms occurred infrequently (3 [10.3%] of 29) patients, in patients abruptly withdrawn from chronic therapeutic dosages of sodium oxybate (anxiety, 2 [7%] patients, insomnia, 1 [3%] patient). These events were considered by the investigators to be of mild severity and probably (both patients with anxiety) or possibly (the 1 patient with insomnia) related to trial medication.

Overall, the results of this study indicate that Xyrem is well tolerated. Few AEs were related to the study drug. Abrupt discontinuation of long-term Xyrem treatment at therapeutic dosages did not appear to result in an increase in AEs that would indicate the presence of a withdrawal syndrome.

4.7 Safety Summary of the Pharmacokinetic Trials

The 8 clinical pharmacokinetic trials included 6 studies done in 125 normal volunteers and 2 studies (OMC-GHB-4, OMC-SXB-10) conducted in 19 narcoleptic patients. All 8 studies involved acute dosing with either 1 or 2 doses of sodium oxybate.

Table 4.10 summarizes the AEs for the 144 subjects in the 8 integrated pharmacokinetic (PK) trials. Approximately half of the subjects (75 subjects, 52%) experienced at least 1 AE, almost all of which were considered study drug-related AEs. Only 2 subjects (1%) discontinued due to AEs. There were no SAEs and no severe AEs. Most AEs were rated as mild in severity and all AEs resolved spontaneously, with no sequelae.

Table 4.10 Summary of Adverse Events — Integrated Pharmacokinetic Trials

	Sodium Oxybate[a]
Number of Subjects	144 (100%)
All events	
Subjects with ≥ 1 AE	75 (52%)
Subjects with SAEs	0
Subjects with related AEs	72 (50%)
Subjects with severe AEs	0
Subjects discontinuing due to AE	2 (1%)
Subject deaths	0

[a]Subjects are counted only once in each category.

The most common AEs experienced in the PK trials were nausea, dizziness, headache and vomiting. In general the frequency of AEs tended to increase with oxybate dosage but the severity and type of AE did not. In the 3 drug interaction studies, no clinically significant changes occurred in either the pattern or severity of AEs when Xyrem was administered together with protriptyline, modafinil or zolpidem. The highest incidence of AEs occurred in the fasted phase of the food effect study in which the subjects experienced 4 times as many AEs when given a 4.5g dose after an 8 hour fast as compared to the same dose given shortly after a high fat meal. The 2 subjects who discontinued due to the occurrence of AEs are detailed below.

In the dose proportionality study (OMC-SXB-9), Subject #012, a 30 year-old female, failed to return for the second dosing period after experiencing headache and nausea subsequent to the first dosing when she was administered 2 doses of 2.25g four hours apart.

In the food effect study (OMC-SXB-11), Subject #003, a 39 year-old female, was exposed to a single maximum therapeutic dose (4.5g) after a controlled 10-hour fast (overnight), with dosing at 7:00am. Initial adverse event reporting consisted of mild dizziness 30 minutes after dosing. Approximately 1 hour post-dosing, while lying supine, she developed a respiratory obstructive episode, characterized by respiratory stridor and "labored respiration". Initial repositioning did not immediately relieve the obstruction and a brief apneic event supervened. In the subsequent data analysis and report, the respiratory episode was coded with the COSTART preferred term "apnea". No positive pressure respiratory support was required since spontaneous respiratory effort followed the stimulation, and continued unassisted. Supplemental oxygen was provided via a facemask. At the time of the event, blood pressure and pulse were normal. Following the stimulation, she awoke and vomited once, after which she again fell asleep with normal respiratory rate. The duration of this entire sequence of events was approximately 2 minutes.

Again, approximately 1 hour later (that is, 2 hours post-dosing) the subject again developed a respiratory obstructive episode, beginning with respiratory stridor and proceeding to a brief pause in spontaneous respiration that resolved with stimulation and

the placement of a facemask for supplemental oxygen. An episode of fecal incontinence accompanied this event, but the patient was arousable, responded to verbal commands and no tonic/clonic activity was part of the event. Again, blood pressure (110/64) and pulse (57/min) remained normal for the subject. The subject again responded to verbal commands to breathe deeply.

There were no other untoward events relating to medication. Two hours later the subject consumed most of the offered lunch. She remained at the study facility for the full 10 hours post-dosing, along with the other study subjects, and was discharged home with no sequelae. She chose not to return for the second dosing one week later. The plasma oxybate versus time curve for Subject #003 was not significantly different from the other 17 normal subjects dosed identically at the same time.

In addition to adverse events, vital signs (blood pressure, heart rate, respiration rate) were recorded before and at multiple time points after each dosing period in all 8 of the PK studies. No clinically significant changes in vital signs were recorded in any patient or normal volunteer in any of the 8 PK trials. Overall, the safety profile of Xyrem from the 125 healthy subjects in the PK trials was not significantly different from that of the narcoleptic patient population.

4.8 Adverse Events of Special Interest

Subsequent to the submission of the NDA, several questions were raised by the FDA regarding both the Scharf trial and the integrated clinical trials. Responses to these questions were provided to the FDA in a Major Amendment on March 23, 2001, and in an Amendment for the Scharf Trial on April 10, 2001.

The major issues are summarized here, including:

- Further description of patients with
  - AEs coded to confusion
  - AEs coded to convulsion
  - Neuropsychiatric AEs
  - AEs of hyperglycemia or diabetes mellitus
- Analysis of the potential for drug-induced lupus
- Analysis of incontinence AEs and the relationship to seizurogenesis
- Characterization of the 80 patients who did not transfer from the Scharf trial into OMC-SXB-7 as of May 31, 1999.
- Characterization of the 75 occurrences in the Scharf trial with "reaction unevaluable" AEs
- Comparison of the incidence of AEs for sodium oxybate and placebo in the controlled trials

An analysis of AEs for sodium oxybate and placebo in the 4 controlled trials is also included in this section.

No patients in the OMC-SXB-21 trial experienced confusion, convulsions, or any neuropsychiatric event. One patient experienced hyperglycemia during the single-blind lead-in period; this was considered mild and not related to trial medication. No patients in the Lammers trial experienced any of these AEs.

4.8.1 ADVERSE EVENTS CODED AS CONFUSION

4.8.1.1 Updated Integrated Clinical Trial Database

Of the 402 patients in the updated integrated clinical trial database, 30 (7%) patients had 47 AEs with the COSTART preferred term of confusion (Table 4.11). Of these, 1 patient was in the placebo group.

Of the 30 patients who experienced confusion, 2 (<1%) had AEs considered serious by the investigator; 29 (7%) had AEs considered related (including the 1 patient on placebo); and 4 (1%) had AEs considered severe. A total of 3 patients (<1%) discontinued due to the AE of confusion. There were no deaths due to AEs of confusion. Two of the patients (0221 and 0815) had also experienced AEs of confusion prior to any treatment with Xyrem. The incidence of confusion among the 29 patients taking Xyrem does not appear to be dose-related.

Table 4.11 Summary of Patients with AE Preferred Term of Confusion by Dosage at Onset—Updated Integrated Clinical Trials

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

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

[b] Some patients were exposed to more than 1 dosage during the trial(s), so the sum of patients exposed to specific dosages exceeds the total number of patients in the updated integrated clinical trial database.

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

Of the 30 patients, 21 (70%) were women, and 20 (67%) were 50 years of age or older (range 25.7 to 73.8 years).

Most of the AEs of confusion were experienced during the first 60 days of trial: 13 patients experienced 15 AEs of confusion during Days 1 to 30; 10 patients

experienced 11 AEs during Days 31 to 60; 5 patients experienced 5 AEs during Days 61 to 120; 7 patients experienced 13 AEs during Days 121 to 365; and 3 patients experienced 3 AEs during Days 366 to 1022. The first occurrence of confusion was during Days 1 to 30 for 13 patients; during Days 31 to 60 for 8 patients; during Days 61 to 120 for 5 patients; during Days 121 to 365 for 2 patients; and during Days 366 to 1022 for 2 patients.

