Sodium oxybate did not impair fertility in rats at doses up to 1000 mg/kg (approximately equal to the maximum recommended human daily dose on a mg/m^2 basis).

Pregnancy

Pregnancy Category B: Reproduction studies conducted in pregnant rats at doses up to 1000 mg/kg (approximately equal to the maximum recommended human daily dose on a mg/m^2 basis) and in pregnant rabbits at doses up to 1200 mg/kg (approximately 3 times the maximum recommended human daily dose on a mg/m^2 basis) revealed no evidence of teratogenicity. In a study in which rats were given sodium oxybate from day 6 of gestation through day 21 post-partum, slight decreases in pup and maternal weight gains were seen at 1000 mg/kg; there were no drug effects on other developmental parameters. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Sodium oxybate has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid, but umbilical vein levels of sodium oxybate were no more than 25% of the maternal concentration. No sodium oxybate was detected in the infant's blood 30 minutes after delivery. Elimination curves of sodium oxybate between a 2-day old infant and a 15-year old patient were similar. Subsequent effects of sodium oxybate on later growth, development and maturation in humans are unknown.

Nursing Mothers

It is not known whether sodium oxybate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sodium oxybate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in patients under 16 years of age have not been established.

Race and Gender Effects

effects on safety or efficacy. More than 90% of the subjects in clinical trials were Caucasian.

The database was 58% female.

The overall percentage of patients with at least one adverse event was slightly higher in women (80%) than in men (69%). The incidence of serious adverse events and discontinuations due to adverse events were similar in both men and women.

ADVERSE REACTIONS

A total of 448 narcoleptic patients were exposed to sodium oxybate in clinical trials. The most commonly observed adverse events associated with the use of sodium oxybate were:

Headache (25%), nausea (21%), dizziness (17%), pain (16%), somnolence (13%), pharyngitis (11%), infection (10%), viral infection (10%), flu syndrome (9%), accidental injury (9%), diarrhea (8%), urinary incontinence (8%), vomiting (8%), rhinitis (8%), asthenia (8%), sinusitis (7%), nervousness (7%), back pain (7%), confusion (7%), sleepwalking (7%), depression (6%), dyspepsia (6%), abdominal pain (6%), abnormal dreams (6%), insomnia (5%).

2 deaths occurred — these clinical trials, both from drug overdoses. Both these deaths resulted from the ingestion of multiple drugs, including sodium oxybate in one patient

In these clinical trials, 13% of patients discontinued because of adverse events. The most frequent reasons for discontinuation (> 1%) were nausea (2%) and headache (1.3%)

Approximately 6 % of patients receiving sodium oxybate in 3 controlled clinical trials (n=147) withdrew due to an adverse event, compared to 1% receiving placebo (n=79).

Incidence in Controlled Clinical Trials

Most Commonly Reported Adverse Events in Controlled Clinical Trials

The most commonly reported adverse events associated with the use of sodium oxybate and occurring with at least 5% greater frequency than seen in placebo-treated patients were dizziness (23%), headache (20%), nausea (16%), pain (12%), sleep disorder (9%), confusion (7%), infection (7%), vomiting (6%) and urinary incontinence (5%). These incidences are based on combined data from Trial 1 and two smaller randomized, double-blind, placebo-controlled, cross-over trials (n=181).

Trial 1, [redacted] used 3 fixed doses of sodium oxybate (3g, 6g, and 9g). In that trial dizziness, nausea, urinary incontinence, and vomiting were more common at higher doses, with the majority of events occurring in the 6g and 9g dose groups.

Adverse Events With an Incidence of > 1% in Trial 1

Table lists the incidence of treatment emergent adverse events in Trial 1. Events have been included for which there are at least 2 episodes in the considered drug group and for which the incidence in at least one dosage group is greater on drug than placebo.

The prescriber should be aware that data provided below cannot be used to predict the incidence of adverse experiences during the course of usual medical practice where patient characteristics and other factors may differ from those occurring during clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for

estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table —

Incidence (%) of Treatment-Emergent Adverse Events in Trial 1

	Sodium Oxybate Dose			
Body System Preferred Term	Placebo (n=34)	3g (n=34)	6g (n=33)	9g (n=35)
Body as a Whole				
Asthenia	1 (3%)	0 (0%)	2 (6%)	0 (0%)
Flu Syndrome	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Headache	7 (21%)	3 (9%)	5 (15%)	11 (31%)
Infection	1 (3%)	3 (9%)	5 (15%)	0 (0%)
Infection Viral	1 (3%)	1 (3%)	3 (9%)	0 (0%)
Pain	2 (6%)	3 (9%)	4 (12%)	7 (20%)
Digestive System				
Diarrhea	0 (0%)	0 (0%)	2 (6%)	2 (6%)
Dyspepsia	2 (6%)	0 (0%)	3 (9%)	2 (6%)
Nausea	2 (6%)	2 (6%)	5 (15%)	12 (34%)
Nausea and Vomiting	0 (0%)	0 (0%)	2 (6%)	2 (6%)
Vomiting	0 (0%)	0 (0%)	2 (6%)	4 (11%)
Musculoskeletal System				
Myasthenia	0 (0%)	2 (6%)	1 (3%)	0 (0%)
Nervous System				
Amnesia	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Anxiety	1 (3%)	1 (3%)	0 (0%)	2 (6%)
Confusion	1 (3%)	3 (9%)	1 (3%)	5(14%)
Dizziness	2(6%)	8(24%)	10(30%)	12(34%)
Dream Abnormal	0 (0%)	0 (0%)	3 (9%)	1 (3%)
Hypertension	1 (3%)	0 (0%)	2 (6%)	0 (0%)
Hypesthesia	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Sleep Disorder	1 (3%)	2 (6%)	4 (12%)	5(14%)

Somnolence	4 (12%)	5 (15%)	4 (12%)	5(14%)
Thinking Abnormal	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Skin				
Increased sweating	0 (0%)	1 (3%)	1 (3%)	4(11%)
Special Senses				
Amblyopia	1 (3%)	2 (6%)	0 (0%)	0 (0%)
Tinnitus	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Urogenital System				
Dysmenorrhea	1 (3%)	1 (3%)	0 (0%)	2 (6%)
Incontinence Urine	0 (0%)	0 (0%)	2 (6%)	5(14%)

Other Adverse Events Observed During All Clinical Trials

[redacted] To establish the rate of adverse events, data from all subjects receiving any dose of sodium oxybate were pooled. All adverse events reported by at least two people are included except for those already listed elsewhere in the labeling, terms too general to be informative, or events unlikely to be drug-induced. Events are classified by body system and listed under the following definitions: **frequent** adverse events (those occurring in at least 1/100 people); **infrequent** events (those occurring in 1/100 - 1/1000 people). These events are not necessarily related to sodium oxybate treatment.

Body As A Whole

Frequent: Allergic reaction, chills, [redacted] **Infrequent:** Abdomen enlarged, [redacted] hangover effect, [redacted], neck rigidity.

Cardiovascular system

[redacted] **Infrequent:** [redacted] syncope,

Digestive system

Frequent: Anorexia, constipation,

Infrequent:

mouth ulceration, stomatitis.

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gamma hydroxybutyrate (GHB), is listed in the most restrictive schedule of the Controlled Substances Act (Schedule I). Thus, non-medical uses of sodium oxybate (Xyrem® or GHB) are classified under Schedule I.

Abuse, Dependence, and Tolerance

Abuse

See applicable directions for use under **HANDLING AND DISPOSAL** below.

Although sodium oxybate has not been systematically studied in clinical trials for its potential for abuse, illicit use and abuse have been reported.

is a psychoactive drug that produces a wide range of pharmacological effects. It is a sedative-hypnotic that produces dose- and concentration-dependent central nervous system effects in humans. The onset of effect is rapid, enhancing its potential for abuse or misuse.

The rapid onset of sedation, coupled with the amnestic potential of particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary (assault victim) user.

GHB is abused in social settings primarily by young adults

GHB has some commonalties with ethanol over a limited dose range and some cross tolerance with ethanol has been reported.

Dependence

depth. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact.

Recommended Treatment of Overdose

General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid-sequence induction (without the use of sedative) should be considered. Vital signs and consciousness should be closely monitored. The bradycardia reported with [redacted] overdose has been responsive to atropine intravenous administration. No reversal of the central depressant effects of sodium oxybate can be expected from naloxone or flumazenil administration. The use of hemodialysis and other forms of extracorporeal drug removal have not been studied in GHB overdose. However, due to the rapid metabolism of sodium oxybate, these measures are not warranted.

Poison Control Center

As with the management of all cases of drug overdose, the possibility of multiple drug ingestion should be considered. The physician is encouraged to collect urine and blood samples for routine toxicologic screening, and to consultat with a regional poison control center (1-800-222-1222) for current treatment recommendations.

DOSAGE AND ADMINISTRATION

Xyrem is required to be taken at bedtime and again 2.5-4 hours later. The recommended starting dose [redacted] is 4.5 g/day divided into 2 equal doses of 2.25 g. The starting dosage can then be increased to a maximum of 9 g/day in increments of 1.5 g/d (0.75 g per dose). Two weeks are recommended between dosage increases to evaluate clinical response and minimize adverse effects. Xyrem is effective at doses of 6-9 g/day. The efficacy and safety of Xyrem at doses higher that 9 g/day have not been investigated, and doses greater than 9 g/day should ordinarily not be administered.

Prepare both doses of Xyrem prior to bedtime. Each dose of Xyrem must be diluted with 2 ounces (60mL) of water in the child resistant dosing cups provided prior to ingestion. The first dose is to be taken at bedtime and the second taken 2.5-4 hours later while sitting in bed. Patients may need to set an alarm to awaken for the second dose. The second dose must be prepared prior to ingesting the first dose, and should be placed in close proximity to the patient's bed. After ingesting each dose patients should then lie down and remain in bed.

Because food significantly reduces the bioavailability of sodium oxybate, [redacted]

Hepatic Insufficiency

Patients with compromised liver function will have increased elimination half-life and systemic exposure along with reduced clearance. (see Pharmacokinetics and Metabolism). As a result, the starting dose should be decreased by one-half and dose increments should be titrated to effect while closely monitoring potential adverse events.

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Preparation and Administration Precautions

Each bottle of Xyrem® is provided with a child resistant cap and two dosing cups with child resistant caps.

Care should be taken to prevent access to this medication by children and pets.

See the Medication Guide for a complete description.

HOW SUPPLIED

Xyrem® (sodium oxybate) is a clear to slightly opalescent oral solution. It is supplied in kits containing one bottle of Xyrem®, a press-in-bottle-adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide, a professional insert, and two 90 mL dosing cups with child resistant caps. Each amber oval PET bottle contains 180 mL of Xyrem® oral solution at a concentration of 500 mg/mL and is sealed with a child resistant cap.

NDC 62161-008-20: Each tamper evident single unit carton contains one 180 mL bottle (500 mg/mL) of Xyrem®, one press-in-bottle-adaptor, one oral syringe, and two dosing cups with child resistant cap.

STORAGE

Store at 25° C (77° F); excursions permitted up to 15° -30° C (59° -86° F) [see USP Controlled Room Temperature]. Solutions prepared following dilution should be consumed within 24 hours to minimize bacteria growth and contamination.

HANDLING AND DISPOSAL

Xyrem® is a Schedule III drug under the Controlled Substances Act. Xyrem should be handled according to state and federal regulations. It is safe to dispose of Xyrem oral solution down the sanitary sewer.

CAUTION

Rx only

Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

Distributed By

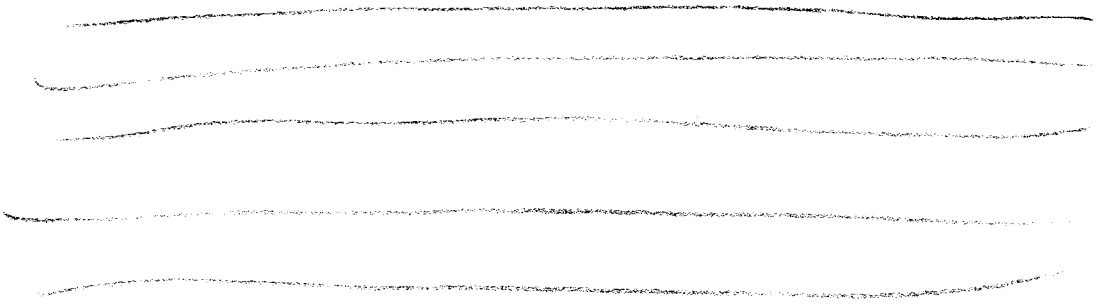
Orphan Medical Inc.
Minnetonka, Minnesota 55305
For questions of a medical nature or to order Xyrem® call the Xyrem® Patient Success Program at
1-877-67-XYREM (877-679-9736).