Two events of confusion were not recorded as resolved:

- Patient 2539 (onset Day 74) experienced mild and intermittent "confused awakening," which was listed as ongoing in trial OMC-SXB-6, but is not listed in the patient's follow-up trial OMC-SXB-7. According to the following comment on the CRF for "action taken" for this episode, it appears that a stop date should have been entered in trial OMC-SXB-6: "Patient notes she may awaken after first dose of Xyrem but before second dose . . . she got up a few times initially but realizes she was confused. Now she intentionally goes back to sleep and avoids getting up."

- Patient 2632 experienced a moderate, probably related episode of "disorientation" on Day 267 in OMC-SXB-7 that was categorized as intermittent. On the same day this event of confusion was reported, the patient discontinued due to "patient request" (confirmed by further medical review); therefore, this patient is not listed as discontinuing due to the AE of confusion. However, the AEs of headache/confusion were contributing factors. In OMC-SXB-6, his previous trial, this patient had a similar complaint (Day 10, 9/22/99), which resolved in January 2000. Follow-up with this patient on 3/21/01 by the trial coordinator confirms that this patient's disorientation resolved soon after trial termination and the patient has had no recurrence of these symptoms.

Most of the verbatim descriptions of AEs with the COSTART preferred term of confusion included some form of the words "confusion" or "disoriented." The actual investigator terms were:

- "Confusion," "acute confusional state," or "confusion on awaking" – 15 patients with 25 events
- "Disoriented," "disoriented upon awakening," or "disorientation" – 13 patients with 15 events
- "Confusion/disorientation" – 2 patients with 2 events
- "Feeling 'drunk' after taking drug" – 3 patients with 3 events
- "Dazed feeling" – 1 patient with 1 event
- "Couldn't comprehend" – 1 patient with 1 event
- "Woozy feeling" – 1 patient with 1 event

4.8.1.2 Analysis of Trial OMC-GHB-2

Eleven (8%) of the 136 patients in OMC-GHB-2 (including 1 patient on placebo) experienced an AE of confusion. Since this trial was only 4 weeks in duration, additional analysis was conducted.

The major difference between trial OMC-GHB-2 and the other studies is that patients were assigned dosages in a blinded, randomized manner that excluded any consideration of body weight or size, sex, or disease severity. This non-titrated dosing assignment produced the majority of occurrences of confusion in the 10 patients on active drug:

- Six patients experienced the AE at the 9.0 g/d dosage level
- Six patients experienced the AE in the first week of drug exposure, with 4 of these 6 assigned to the 9.0 g/d dosage

The emergence of these AEs, especially at the 9.0 g/d level, in the short 4 weeks of active treatment gives further support to the proposed dosing strategy, with initial dosing at the 4.5 g/d level and subsequent optimization of clinical response by dosing adjustments of 1.5 g/d every 2 weeks.

Nine of these patients continued into future trials, and only 2 had a recurrence of confusion.

4.8.1.3 Scharf Trial

All patients who had AEs with the COSTART preferred term of confusion during the Scharf trial through the data cutoff of May 31, 1999, were included in this analysis.

Of the 143 patients in the trial, 10 (7%) experienced a total of 15 AEs with the COSTART preferred term of confusion (Table 4.12). One patient experienced an SAE, 5 AEs were possibly or probably related to trial medication, 1 patient had 3 severe AEs, and no patients discontinued due to an AE of confusion.

Table 4.12 Summary of Patients with AE Preferred Term of Confusion by Dosage at Onset – Scharf Trial

Confusion: All Events	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset[b]				
		3.0	4.5	6.0	7.5	9.0
Patients with: At least 1 AE	10[c]	0	3	3	4	0
SAEs	1	0	0	0	1	0
Related AEs	5	0	1	2	2	0
Severe AEs[c]	1	0	1[c]	0	0	0
Discontinuations due to an AE	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

[a] Patients are counted only once in each category.

[b] Dosage at onset. Dosage for patient 248 is listed as "0."

[c] Patient 027 experienced 3 events of "disoriented," all of which were considered severe.

All 15 AEs used verbatim terms including the words "confusion" or "disoriented." Five events were considered possibly or probably related to trial medication, 6 were of unknown relationship, and 4 were not related.

Of the 10 patients, 6 were men and 4 were women. For 8 of these 10 patients, the event of confusion was reported only once. Age at the time of onset ranged from 27.7 to 76.8 years. Of the 15 events, 5 occurred in the first 60 days, 4 occurred from 61 days to 1 year, 3 occurred from 1 year to 2 years, and 3 occurred at > 2 years (Days 3185, 3301, and 3314) on trial medication. The dosage at onset for these events ranged from 4.5 to 7.5 g/d.

Most events (10 of 15, 66.7%) were transient in nature, (single episodes) lasting 1 day or less. One event lasted 15 days; the remaining events (1 in each of 4 patients, 235, 248, 251, and 266) had no stop date listed. Two of these patients (248, "mental confusion", and 251, "confused") discontinued for non-compliance) on Days 89 and 218, respectively); onset of their AEs was Days 5 and 62, respectively. The other 2 patients (235, "disorientation [when awakening from sleep]," and 266 "confused sometimes [not a lot]," with onset of AEs on Days 1 and 273, respectively, transferred into OMC-SXB-7 on Days 4456 and 5623, respectively, with no confusion AEs reported in the OMC-SXB-7 trial.

Only 1 patient (012, "disoriented") experienced an SAE, which resulted in overnight hospitalization. This patient returned to study drug with no further recurrences. No patients discontinued due to AEs of confusion.

4.8.2 ADVERSE EVENTS CODED AS CONVULSION

4.8.2.1 Updated Integrated Clinical Trial Database

Of the 402 patients in the updated integrated clinical trial database, 14 (3%) had AEs with the COSTART preferred term of convulsion(s). Thirteen (93%) of these 14 patients had investigator verbatim terms relating the event to cataplexy (Table 4.13). The single event with the investigator term of "seizures" also appeared to be cataplexy-related (see discussion below).

Table 4.13 List of COSTART and Verbatim Investigator Terms for AEs of Convulsion – Updated Integrated Clinical Trial Database

Patient Number	COSTART Term	Verbatim Term
0221	Convulsions	Increase in major cataplexy attacks
0231	Convulsion	Increased duration of cataplectic events
0243	Convulsion	Increase partial cataplexy
0545	Convulsion	Increase in cataplexy
	Convulsion	Increase in cataplexy
0608	Convulsion	Increased cataplexy
0814	Convulsion	Seizures
0835	Convulsion	Increased cataplexy
	Convulsion	Cataplexy
1130	Convulsion	Cataplexy
1302	Convulsion	Increased cataplexy (significant)
	Convulsion	Increased cataplexy (significant)
1306	Convulsion	Increase in cataplexy
1509	Convulsion	Multiple cataplexy attacks for 10 min. (due to protocol violation of patient: got out of bed to use bathroom 1½ hr. after taking 1st dose of sodium oxybate)
1703	Convulsion	Bit tongue (due to falling faster to ground: cataplexy)
	Convulsion	Hit temple against furniture (due to falling faster to ground: cataplexy)
2936	Convulsion	Cataplexy
3937	Convulsion	Cataplexy

There were 7 patients (2%) with related AEs coded as convulsion and 2 patients (<1%) with severe AEs coded as convulsion (Table 4.14). There were no SAEs, discontinuations, or deaths associated with AEs coded as convulsion. A higher incidence of AEs coded as convulsion was seen in the 9.0 g/d dosage at onset group (5%, compared with 2% for 6.0 g/d, 1% for 4.5 g/d, and 0 for 3.0 and 7.5 g/d). However, patients with the most severe cataplexy are potentially titrated to the highest dosage, which may explain the slightly higher incidence of these cataplexy related AEs, which were coded as convulsion, at 9.0 g/d.