US Patents Pending
Rev. October 2001
Part No.

Comments

My comments on individual sections of the label are below

Black Box Warning



Description

The sponsor's changes to the label are acceptable

Clinical Pharmacology

Mechanism of Action

I have deleted the sponsor's description of the proposed mechanism of action of GHB as it is unclear that the mechanism of action of this drug in cataplexy is clearly understood.

Pharmacokinetics and Metabolism, Absorption and Distribution, Metabolism and Elimination

The sponsor's minor changes to the draft labeling that accompanied the Approvable letter of 7/2/01 are acceptable, pending Biopharmaceutics review

Special Populations,

The sponsor's minor changes to the draft labeling that accompanied the Approvable letter of 7/2/01 are acceptable, pending Biopharmaceutics review.

Drug-Drug Interactions

The sponsor has made changes to the draft labeling that accompanied the Approvable letter of 7/2/01 based on the results of an in-vitro study of the interaction of GHB with human hepatic microsomal CYP450 isoenzymes. These changes are acceptable pending Biopharmaceutics review.

Clinical Trials

- In a table depicting the results of the primary efficacy analysis for OMC-GHB-2 trial, the sponsor has changed the p-values for the comparison of the 3 g/day, 6 g/day, and 9 g/day doses of GHB with placebo to reflect the sponsor's own analysis (an ANCOVA on log-transformed data which was not specified a priori in either the original protocol or in protocol amendments). I have changed these p-values to those contained in the Approvable letter dated 7/2/01 which reflect the protocol-specified analysis (ANOVA on log-transformed data) as performed by Dr Sharon Yan, Agency statistician.
- Statements regarding stimulant drug usage in 2 key efficacy trials have been verified and are acceptable
- Other changes to the labeling made by the sponsor in the current submission are minor and acceptable.

Indications And Usage

The changes made by the sponsor to the labeling that accompanied the Approvable letter are consistent with previous discussions with the Division

Contraindications

The labeling submitted by the sponsor is acceptable but has been altered slightly.

Warnings

Key changes made by the sponsor to the draft labeling accompanying the Approvable letter of 7/2/01, or by me to the draft labeling that accompanied this submission. are summarized below. Other changes are minor.

Central Nervous System Depression/Respiratory Depression

I have deleted the description of the OMC-SXB-20 trial as the results of that study were inconclusive in regard to demonstrating the presence, or absence thereof, of depressed respiration.

Confusion/Neuropsychiatric Adverse Events

- These adverse events were previously evaluated by me in my review of the earlier Major Amendment submitted 3/23/01 (review completed 6/14/01; please see that review for full details). Based on those data, as updated in the current submission, I have made the following changes to the proposed labeling that accompanied this submission
  - The incidence of confusion at the 9 g/day dose in the OMC-GHB-2 trial was 17.1% (6/35) and not 14% (5/35) as stated by the sponsor in the labeling. The incidence of 17.1% was based on the sponsor's own listing as contained in the Major Amendment of 3/23/01. I have therefore changed the percentage in question to 17%
  - A statement that most events of confusion in the Scharf trial were transient in nature (single episodes) and of short duration has been deleted. The veracity of such data for the Scharf trial is open to question.

- I have confirmed that, with the exception of the above, the incidence figures contained in this section are accurate and updated based on data in the current submission.

Depression

- This adverse event was also previously evaluated by me in my review of the earlier Major Amendment submitted 3/23/01. Based on that review and on updated information included in the current submission, the incidence figures cited in the application are accurate.
- I have however deleted statements about the brevity of episodes of depression since they have not been further qualified in regard to duration
- I have also deleted a statement about the incidence of patients with depression who were put on treatment, since I did not feel that that was clinically useful information
- I have provided a few more details about patients who attempted suicide while taking GHB.
- I have also indicated that in patients with a prior history of depression and/or suicide attempts careful monitoring is needed for the emergence of symptoms of depression while taking Xyrem®

Precautions

Incontinence

- The incidence rates cited by the sponsor in this section are based on data submitted previously with this application and to a lesser extent on data included in the current submission. I have confirmed that the data are accurate
- As data from a fixed-dose parallel-arm study are more clinically meaningful (e.g., in indicating whether a dose-response is present) I have included a short summary of data from OMC-GHB-2 in place of the information supplied by the sponsor
- I have deleted a statement that the episodes were either isolated or intermittent as the statement is redundant.
- I have deleted a statement that the events required no treatment other than the patient reasonably restrict fluid intake at bedtime (there is evidence of how widely this measure was used or how effective it was).
- I have added a statement that there was no firm evidence that episodes of urinary and fecal incontinence in patients treated with GHB were due to seizures

Somnambulism/Sleepwalking

- I have deleted the term "somnambulism" from the heading for this section and from the text. The sponsor's reason for preferring "somnambulism" is stated to be as follows: the clinical term for sleepwalking is "somnambulism" and the common term "sleepwalking" is included in the first paragraph for clarity. However, the medical term "somnambulism" refers to a very specific NREM parasomnia and there is no evidence at all that any or most of the episodes

described in this section represent that entity. The more commonly used term "sleepwalking" has therefore been reinstated. In the clinical trials subsumed under this NDA the term "sleepwalking" appears to have been used loosely by investigators to described confused and/or wandering behavior at night; as adequate clinical descriptions are not provided in the vast majority of instances it is unclear what specific medical disorder or disorders this condition represents and I have attempted to make that clear in the label .

- I have deleted a statement about the frequency of somnambulism in the adult population: this statement refers to the incidence of the NREM parasomnia, somnambulism.
- I have inserted a statement about the actual adverse sequelae of sleepwalking that were seen in clinical trials. I have also indicated that episodes were multiple in a number of patients.

Sodium Intake

Changes made by the sponsor to the draft labeling accompanying the Approvable letter of 7/2/01 are minor and acceptable

Hepatic Insufficiency

No changes have been made by the sponsor to the draft label that was attached to the Approvable letter of 7/2/01

Renal Insufficiency

Changes made by the sponsor to the draft labeling accompanying the Approvable letter of 7/2/01 are minor and acceptable. Agency biopharmaceutics comments are pending.

INFORMATION FOR PATIENTS

The sponsor's changes to the draft label that accompanied the Approvable letter are minor and acceptable. I have substituted the word "procedure" for "mechanics" in regard to dose preparation.

Laboratory Tests

Changes made by the sponsor to the draft labeling attached to the Approvable letter of 7/2/01 are minor and acceptable.

Drug Interactions

Changes made by the sponsor to the draft labeling accompanying the Approvable letter of 7/2/01 are minor and acceptable. Agency biopharmaceutics comments are pending.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Changes made by the sponsor to the draft labeling accompanying the Approvable letter of 7/2/01 are minor and acceptable. Agency pharmacology comments are pending.

Pregnancy

No changes have been made by the sponsor to the draft label that was attached to the Approvable letter of 7/2/01. Agency pharmacology comments are pending

Labor and Delivery

No changes have been made by the sponsor to the draft label that was attached to the Approvable letter of 7/2/01

Nursing Mothers

No changes have been made by the sponsor to the draft label that was attached to the Approvable letter of 7/2/01

Usage in the Elderly

This section uses exactly the same language that was used in the draft labeling that accompanied the Approvable letter of 7/2/01 but in the current version has been transposed from the Warnings section to the Precautions section. The sponsor states that since no serious adverse event profile has been documented in the elderly, this statement is more appropriate as a precaution. This section is acceptable to this reviewer

Pediatric Use

No changes have been made by the sponsor to the draft label that was attached to the Approvable letter of 7/2/01

Race and Gender Effects

The text of this section has been written entirely since the draft label that was attached to the Approvable letter of 7/2/01 was received. The text is based on data that I had reviewed earlier (see my main Efficacy and Safety reviews of this NDA), and is factually correct and acceptable.

Adverse Reactions

- All adverse event percentages in the text have been placed in parentheses, in keeping with standard practice, and to be consistent in this document as a whole.
- I have included a short statement about deaths in clinical trials (excluding the Scharf trial)
- I have deleted the list of adverse events that led to discontinuation and occurred at a frequency of < 1%
- I have abbreviated the description of adverse event discontinuations in controlled clinical trials.
- In the "Other Adverse Reactions During All Clinical Trials" subsection I have expanded the description of the extent to which patients have been exposed to GHB, both in reference to all patients and in reference to those exposed to a dose of 9 g/day.
- Other changes to the draft labeling submitted are acceptable

Drug Abuse and Dependence

- The changes proposed to this section appear acceptable to this reviewer
- However, the formal input of the Controlled Substances Staff is awaited.

Overdosage

- I have added some clinical details to the description of the first patient who took an overdose of GHB. The sponsor states that the patient "did not require medical intervention" which might even suggest that the patient was cared for at home by a relative; however the patient did require emergent hospitalization.
- In the case of the second patient who took an overdose of GHB and multiple other drugs, I have merely stated the names of the drugs that she took, deleting indications for their use which do not seem to need to be included in labeling.
- Changes made by the sponsor to the draft label that accompanied the Approvable letter of 7/2/01 are otherwise acceptable

Dosage and Administration

- Changes to this section in the current submission involve for the most part a reorganization of the text of the draft labeling that accompanied the Approvable letter without omission of any items
- Additions to this section are minor
- Changes to this section in the current submission are essentially acceptable

How Supplied

Changes made by the sponsor to the draft labeling accompanying the Approvable letter of 7/2/01 are minor and acceptable. Agency chemistry comments are pending

Storage

No changes have been made by the sponsor to the draft label that was attached to the Approvable letter of 7/2/01. Agency chemistry comments are pending

Handling and Disposal

Changes made by the sponsor to the draft labeling accompanying the Approvable letter of 7/2/01 are minor and acceptable. Agency chemistry comments are pending.

Caution

Changes made by the sponsor to the draft labeling accompanying the Approvable letter of 7/2/01 are minor and acceptable. They include deleting the name of the manufacturer (presumably, for security reasons). Agency chemistry comments are pending.

Additional Comment

The incidence (both numerator and denominator) and exposure data for adverse events included in the Warnings, Precautions, and Adverse Reactions sections are based on information included in the Major Amendment (dated 3/23/01) and earlier submissions under this application; the sponsor's cut-off date for these data was 9/30/00. On the other hand, the cut-off date for data in the current submission is 6/30/01. The number of patients exposed in clinical trials (except the Scharf open-label trial) through 6/30/01 has risen from 448 (the number used

as a denominator in labeling) to 466. Adverse event data have not been updated to include those in the current submission.

Ranjit B. Mani, M.D.
Medical Reviewer

J. Feeney, M.D. _____

rbm 2/22/02
cc:
HFD-120
NDA 21196 (N-B2)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ranjit Mani
3/19/02 10:31:18 AM
MEDICAL OFFICER

John Feeney
3/30/02 03:42:10 PM
MEDICAL OFFICER
Labeling negotiations continue. My review outlines a different approach to the application than Dr. Mani's.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL SAFETY REVIEW OF NDA

Brand Name:	Xyrem
Generic Name:	Sodium Oxybate
Sponsor:	Orphan Medical, Inc.
Indication:	Narcolepsy
NDA Number:	21196
Original Receipt Date:	10/3/00
Clinical Reviewer:	Ranjit B. Mani, M.D.
Review Author:	Ranjit B. Mani, M.D.
Review Completed:	6/15/01

2. Review Sources

2.1 Materials from NDA

In reviewing this application I have read the following volumes of the NDA submission of 9/30/00. These volumes have been read almost entirely in electronic format. They include

- Volume 1, containing the application summary
- Volumes 36-63, containing the full reports for the following studies: OMC-GHB-2, Scrima and Lammers
- Volume 100 containing the Integrated Summary of Efficacy

I have also reviewed the following:

- A separate submission dated 12/16/00 containing the final report for the following long-term efficacy trial: OMC-SXB-21. This application also contained updated draft labeling
- The sponsor's responses to a number of requests for information from this reviewer

2.2 Related Reviews, Consults

I have utilized the many reviews that I have done, since 1997, of submissions under IND # ——— and Treatment IND # ——— for details about this drug.