Table 4.14 Summary of Patients with AE Preferred Term of Convulsion, by Dosage at Onset – Updated Integrated Clinical Trials

Convulsion: All Events	Total [a]	Placebo	Xyrem Oral Solution Dosage (g/d) at Onset					
			Total [a]	3.0	4.5	6.0	7.5	9.0
Number of Patients	402 (100%)	54 (100%)	399 (100%)	97 (100%)	269 (100%)	290 (100%)	133 (100%)	129 (100%)
Patients with: ≥ 1 AE of convulsion	14 (3%)	0	14 (4%)	0	3 (1%)	5 (2%)	0	6 (5%)
Convulsion SAEs	0	0	0	0	0	0	0	0
Related convulsion AEs	7 (2%)	0	7 (2%)	0	1 (<1%)	4 (1%)	0	2 (2%)
Severe convulsion AEs	2 (<1%)	0	2 (1%)	0	1 (<1%)	1 (<1%)	0	0
Discontinued due to convulsion AE	0	0	0	0	0	0	0	0
Deaths due to convulsion AE	0	0	0	0	0	0	0	0

[a] Patients are counted only once in each category.

Of the 14 patients, 8 were women and 6 were men. Age ranged from 21.2 to 70.6 years, with 6 patients under the age of 50. Of the 17 events, 5 occurred within the first 30 days after first administration of Xyrem; 1 occurred 31 to 60 days after; 3 occurred 61 to 90 days after; 1 occurred 91 to 120 days after; 1 occurred 236 days after; 1 occurred 333 days after; 3 occurred 1 to 2 years after; and 2 occurred between 2 and 3 years after. The event termed "seizures" in patient 0814 occurred 935 days (2.6 years) after first taking Xyrem. Three of the 17 events (patients 0231, 0608, and 1302) were ongoing at last contact; however, the event for patient 1302 ("increased cataplexy, significant") was recorded as resolved on Day 38 (duration 7 days) at trial entry into OMC-GHB-3. Duration for the remaining 14 events was ≤ 1 day for 5 events, 2 to 7 days for 4 events, 8 to 14 days for 2 events, 34 and 38 days for 2 events, and 151 days for 1 event.

Of the 14 patients, 13 had events related to cataplexy; only 1 patient (0814) had a less definitive assignment of "seizures," which were considered mild, with relationship to trial medication unknown.

Patient 0814, a 58 year old male, had a history of narcolepsy for twenty years prior to the start of cataplexy. He participated in the OMC-GHB-2 trial (beginning treatment on May 28, 1997) and proceeded into OMC-GHB-3 (beginning June 30, 1997). His dose of sodium oxybate was 4.5g/day. He continued into the OMC-SXB-7 trial, beginning May 13, 1999 at the 4.5g/d dose, and remains at this dose. He had a past history of headaches, left breast cancer, and numerous falls with closed head injury due to cataplexy. He sought neurological consultation (April 15, 1999) with a two-year history of memory problems, complicated by getting lost, and a description of "losing gaps of time". Two such adverse events were reported during the study (trial days 220 and 558) with verbatim descriptive terms "fugue state; patient reports being in limbo", and "trance-like state", both of which have been COSTART coded as convulsions. It is important to

note that this neurologic symptomatology preceded study commencement. Neurologic examination on all occasions was normal. His neurologist initiated investigation for these memory lapses, with a possible association of partial complex seizures, or possible early mild dementia or encephalopathy. MRI scan (April 15, 1999) was normal and specifically excluded metastatic disease. His EEG was normal during quiet wakefulness and stage II sleep, and during photic stimulation (hyperventilation was not done). A follow-up ambulatory, twenty-four hour EEG did indicate polyspike and wave activity that could indicate possible generalized seizure activity, but artifact could not be excluded. Overall clinical correlation was advised. A trial of Dilantin 300 mg/day was conducted over a three-month period, with no change in symptomatology. Psychiatric assessment did not contribute explanation for the confusional episodes. These events continue intermittently, and have been suggested by the principal investigator to be possibly related to the narcolepsy syndrome.

4.8.2.2 Scharf Trial

Nine patients experienced 20 AEs that coded to COSTART preferred terms of convulsion or convulsion grand mal (Table 4.15).

Table 4.15 Summary of Patients with AEs of Convulsion, by Dosage at Onset – Scharf Trial

		Sodium Oxybate Oral Solution Dosage (g/d) at Onset				
Convulsion: All Events	**Total [a]**	**3.0**	**4.5**	**6.0**	**7.5**	**9.0**
Number of convulsion AEs	20					
Patients with at least 1 AE	9	0	0	5	2	2
Convulsion SAEs	1	0	0	0	0	1
Related convulsion AEs	1	0	0	0	0	1
Severe convulsion AEs	1	0	0	0	0	1
Discontinuations due to a convulsion AE	2	0	0	1	1	0
Convulsion Deaths	0	0	0	0	0	0

[a] Patients are counted only once in each category, at the highest dosage at onset.

Table 4.16 summarizes the COSTART and verbatim terms for the 20 events in these 9 patients. Ten AEs in 4 patients included the verbatim term "seizure," including the 1 SAE and 1 related AE (same event) and 2 discontinuations. The remaining five patients reported cataplexy that was reported as convulsion.

Table 4.16 List of COSTART and Verbatim Investigator Terms for Convulsion AEs – Scharf Trial

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

[a] This event was serious and determined to be possibly related to study medication.

[b] Patient 064, who had a pre-existing left frontal lobe lesion that may have contributed to the seizure activity, discontinued due to series of 7 seizures over 14-month period.

[c] Patient 247 discontinued due to the AE.

[d] Patient 255 had a history of seizures of unknown etiology at enrollment.

[e] This AE was most likely associated with fever and chills due to a severe tonsillar infection.

[f] AE was considered by the investigator to be severe.

Of the 9 patients, 6 were women and 3 were men. Age at onset ranged from 14.5 to 47.7 years, with 2 of the patients (both women) under the age of 20. Of the 20 events, 1 occurred in the first 60 days, 8 occurred from 6 months to 1 year, 5 occurred from 1 to 2 years, and 6 occurred at > 2 years (Days 1878 to 4537) following the start of trial medication. The 10 seizure-related events occurred on Days 275 to 681 (064, 7 events), day 276 (patient 247), day 310 (patient 255), and day 1931 (patient 048) of sodium oxybate treatment.

Four (043, 049, 051, and 219) of the 9 patients with AEs coding to "convulsion" had events related to cataplexy. One patient (257) had 5 events coded to convulsion,

4 events were related to cataplexy and 1 event, verbatim term, violent shaking and vibrations, was considered to be most likely due to a concurrent infection.

Of the 4 remaining patients that had events coded to COSTART term convulsion, 2 patients (064 and 255) had events of verbatim terms seizure (064 experienced 7 separate events of unknown relationship to trial medication) and brief grand mal seizure (255), which was considered unrelated to trial medication. Patient 255 had a previous history of seizure disorders, and patient 064 had a pre-existing left frontal lobe lesion that may have contributed to the seizure activity as suggested by focal EEG changes and continuation of seizures since discontinuation of sodium oxybate study medication in May, 1989. Two patients (048 and 247) had events of verbatim terms convulsive-like seizure and seizure (continuous jerking all over body) that were possibly complicated by polypharmacy, but are considered to represent potential seizurogenesis.

4.8.3 NEUROPSYCHIATRIC ADVERSE EVENTS

Published studies indicate that symptoms of depression and other symptomatology of psychiatric illnesses are seen in 50% or more of narcolepsy patients, making it difficult to accurately characterize the reports of neuropsychiatric AEs. A review of literature concerning the incidence of psychopathology associated with narcolepsy is provided as follows:

Strong associations between neuropsychiatric pathology and sleep disorders, in particular narcolepsy, are proposed in the literature by both retrospective reviews (Sours 1963, Wilcox 1985) with comparative sex- and age-matched controls. Central mechanistic associations have been proposed to link the pathophysiology of psychosis and abnormal central sleep controls (Howland 1997, Saucerman 1997). Further psychiatric morbidity in narcoleptics on chronic high-dose stimulant therapy is well established (Pawluk 1995).