3. Tabular Summary Of Key Efficacy Studies In Original NDA Submission

3 studies have been used in the main submission to support the efficacy of Xyrem® in the treatment of narcolepsy.

3.1 Study OMC-GHB-2

Study #	OMC-GHB-02 Orphan Medical			
Design	Randomized, double-blind, placebo-controlled, parallel-arm			
Duration	4 weeks			
Dosage	9 g	6 g	3 g	Placebo
Number randomized	35	33	34	34
Number completed	28	29	30	33
Main inclusion criteria	Narcolepsy for at least 6 months with both excessive daytime sleepiness and cataplexy			
Primary outcome measures	Total number of cataplexy attacks			
Main efficacy analysis (statistically significant results)	9 g dose superior to placebo, based on ANCOVA ($p = 0.0008$)			

3.2 Scrima Study

Study #	Scrima	
Design	Randomized, double-blind, placebo-controlled, cross-over	
Duration	4 weeks	
Dosage	50 mg/kg/day	Placebo
Number randomized	20	20
Number completed	20	20
Main inclusion criteria	Excessive daytime sleepiness, a history of cataplexy with ≥ 10 cataplexy attacks over the 2 week baseline period and ≥ 2 REM onsets and a sleepiness index of ≥ 75 on the a multiple sleep latency test	
Primary outcome measures	Total number of cataplexy attacks per day	

Study #	Scrima
	Sleepiness Index on Multiple Sleep Latency Test
Main efficacy analysis (statistically significant results)	GHB superior to placebo on total number of cataplexy attacks (p = 0.013)

3.3 Lammers Study

Study #	N -1 (R 55 667 082) Lammers et al	
Design	Randomized, double-blind, placebo-controlled, cross-over	
Duration	4 weeks	
Dosage	4.75 g *	Placebo
Number randomized	25	25
Number completed	25 **	25 **
Main inclusion criteria	Excessive daytime sleepiness and at least one of the following: cataplexy, hypnagogic hallucinations, and sleep paralysis	
Primary outcome measures	Total number of cataplexy attacks Global therapeutic impression (patient) Global clinical impression (clinician)	
Main efficacy analysis (statistically significant results)	GHB superior to placebo on first two of above measures, numbered as above p = 0.002 (ANCOVA)*** p = 0.001 (McNemar's test) Not measured	

*This dose is the mean of the protocol-specified dose of 60 mg/kg/day (range 3.78 to 5.52 g/day)
** The number included in the efficacy analysis was 24 for reasons which are described below in a more detailed review of the study
***This was not the protocol specified analysis. The ANCOVA was performed by the current sponsor several years after the study blind was broken and after the initial report of this study was published. The protocol-specified analysis (which was cited in the publication) was the Wilcoxon Signed Rank Test which yielded a p-value of 0.42, but which may have been an inappropriate analysis.

4. Rating Scales Used

4.1 Epworth Sleepiness Scale

The Epworth Sleepiness Scale is a patient-rated measure of daytime sleepiness. Patients are asked to rate their chances of dozing during each of the following 8 activities on a scale from 0-3 (0=never; 1=slight; 2=moderate; 3=high): sitting and reading; watching TV, sitting inactive in a public place; 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 a lunch without alcohol; in a car while stopped for a few minutes in traffic

4.2 Clinical Global Impression Of Severity (CGI-S)

The following description applies to this measure as used in the OMC-GHB-2 study

This measure involved rating the severity of the patient's narcolepsy at baseline. The rating was made in relation to the investigator's total experience with the narcoleptic population and graded with one of the following:

Not assessed
Normal-no signs of illness
Borderline ill
Slightly ill
Moderately ill
Markedly ill

Among the most extremely ill.

4.3 Clinical Global Impression Of Change (CGI-C)

The following description applies to this measure as used in the OMC-GHB-2 study

This measure assessed the overall change in the patient's severity of narcolepsy using the following rating scale:

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

5. Human Pharmacokinetics

The following pharmacokinetic summary is based on a summary supplied by the sponsor in this submission.

Orally administered GHB is rapidly absorbed with a t_{max} of 30 - 75 minutes and to a similar degree in narcoleptic and other patient populations; absorption characteristics are similar in males and females and are not altered by chronic dosing; t_{max} is delayed, at higher doses (suggesting a limited absorption capacity) and by the administration of food. C_{max} and AUC_{α} are reduced by the administration of the drug with food. The absolute bioavailability of the drug is < 30%.

The apparent volume of distribution divided by absolute bioavailability (V_2/F) ranges between 190 and 384 mL/kg. Inter-subject variability in the volume of distribution is high as indicated by the coefficient of variation which ranges between 16% and 84%. The drug readily crosses the placental and blood-brain barriers. Protein binding has been estimated at about 1%.

Less than 5% of an oral dose of GHB is excreted unchanged in the urine. Based on a review of the scientific literature the sponsor states that the end-product of metabolism, regardless of biotransformation pathway, is carbon dioxide. 2 main biotransformation pathways have been identified:

- A β-oxidation pathway
- A pathway involving the entry of succinic acid into the tricarboxylic acid cycle, through the initial formation of succinic semialdehyde

First-pass metabolism occurs with orally administered GHB, probably through the β-oxidation pathway, resulting in an oral bioavailability of < 30%. Intermediate compounds in the metabolic pathways for GHB do not appear to be pharmacologically active

The pharmacokinetics of GHB are non-linear. Plasma clearance is dose-dependent across the therapeutic range: following a total dose of 9 g (2 doses of 4.5 g each administered 4 hours apart) the apparent elimination half-life of GHB was 0.83 hours, which was approximately 40% longer than the mean elimination half-life following a total dose of 4.5 g (2 doses of 2.25 g each administered 4 hours apart). Chronic dosing with GHB did not alter its pharmacokinetics in a clinically significant manner: treatment with this drug for 8 weeks resulted in 13% and 16% increases in $AUC_{infinity}$ and C_{max}, respectively; these increases were not considered clinically significant.

There are no significant gender differences in the pharmacokinetics of GHB. Neither are there significant differences in pharmacokinetics between healthy subjects and narcoleptic patients, and between healthy patients and those who are alcohol-dependent. Oral clearance of GHB is altered

in the presence of cirrhosis with or without ascites. Renal disease is not expected to alter the pharmacokinetics of GHB; studies in that setting have therefore not been carried out.

Formal studies indicated that GHB had no interactions with protryptiline, zolpidem and modafinil. In-vitro pooled human liver microsomal studies showed that GHB did not significantly inhibit or enhance the activities of human CYP450 isoenzymes.

6. Study # OMC-GHB-2

6.1 Objectives

6.1.1 Primary

To evaluate and compare the efficacy of 3 doses (3 g, 6 g and 9 g) of GHB and placebo in the treatment of the symptoms of narcolepsy

6.1.2 Secondary

To evaluate and compare the safety of 3 doses (3 g, 6 g and 9 g) of GHB and placebo in the treatment of the symptoms of narcolepsy

6.2 Design

Randomized, double-blind, placebo-controlled, parallel-group, 4-arm, multicenter study

The study comprised 5 phases

Screening Period: This was intended to last 1 day to 4 weeks and permitted withdrawal of tricyclic antidepressants and other drugs used to treat cataplexy

Washout Period: This was intended to last 5 - 28 days and allowed for the clinical effects of tricyclic antidepressants and other medications for cataplexy to be eliminated, for rebound cataplexy to abate and to train patients in the use of the diary; this lasted a minimal period of 5 days in those in whom no medications were being withdrawn so that they could be trained in the use of the diary

Baseline Period: This period was intended to last 2 - 3 weeks and was intended to assess the patient's periods of cataplexy and establish a stable number of attacks; if the frequency of attacks was not stable at the end of the 3-week period the patient was discharged from the study; the judgement of the investigator was to determine whether the frequency of attacks of cataplexy was stable

Double-blind Treatment Period: This was intended to last 4 weeks

Follow-up Period: This was proposed as a period of 3 -5 days after study medication was stopped

6.3 Inclusion Criteria

- Informed consent
- Age ≥ 18 years
- Willing and able to complete the entire trial
- History of excessive daytime sleepiness
- History of cataplexy. In addition, patients must have recorded a period of 3 or more complete and/or partial cataplexy attacks per weeks during the last 2 weeks of the baseline period
- Valid polysomnography (PSG) scores
- Current diagnosis of narcolepsy for at least 6 months, according to the criteria below

  - Recurrent naps or lapses into sleep that occur almost daily for at least 6 months
  - Sudden loss of bilateral postural muscle tone in association with intense emotion
- If female must be
  - Surgically sterile OR
  - 2 years post-menopausal OR
  - If of child-bearing potential must be using effective contraception and must continue this treatment during the study

6.4 Exclusion Criteria

- Unstable diseases in any body system, other than narcolepsy, which would place the patient at risk or compromise the trial objectives
- Psychiatric disorders that would preclude participation in, or completion of, the trial
- History of seizure disorder or of anticonvulsant therapy
- History of substance abuse, as defined by DSM-IV, currently or within the past year
- Serum creatinine > 2 mg/dl; AST or ALT > 2 x upper limit of normal; pre-trial electrocardiogram results demonstrating a clinically significant arrhythmia or 2^{nd} or 3^{rd} degree A-V block; history of myocardial infarction within the past 6 months
- Any untreated disorder other than narcolepsy that could be considered a primary cause of excessive daytime sleepiness, including sleep apnea syndrome (criteria specified)
- Occupation requiring variable shift or routine night shift work
- Participation and use of GHB in a previous study
- No clinically significant history of head trauma or of a seizure disorder
- Inadequate support for the duration of the study
- Willing to not operate a car or heavy machinery if the clinical investigator feels such a restriction is warranted
- Use of medication for narcolepsy during baseline period, other than a stable dose of stimulant medication ("stable dose" defined as one without any significant change in dose for the 5 - day period just prior to the baseline period)
- Use of hypnotics, tranquilizers, antihistamines (except for the non-sedating variety of such drugs) and clonidine at the start of the baseline period.

6.5 Concomitant Medication

- The following medications were prohibited: hypnotics, tranquilizers, antihistamines (except for the non-sedating variety of such drugs), clonidine, tricyclic antidepressants, selective serotonin reuptake inhibitors, MAO inhibitors, tetracyclic antidepressants, anticonvulsants and alcohol.
- Patients were cautioned regarding the use of opioid analgesics and alcohol
- Oral contraceptives were permitted in women of child-bearing potential
- Over-the-counter medications needed careful review by the clinical investigator prior to use

6.6 Dosage

- No study medication was to be used during the screening, washout, baseline and follow-up periods of the study
- Those entering the randomized, double-blind phase of the study were assigned to one of the following arms:
  Placebo
  GHB 3 g daily
  GHB 6 g daily
  GHB 9 g daily
- The total nightly dose was divided into 2 equal portions. These were dissolved in water and administered at bedtime and again 2.5 to 4 hours later
- Note that no dose titration was used for this study.