An example of the associated psychotherapy with narcolepsy was defined by John Sours in 1963 when he reviewed clinical records of patients admitted to a New York Hospital from 1932 – 1964 and coded under the categories of hypersomnia, somnolence and narcolepsy. He identified eight patients with schizoid personality disturbances and another ten patients that developed frank schizophrenic psychoses which required prolonged hospitalization. Such an association was established in the 1985 sex- and age-matched review by James Wilcox at the University of Iowa between narcolepsy and the symptoms of schizophrenia. 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 who had a current complaint of sleep attacks and cataplexy by Kales et al in 1982 indicated a "high level of psychopathology compared to controls". However, these authors considered this to be primarily a reaction to the disorder and its effects.

Robert Howland (1997) established clear association between the sleep-onset REM characteristics of narcolepsy and schizophrenia, psychotic depression, and delirium tremors. He proposed this objective EEG measure as an objective surrogate of neurochemical abnormality representing a common mechanistic link.

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 (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.

Patient status in narcolepsy is obviously a complicated and dynamic representation of:

- Disease-associated psychosocial morbidity.
- Stimulant-induced personality changes.
- Stress variations in daily life.
- Treatment-related co-morbidities.

It is very difficult to interpret causality of events to any single contributor.

4.8.3.1 Updated Integrated Clinical Trial Database

AE terms suggestive of neuropsychiatric events – overdose, coma, death, depression, hallucinations, intentional overdose, manic depressive reaction, overdose, paranoid reaction, personality disorder, psychosis, stupor, suicide, and suicide attempt – were analyzed for the updated integrated clinical trial database.

Of the 402 patients, 52 patients (13%) reported AEs for the specified neuropsychiatric COSTART terms. Of these, 9 patients (2%) had SAEs, 12 patients (3%) had AEs classified as severe, 27 patients (7%) had AEs considered related to trial medication, 12 patients (3%) discontinued the study due to these AEs, and 2 patients (<1%) died in association with these AEs.

There was no clear relationship between incidence of neuropsychiatric AEs and dosage at onset.

Table 4.17 Summary of Patients with Neuropsychiatric AEs, by Dosage at Onset — Updated Integrated Clinical Trials

Neuropsychiatric AEs: All Events	Total[a]	Placebo[b]	Xyrem Oral Solution Dosage (g/d) at Onset[c]				
			3.0	4.5	6.0	7.5	9.0
Number of Patients with:	**402 (100%)**	**54 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
≥ 1 AE	52[c] (13%)	1 (2%)	5 (5%)	6 (2%)	25 (9%)	5 (4%)	14 (11%)
SAEs	9 (2%)	0	0	2 (1%)	4 (1%)	0	3 (2%)
Related AEs	27 (7%)	1 (2%)	1 (1%)	3 (1%)	12 (4%)	0	12 (9%)
Severe AEs	12 (3%)	0	0	3 (1%)	6 (2%)	0	3 (2%)
Discontinued due to AEs	12 (3%)	0	0	3 (1%)	3 (1%)	1 (1%)	5 (4%)
Patient deaths	2 (<1%)	0	0	0	2 (1%)	0	0

Note: One patient in the 6.0 g/d dosage group (0936, possible overdose) had an SAE resulting in death on 2/24/01, which was 5 months after the data cutoff (9/30/00), but is included here for completeness.

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

[b] Patients were on placebo for a short time (4 weeks) relative to the long-term exposure of those treated with Xyrem.

[c] Some patients were exposed to more than 1 dosage during the trial(s), so the sum of patients exposed to specific dosages exceeds the total number of patients in any category.

Table 4.18 summarizes the neuropsychiatric AEs by COSTART preferred term.

Table 4.18 Summary of Patients with Neuropsychiatric AEs, by COSTART Preferred Term – Updated Integrated Clinical Trials

COSTART Term	Number of Patients[a]
Total	**52[b]**
Depression	27
Hallucinations	9
Stupor	6
Suicide, Suicide Attempt, and Overdose	4[b]
Paranoid Reaction	4
Coma	2
Psychosis	2
Manic Depressive Reaction	1
Personality Disorder	1

[a] Patients may have had more than 1 neuropsychiatric AE, so the sum of patients in all categories exceeds the total number of patients.

[b] One patient (0936, possible overdose) had an SAE resulting in death on 2/24/01, which was 5 months after the data cutoff (9/30/00), but is included here for completeness.

Of the 52 patients, 31 were women and 21 were men. Age ranged from 17.7 to 68.0 years, with 31 patients (62%) under the age of 50. There was no apparent relationship between the incidence of neuropsychiatric AEs and the length of time on sodium oxybate. Of the 64 events, 10 occurred within the first 30 days after administration of Xyrem; 16 occurred 31 to 60 days after; 13 occurred 61 to 90 days after; 9 occurred 91 to 180 days after; 8 occurred 6 to 12 months after; 5 occurred 1 to 2 years after; and 2 occurred more than 2 years later (patient 1704, 2.8 years later; patient 14043. 11.7 years later). Sixteen of the 64 events were ongoing at last contact. Duration for the remaining 48 events was $\leq$ 1 day for 20 events, 2 to 7 days for 8 events, 8 to 14 days for 5 events, 2 to 4 weeks for 6 events, 1 to 2 months for 4 events, 2 to 3 months for 2 events, 3 to 6 months for 2 events, and 230 days for 1 event.

4.8.3.2 Scharf Trial

Of the 143 patients in the Scharf trial, 41 patients (28.7%) reported neuropsychiatric AEs (terms included overdose, suicide attempt, depersonalization, depression, emotional lability, hallucinations, hostility, neurosis, paranoid reaction, stupor, and thinking abnormal) (Table 4.19). Twelve patients (8.4%) had events that were considered definitely, probably, or possibly related to study drug, 4 patients (2.8%) had SAEs (2 of these patients experienced 2 neuropsychiatric SAEs each), 7 patients (4.9%) had AEs classified as severe (1 patient experienced 2 severe neuropsychiatric events), and 2 patients (1.4%) discontinued from the study due to these AEs.

There was no apparent dose relationship to either the frequency or severity of the selected neuropsychiatric events.

Table 4.19 Summary of Patients with Neuropsychiatric AEs, by Dosage at Onset – Scharf Trial

Neuropsychiatric AEs : All Events	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
Number of Neuropsychiatric AEs	84	3	14	23	25	19
Patients with: at least 1 AE	41	1	9	12	11	8
SAEs	4	0	1	0	1	2
Related AEs	12	0	1	4	3	4
Severe AEs	7	2	2	0	2	1
Discontinuations due to an AE	2	0	0	1	0	1
Deaths	0	0	0	0	0	0

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

Table 4.20 summarizes the neuropsychiatric events by COSTART preferred term, in order of decreasing frequency.

Table 4.20 Summary of Patients with Neuropsychiatric AEs, by COSTART Preferred Term – Scharf Trial

COSTART Term	Number of Patients[a]	Number of Events
Total	41	84
Depression	22	28
Emotional lability	10	14
Thinking abnormal	9	13
Depersonalization	7	7
Hostility	6	8
Stupor	6	7
Neurosis	2	2
Overdose	2	2
Suicide attempt	1	1
Hallucinations	1	1
Paranoid reaction	1	1

[a] Patients may have had more than 1 AE.

Of the 41 patients, 23 were men and 18 were women. Age at the time of AE onset ranged from 14.2 to 76.8 years. There was no apparent relationship between the incidence of neuropsychiatric AEs and the length of time on sodium oxybate. Of the 84 events, 22 occurred in the first 60 days of sodium oxybate treatment; 6 occurred at 61 to 120 days; 21 occurred at 121 days to 12 months; 9 occurred at 1 year to 2 years; and 15 occurred at > 2 years. Eleven events had an unknown onset date.

4.8.3.3 Depression

The assignment of the COSTART term depression to verbatim terms of "depression," "depressed mood," "situational depression," "patient reports 'down in the dumps,'" and "dysphoria" (reported in the updated integrated clinical trial database) and to verbatim terms of "depression," "feels quite depressed," "very down," "not happy," or "possible depression" (reported in the Scharf trial) does not constitute a definitive psychiatric diagnosis of Major Depressive Disorder. The essential features of a Major Depressive Disorder (DSM-IV) include a period of at least 2 weeks during which there is either depressed mood or loss of interest or pleasure in nearly all activities. The individual must also experience 4 additional related symptoms. Thus, it is important to distinguish between a transient symptom of feeling depressed and depression as a major psychiatric disorder.