6.7 Schedule

- 7 study visits were scheduled in all as follows; patients were due to be contacted at least 3 times per week during all study periods

Visit Number	Timing
1	Screening period
2	Washout period
3	Baseline period
4	Beginning of double-blind phase
5	Day 14 of double-blind phase
6	Day 28 of double-blind phase
7	During follow-up period and within 3-5 days of Visit 6

- At the screening visit the following were to be obtained or checked: informed consent, medical history, inclusion and exclusion criteria, concomitant medication, determination of duration of screening and washout phases, plan for withdrawal of tricyclic or other prohibited medication and other procedures listed below
- Physical examinations (including neurological examinations), and electrocardiograms were to be performed at screening and at Visit 6
- Vital signs were to be checked at every visit
- Clinical laboratory tests (hematology, clinical chemistry, urinalysis and urine pregnancy test were to be checked at screening and at all subsequent visits, other than Visit 2
- Adverse events and concomitant medication use were to be checked at every visit
- Fresh daily diaries were to be provided at each visit; at each visit the study diary for the period just completed was to be collected; instructions regarding the use of the diaries was provided at every visit
- The state of the patient's cataplexy was to be assessed at Visit 2 and every subsequent visit
- The Epworth Sleepiness Scale was to be assessed at Visits 4, 6 and 7
- A Clinical Global Impression of Severity of the patient's narcolepsy was to be assessed at Visit 4
- A Clinical Global Impression of Change in the severity of the patient's narcolepsy was to be assessed at Visits 6 and 7

6.8 Efficacy Outcome Measures

6.8.1 Primary

Total number of cataplexy attacks (sum of complete and partial cataplexy attacks) per week

6.8.2 Secondary

- Complete cataplexy attacks
- Partial cataplexy attacks
- Daytime sleepiness as assessed with the Epworth Sleepiness Scale
- Clinical Global Impression of Severity of the patient's narcolepsy (not, strictly speaking, an outcome measure). This was made in relation to the investigator's total experience with the narcoleptic population and graded with one of the following: not assessed, normal-no signs of illness, borderline ill, slightly ill, moderately ill, markedly ill, and among the most extremely ill.
- Clinical Global Impression of Change in the severity of the patient's narcolepsy using the following rating scale: very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse
- Number and duration of awakenings each night
- Total amount of sleep each night
- Number and duration of inadvertent naps and sleep attacks
- Number and occurrences of hypnagogic hallucinations or sleep paralysis
- Quality of sleep, level of alertness and overall ability to concentrate using the following scale: 1-excellent, 2-good, 3-fair and 4-poor (this analysis was intended to be purely "exploratory")

6.8.3 Safety Outcome Measures

Adverse events, vital signs, electrocardiograms, safety laboratory tests and concomitant medication use

6.9 Analysis Plan

All statistical tests were to be declared significant if the two-sided p-value was < 0.05

6.9.1 Demographic And Baseline Characteristics

Quantitative variables were to be analyzed using ANOVA or the Kruskal-Wallis test as appropriate; qualitative variables were to be analyzed using Fisher's exact test. If any site failed to reach a minimum of 8 patients, these sites were to be pooled and treated as a single site for purposes of statistical analysis.

6.9.2 Primary Efficacy Analysis

- The primary efficacy analysis was to be on the intention-to-treat population defined as all patients who received study drug on whom a post-treatment evaluation visit was completed.
- As noted above the primary efficacy variable was the total number of cataplexy attacks per week.

- The primary efficacy analysis was directed to comparing the treatment groups for the change from baseline to endpoint in the total number of cataplexy attacks. Baseline was defined as the 2-week period immediately prior to receiving the study drug. Endpoint was defined as the final 2-week period on study drug.
- **The primary efficacy analysis was to be based on ANOVA with the model including treatment group, trial site and treatment-by-site interaction; if the interaction was found not to be statistically significant, the analysis would be rerun excluding that term from the model.**
- **If the ANOVA demonstrated statistically significant differences among the products, each of the active treatment groups were to be compared with the placebo group using least significant differences**
- **A within-group analysis was also to be performed comparing assessing the significance of the median change from baseline using the paired t-test**
- **If the assumptions for the above proposed between-group and within-group analyses were not met, the between-group analysis would use a blocked Wilcoxon test, and the within-group analysis would be based on the Wilcoxon signed-rank test**
- For the primary efficacy variable (between-group comparison) an ANCOVA was **also** to be performed using the baseline observation as a covariate; no further specifications about the ANCOVA are in the original protocol (in its revised version dated 12/5/96), or in the amendment submitted as serial # 007 on 2/7/97; however in the study report the sponsor states that "prior to the completion of the study and database lock, an analysis plan was written and approved" (although seemingly not in a submitted protocol amendment) that detailed performing a log transformation of the data if the assumptions for ANCOVA were not satisfied. The sponsor further states that "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". Such a log transformation was eventually needed for all the primary and secondary efficacy variables except for the Epworth Sleepiness Scale, total amount of sleep each night and number of inadvertent naps per day; Fisher's Exact Test was used for the Clinical Global Impression of Change. Eventually an ANCOVA on log-transformed data was used as the primary efficacy analysis, as presented in the study report
- An additional analysis was also to be performed to look for a possible dose-response relationship

6.9.3 Secondary Efficacy Measures

The secondary efficacy measures were to be analyzed using measures similar to the above.

6.9.4 Sample Size Calculation

The sample size calculation was based on the primary efficacy variable

In the calculation:

- Based upon previous trials with GHB, a mean reduction of at least 2 cataplexy events per week was to be expected over a one-month treatment period, with a standard deviation of 2.5.
- Using a power of 80 % and a 2-sided significance level of 0.05, it was calculated that 25 patients would be needed per treatment group to detect a difference of 2 with respect to change in cataplexy events

6.9.5 Safety Analysis

Safety data are discussed as part of the NDA Safety Review

6.10 Protocol Changes

The above represents the **revised** protocol. The original protocol was submitted 1/10/96. Major changes to the original protocol, which were all made in a single submission (serial # 007 under IND # ——— amendment # 1; dated 2/7/97) are as follows:

- In the original protocol, 3 primary efficacy variables were listed: number of cataplexy attacks, number of sleep attacks and duration of daytime naps. The revised protocol uses only a single primary outcome measure: the total number of cataplexy attacks
- In the original protocol the interval between the two nightly doses of medication was 4 hours. The revised protocol changed the dosing interval to 2.5 to 4 hours
- In the original protocol valid Multiple Sleep Latency Test scores were considered an inclusion criterion; in the revised protocol this requirement was dropped as the other inclusion criteria satisfied the need for an appropriate diagnosis.

The above changes were reviewed by Bob A. Rappaport, M.D., then of this Division, and determined to be acceptable. In his comments, R. Katz, M.D., then Group Leader in this Division, believed that the change to a single primary efficacy variable was acceptable provided the sponsor had not already examined the data for this trial.