4.8.3.3.1 Updated Integrated Clinical Trial Database

Of the 402 patients in the updated integrated clinical trial database, 27 patients (6.7%) had 30 AEs that were coded to depression. Seventeen of the 30 events were considered not related, 1 was probably related, 8 were possibly related, and 4 were of unknown relationship to test medication administration. Of the 9 related AEs, 7 lasted longer than 2 weeks. Sixteen of the 30 events were continuous, 12 intermittent, and

2 were unknown as to frequency. None of the events was considered serious. Two patients had a previous history of depression.

The actions taken with trial medication included no change in treatment for 26 events, temporary discontinuation of medication for 2 events, and permanent discontinuation for 2 events. Medication was initiated for management of 5 events (3 with Zoloft, 1 with Nortriptyline, and 1 with Sertraline). Depression was considered related to test medication for only 2 of these 5 events.

4.8.3.3.2 Scharf Trial

Twenty-two (15.4%) of the 143 patients participating in the Scharf open-label clinical trial for up to 16 years reported 28 AEs of depression. This included 14 men, with a mean age of 44 years (range 14.8 to 73.6 years) and 8 women, with a mean age 47.6 years (range 18.4 to 63.5 years). The mean dosage at onset was 5.6 g/d (range 2.3 to 9 g/d).

Two of the 28 depressive events were considered possibly related (218 and 238), 25 not related, and 1 of unknown relationship to trial medication. The intensity was considered severe in 5, moderate in 1, mild in 2, and not indicated in 20 of the AEs.

One patient was hospitalized for depression; the event was reported as an SAE (patient 019). This event (considered unrelated to study drug) started 217 days following the start of treatment and while the patient was receiving 6 g/d of sodium oxybate. The patient had a previous history of depression, suicidal ideation, and possible anxiety neurosis.

Three other patients reported relevant medical histories prior to treatment – patient 202 (psychiatric disorder with visual and auditory hallucinations), patient 255 (paranoia and difficulty controlling his temper), and patient 286 (depression).

Of the 2 patients with AEs coded to depression that were considered possibly related to study drug, 1 (238) lasted 2 days and 1 (218) was of unknown duration.

Six of the 28 AEs lasted 1 day, and 1 lasted 30 days. There was no reported stop date for 17 AEs; the start date for these ranged from 1 month to 14.5 years after initiation of sodium oxybate treatment, with a mean of 3.9 years. Four AEs had neither start nor stop date.

The incidence of depression reported in the Scharf trial appears to approximate that reported in the literature. Given the very long duration (over 16 years) of the trial, and the propensity of the narcoleptic population toward recurrent episodes of depression (Broughton 1984), there does not appear to be a causal relationship between depression and sodium oxybate treatment in this setting.

4.8.3.4 Hallucinations

4.8.3.4.1 Updated Integrated Clinical Trial Database

Nine (2.2%) of the 402 patients reported hallucinations. In 3 of these patients, the hallucinations were hypnagogic in nature and are probably attributable to the narcolepsy disease state. A fourth patient experienced unspecified hallucinations that stopped when her sodium oxybate dosage was increased, indicating that these hallucinations were most likely hypnagogic in nature as well.

One patient reported an isolated event (unspecified hallucinations), which was considered possibly related to trial medication. Another patient had hallucinations (described as "colors and shapes"), which were described as continuous and lasted 1 day; this was considered to be probably related to trial medication.

One patient reported on 2 consecutive clinic visits that she experienced a total of 9 auditory hallucinations ("voices"). These occurred over the course of 55 days; they resolved spontaneously and did not recur during the remainder of the trial.

After 20 days on trial medication, another patient experienced confusion, forgetfulness, and unspecified hallucinations and her trial medication was stopped. Ten days later, she developed nausea and after an additional day, intermittent paranoia. All of her symptoms resolved 2 weeks after stopping medication.

A final patient had a previous history of mental illness, including auditory hallucinations, prior to entry in the trial (this information had been intentionally withheld by the patient). On Day 84, she developed moderately severe auditory hallucinations requiring hospitalization. Given her subsequently disclosed past psychiatric history, these symptoms were deemed unrelated to the study medication. Her symptoms subsided following therapy with antipsychotic medication.

4.8.3.4.2 Scharf Trial

One of the 143 patients reported an AE that coded to the COSTART term hallucinations. This event occurred on Day 1918 at a dosage of 9.0 g/d. The patient experienced a hypnagogic hallucination, a REM-related symptom of narcolepsy, during which he dove out of bed and jammed his head against the wall. The event was not considered serious, but did necessitate a visit to the clinic for a neck radiograph. The patient was placed in a neck collar and prescribed Naprosyn and aspirin. The event was considered to be probably related to study medication by the investigator.

4.8.3.5 Stupor

4.8.3.5.1 Updated Integrated Clinical Trial Database

Six (1.5%) of the 402 patients reported AEs that coded to stupor. The verbatim terms all included the terms "drunk" or "intoxicated." Each of the 6 patients reported this AE only

once, with each occurrence lasting 1 day or less. All 6 patients were in OMC-GHB-3; there were 4 women and 2 men, ranging in age from 25 to 55 years. The events occurred following 34 to 66 days of sodium oxybate treatment. Dosage at onset was 4.5 g/d for 1 patient, 6.0 g/d for 3 patients, and 9.0 g/d for 2 patients. Five of the AEs were considered possibly or probably drug-related, while the relationship for the sixth was unknown.

4.8.3.5.2 Scharf Trial

Six (4.2%) of the 143 patients reported 7 AEs that coded to the COSTART term stupor. The verbatim terms used to describe 4 of these events in 3 patients include the words "drunk," "intoxicated," and "tipsy." One of these 4 events was considered probably related, 2 possibly related, and 1 of unknown relationship to trial medication. Two events had a duration of 1 day, 1 event lasted 15 days, and 1 event did not have a stop date recorded These 4 AEs occurred after 1 to 134 days of Xyrem administration, with the dosage at onset ranging from 6.0 to 7.5 g/d. None of these events was considered serious.

One additional patient (257) experienced an AE of verbatim term "acting 'like he's retarded.'" The time of the event and dosage at onset were unknown. The event was not serious and was of unknown relationship to trial medication. The patient continued in the trial through the May 31, 1999 data cutoff.

Two additional patients experienced 2 AEs that were considered serious. Patient 017 experienced an event of verbatim term "unresponsive" that was part of an overdose (see Table 4.9). The second patient (012) experienced an event with verbatim terms "disoriented," "stupor," and "weak" on Day 725 (7.5 g/d). The patient was hospitalized overnight. The patient continued the trial for an additional 8 years with no recurrence of the event.
These descriptive events do not appear to qualify as psychopathology.

4.8.3.6 Suicide Attempt, Overdose, Intentional Overdose

4.8.3.6.1 Updated Integrated Clinical Trial Database

Two suicides (0531 and 0936), 1 attempted suicide (14043), and 1 intentional overdose (1131) were recorded among the neuropsychiatric AEs in the 402 patients in the updated integrated clinical trial database.

One suicide (0531, coded as death) was due to multiple drug toxicity that included toxic levels of 6 psychotropic drugs other than sodium oxybate. The second suicide (0936) by a patient with a history of depression and a subsequent suggested diagnosis of bipolar disease, was officially ruled as a death due to cardiovascular disease (without autopsy by the Medical Examiner) but later evidence pointed to a possible overdose that included lithium, Paxil, and Percocet as well as sodium oxybate. This event occurred on 2/24/01, which was 5 months after the data cutoff (9/30/00), but is included here for completeness.

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		$T_{1/2}$ 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				
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)

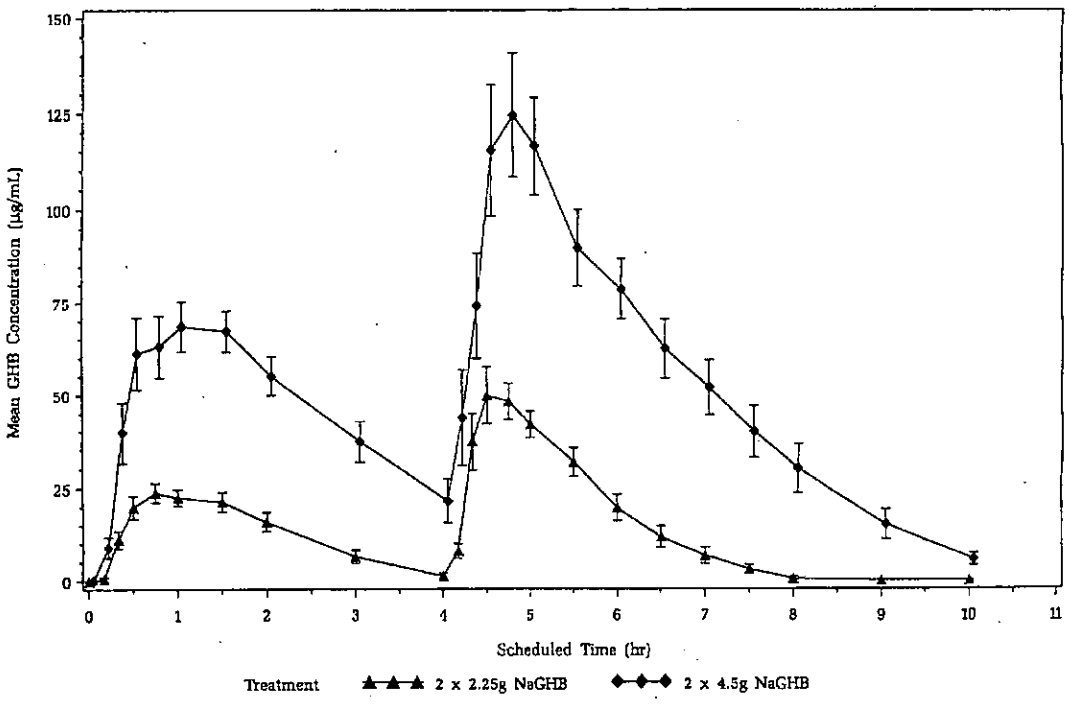
This was a 2-way crossover study that examined the pharmacokinetics of Xyrem (sodium oxybate) oral solution in 10 male and 3 female healthy adult volunteers. Each subject received two treatments with sodium oxybate, one at a dose of 4.5 g and the other at a dose of 9.0 g. For each treatment, doses were 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.

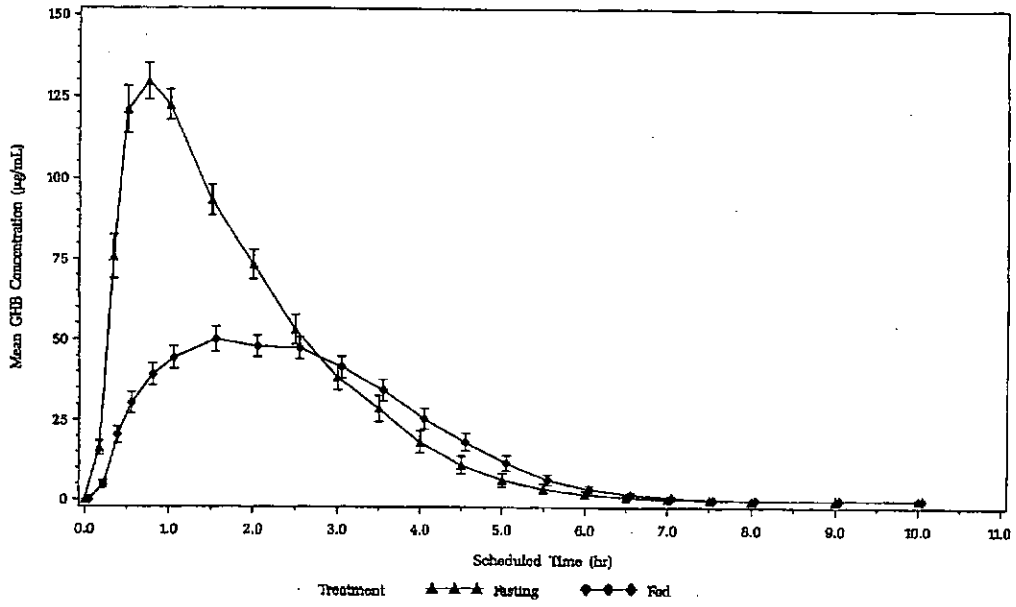
The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 34 subjects who completed the study.

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

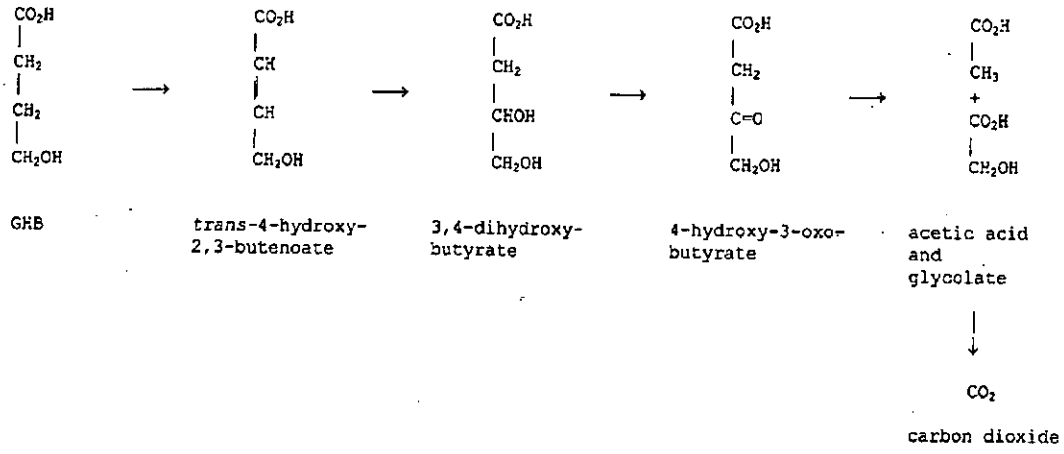
On average, less than 5% of an oral oxybate dose is eliminated unchanged in human urine (OMC-SXB-8, OMC-SXB-9, and OMC-SXB-11). Hence, metabolism is the major elimination pathway for oxybate.

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.

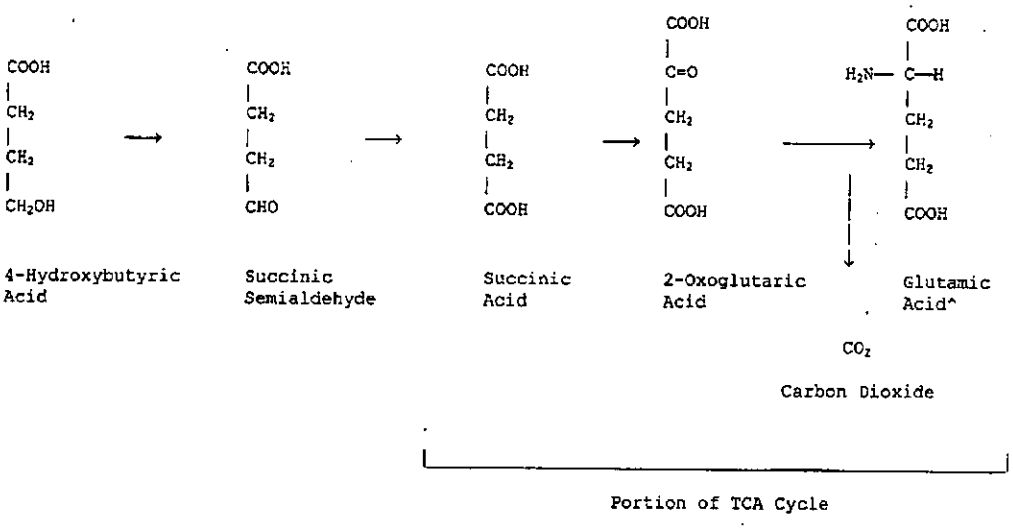
A review of the scientific literature shows that GHB may be metabolized via two distinct biotransformation pathways (Figure 5.3), one involving a β-oxidation pathway (Figure 5.3, upper panel) and the other involving the entry of an intermediate metabolite, succinic acid, into the tricarboxylic acid cycle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

Martelliotta 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 dandestine 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 publichealth, 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 1998

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 10-67 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 (0.3-2.0 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 59% 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 (CIII). 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 µg/kg/injection) under a FR 10 schedule of reinforcement. Upon completion of training, the maintenance dose of PCP was established at 10.0 µg/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 µg/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, occasio nally 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 s tated that the number of injections did not exceed the number of saline injectio ns and were considerably less than the number of infusions for methohexital.

Experiment 3: (Aror, 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 ng 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 tween 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. Rats 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 pharmacolog 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, 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 udies 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 cortical 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 113-115°.[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 $\forall$ half-life of 1.02 hours and a $\exists$ 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 5100 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 mg/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 hat 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 e 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 Cernep and Kohler who supply it for use as a g neral 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 Z ealand 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 ireated 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 sl ould receive an

initial dose of 1.5 grams to avoid development of sedation, dizziness, and/or ataxi . 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 we r off.

GHB is currently being commercially developed for the treatment of cataplexy a sociated with narcolepsy. The FDA has granted a sponsor orphan status for its GHB product fo 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 or er. GHB was sold in California Bay Area retail stores and distributed by San Francisco-bas d companies. Marketed as a sleep and diet aid, GBH was initially used by bodybuilders for its a eged role as a growth hormone releaser, as a diet aid, to counter the effects of stimulants, and o 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, a verage age of 30, and primarily male. In their report, 71% described themselves as regular use s; 18% mixed GHB with alcohol.

Bodybuilders have accounted for a significant number of emergency room case 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 he time GHB was legally available, medical, law enforcement and poison control center re orts appeared indicating that those who began using the drug as a sleep or diet aid continued t use it for its euphoric effects [74]

In 1990, FDA issued a health alert and prohibited the sale of GHB.[75] Although sq e abuse in the bodybuilding community continues, the pattern of GHB use and distribution ha changed. Dyer *et al.* (1994) concluded that although GHB has a history of abuse by bodybui ders, in recent years it has been used for its euphoric effects predominantly by young people at da ce parties. Since the early 1990's, GHB has been sold at nightclubs, rave parties, and bars. K s 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, ju e, or alcohol). GHB abuse at nightclubs and rave parties is intended for the purpose of getting hi h, producing a more profound effect from alcohol, countering the effects of stimulants, "regulat g" the effects of hallucinogens, or alleviating withdrawal effects from alcohol. Users claim t at GHB elicits effects common to alcohol and CNS depressants, marijuana, hallucinogens, and n rcotics. GHB euphorigenic effects at low doses or in the early stages of intoxication have bee n compared to those produced by alcohol, barbiturates, marijuana, or MDMA Thus, abusers rep ort 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.[76]

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

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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

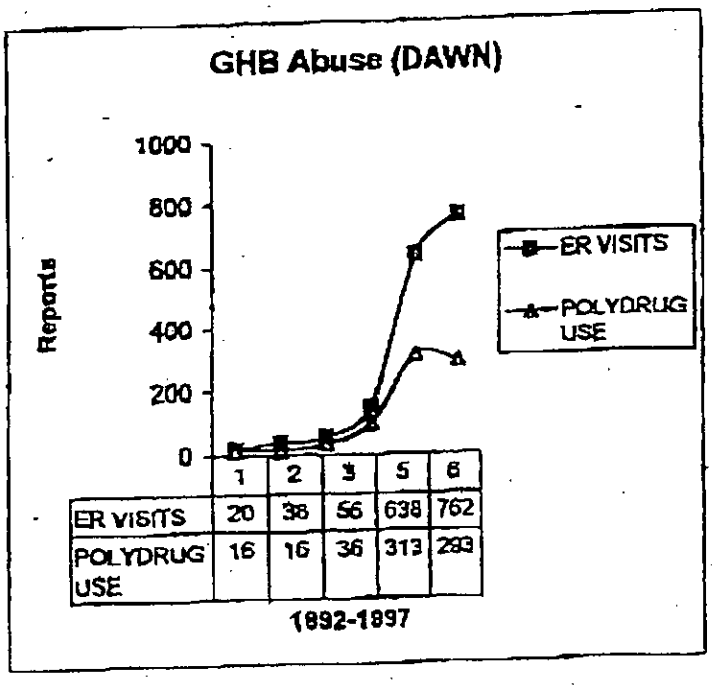
AGES OF DECEASED	NUMBER	PERCENT
10-19 years	3	9%
20-29 years	17	53%
30-39 years	7	22%
40-49 years	3	9%
50-59 years	1	3%
70-79 years	1	3%

Source: DEA

GHB emergency room episodes have been documented in the Drug Abuse Wa ning Network (DAWN). DAWN reported 1664 GHB-related emergency department episodes from 1991 to 1997. GHB-related emergency department episodes increased from 20 in 1992 t 762 in 1997 (TABLE 4, FIGURE 1) The source of the drug has been clandestinely manufac ured GHB of unknown purity. Most of the reports involved Caucasian males, followed i y "other" or "unknown" ethnicity. The majority of episodes involved individuals 18 to 25 yea s of age. The motivation for taking GHB was primarily for recreational use, followed by de pendence and suicide. In 60% of the episodes, GHB was taken in combination with alcoho 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 a dition, 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 res arch material covered under FDA IND (Source: DEA and DAWN)

These findings suggest that recreational use of GHB has been increasing over th past 5 years, but that the number of deaths relative to that increase is infrequent. The frequen y 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	775
26-34	-	-	16	48	163	401
35 +	-	-	-	-	30	58
Sex						
Male	-	-	29	98	506	830
Female	12	13	12	51	125	128
Unknown	-	-	-	-	-	-
Race/Ethnicity						
White	18	25	47	105	336	570
Black	-	-	-	-	6	8
Hispanic	-	-	-	12	15	46
Other/Unknown	-	-	-	15	281	368
Motive for Taking Drug[1]						
Dependence	-	-	-	15	25	29
Suicide	-	-	-	-	13	18
Recreational Use	14	31	25	85	421	736
Other Psychic Effects	-	-	-	-	17	1
Unknown	-	-	22	41	160	16
Reason for Visit[1]						
Unexpected Reaction	-	-	-	49	172	329
Overdose	11	34	38	94	312	576
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 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 swearing. 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 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 sch. dule 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 tr ament 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 a sociated 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

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[3] Galloway et al., 1997
[4] Winter, 1981; Colombo, et al , 1995b,c, Beardsley, et al., 1996
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[36] (Jenney et al., 1962; Mamelak et al., 1977, 1986; Mamelak, 1989; Laborit, 1964)
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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 /JHK
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

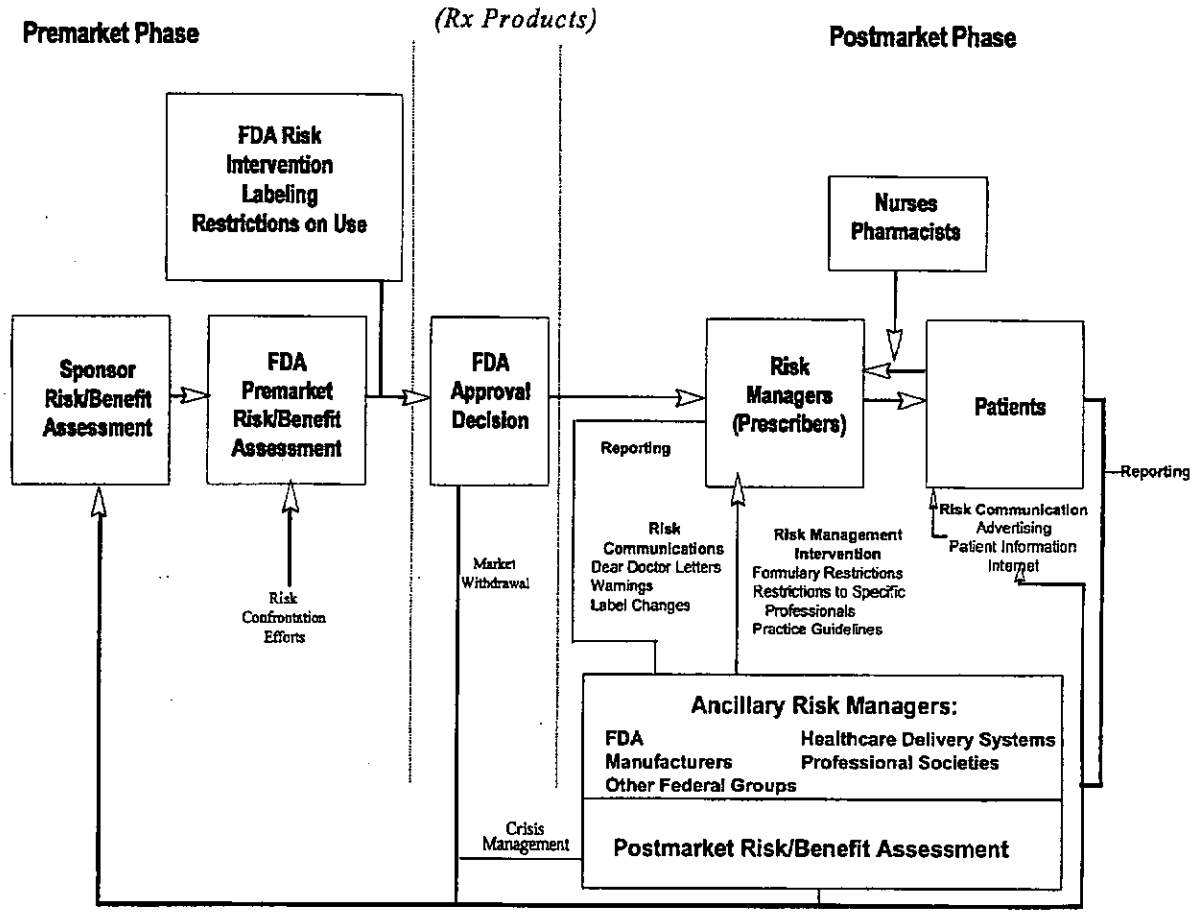
SECTION 8
RISK MANAGEMENT

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.

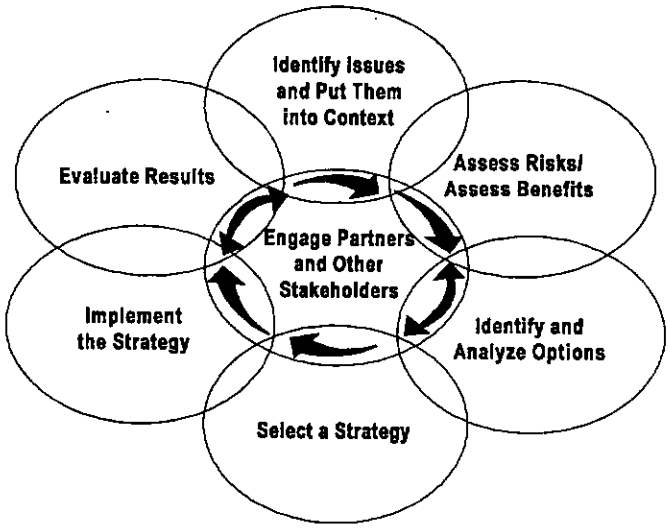
An example is the reporting of adverse events. All pharmacists are trained to identify adverse events, and to report them to the manufacturer, which, in turn, reports them to the FDA. This process is not always effective within the current healthcare environment, in which patients can make several visits 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.

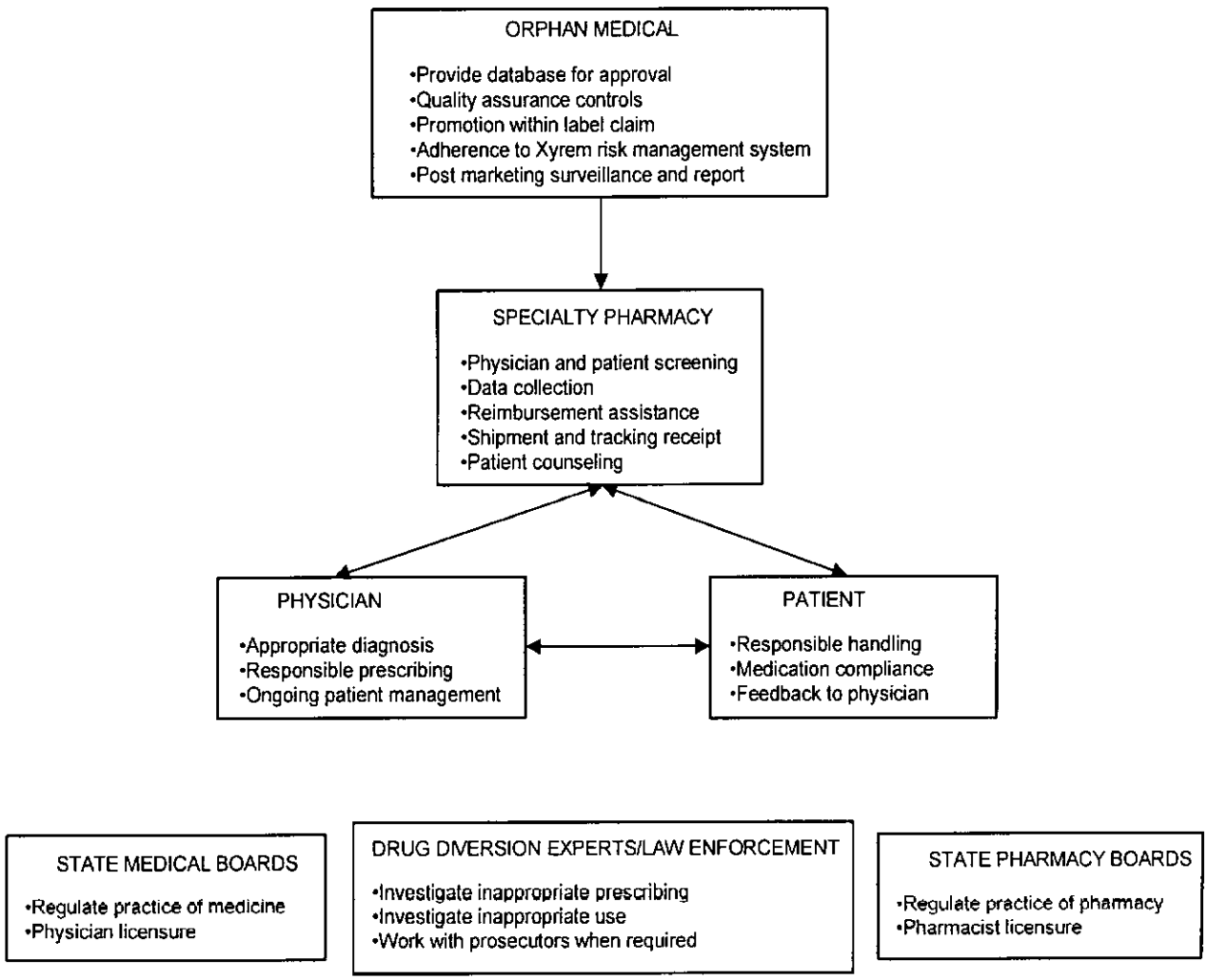
The Xyrem risk management system ensures that the centralized pharmacy will identify patients who are attempting to duplicate prescriptions. All data collected will be available to state and federal authorities, on whatever timeframe they determine to be appropriate. This allows law enforcement agencies 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 (including 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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