Note also that primary efficacy analysis, both in the original and in the amended protocols, was not to be based on ANCOVA, which was intended to be an additional analysis. However in the primary efficacy analysis in the study report ANCOVA, using log-transformed data was used for the primary efficacy analysis and for the analysis of most secondary efficacy measures.

6.11 Efficacy Results

6.11.1 Number of Patients and Disposition

136 patients from 16 centers were enrolled in the study. 120 patients completed the study. Their disposition is outlined in the table below which has been copied from the submission

Disposition	All patients	Placebo	GHB Dose (g/day)		
			3	6	9
RECEIVED STUDY MEDICATION	136	34	34	33	35
WITHDREW FROM STUDY					
Adverse Event	10	1	1	2	6
Protocol Deviation	1	0	1	0	0
Patient Request	2	0	1	0	1
Lost to Follow-up	1	0	0	1	0
Lack of Efficacy	2	0	1	1	0
Total Withdrawals	16	1	1	4	7
COMPLETED STUDY	120	33	30	29	28

As the table indicates the primary reason for withdrawal was the development of adverse events; these were more frequent in the 9 g/day group than in any other group. The highest proportion (20 %) of withdrawals due to all causes occurred in that group

6.11.2 Duration of Treatment

The mean and standard deviation for duration of treatment in each treatment group is indicated in the following table

Treatment Group	Number	Mean (days)	Standard deviation (days)
All subjects	136	27.39	7.22
Placebo	34	29.00	1.95
3 g	34	28.03	7.72
6 g	33	26.82	7.48
9 g	35	25.43	9.18

As the table indicates the groups are comparable as regards their means, although the standard deviation for the placebo group is substantially less than that for the placebo group

6.11.3 Protocol Deviations

Major protocol deviations are summarized in the following table

Deviation	All patients	Placebo	GHB Dose (g/day)		
			3	6	9
Concomitant Medications	9	1	5	1	2
Dosing Error	6	2	2	2	0
Laboratory Procedures	7	1	1	1	4

Errors in concomitant medication were thus the commonest form of protocol deviation. In the above each protocol deviation was counted separately; thus if a single patient had more than 1 protocol deviation of the same kind, each of these deviations was considered a separate event; the total number of events in each category is listed in the above table

6.11.4 Dataset Analyzed

Only an intention-to-treat analysis was performed. This dataset was defined in the protocol as consisting of all those who received a dose of study drug and had a post-treatment follow-up evaluation carried out. No patients were excluded from this dataset whose overall size and distribution by treatment group varied slightly depending upon the outcome measure analyzed. Their distribution according to treatment group is indicated under "Number of Patients and Disposition" above

6.11.5 Demographic Characteristics

These are summarized in the following table

Disposition	All patients	Placebo	GHB Dose (g/day)			p-value
			3	6	9	(ANOVA)
Randomized	136	34	34	33	35	
Mean Age (years)	43.06	40.82	47.06	43.52	40.91	0.2737
Male (%)	41.9	35.2	20.5	63.6	48.6	0.0027
Caucasian (%)	91.2	85.3	97.1	93.9	88.6	0.1379
Mean Height (cm)	170.91	171.97	166.7	173.1	171.9	0.0283
Mean Weight (kg)	82.87	83.98	78.86	85.04	83.56	0.4847

As the above table indicates there were statistically significant differences in gender and height between treatment groups

6.11.6 Baseline Severity of Narcolepsy

The baseline severity of patient symptoms is indicated in part by the following table which depicts the number of patients reporting symptoms in each category during the 3 months prior to screening.

Symptoms	Number (%) of patients with symptoms			
	Placebo (n=34)	3g GHB (n=34)	6g GHB (n=33)	9g GHB (n=35)
Cataplexy	34 (100%)	34 (100%)	32 (97%)	35 (100%)
Excessive day-time sleepiness	34 (100%)	34 (100%)	32 (97%)	34 (97%)
Awakenings at night	27 (79%)	31 (91%)	27 (82%)	30 (86%)
Inadvertent naps/sleep attacks	32 (94%)	33 (97%)	31 (94%)	33 (94%)
Sleep paralysis	26 (76%)	25 (74%)	25 (76%)	24 (69%)
Hypnagogic hal-lucinations	27 (79%)	29 (85%)	26 (79%)	26 (74%)

As the above table indicates the severity of narcolepsy appears to have been roughly similar across treatment groups at baseline based on the above measures; however a statistical analysis comparing treatment groups does not appear to have been performed.

Since the total number of cataplexy attacks per week was the designated primary outcome measure, the mean number of cataplexy attacks per week over the 3-month period prior to the screening visit has also been used to compare

the treatment groups as shown in the following table copied from the sponsor's submission.

		GHB Dose (g)		
Statistic	**Placebo**	**3**	**6**	**9**
N	34	33	33	35
Mean	15.5	12.3	16.6	16.7

NOTE: The 4 treatment groups appear roughly comparable in regard to this measure, but a statistical analysis comparing this measure among the treatment groups does not appear to have been performed. This measure was recorded based on patient recall, as part of the narcolepsy history, at the screening visit; its validity and reliability are questionable.

A more reliable and valid estimate of the baseline severity of cataplexy is from data obtained at the baseline visit for the double-blind phase (Visit 4) which is derived from diary records and after stability of the patient's condition was established. These data are provided in the next table which indicates that the treatment groups were comparable, based on the p-value derived from the Kruskal-Wallis test.

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Type of event	Placebo	GHB Dose (g) 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	

Other baseline narcolepsy symptoms based on diary recordings assessed at Visit 4 are depicted in the following table; again the p-value based on the Kruskal-Wallis test indicates that the groups are comparable

Event (Mean Daily Frequency)	Placebo	GHB Dose (g/day)			p-value (Kruskal -Wallis)
		3	6	9	
Hypnagogic hallucinations	0.57	0.58	1.14	0.53	0.9766
Sleep paralysis episodes	0.51	0.42	0.73	0.47	0.9597
Inadvertent naps daily	1.71	1.91	1.70	1.72	0.7008

Baseline Epworth Sleepiness Scale results are depicted in the next table copied from the submission; here again the groups appear to be comparable

		GHB 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

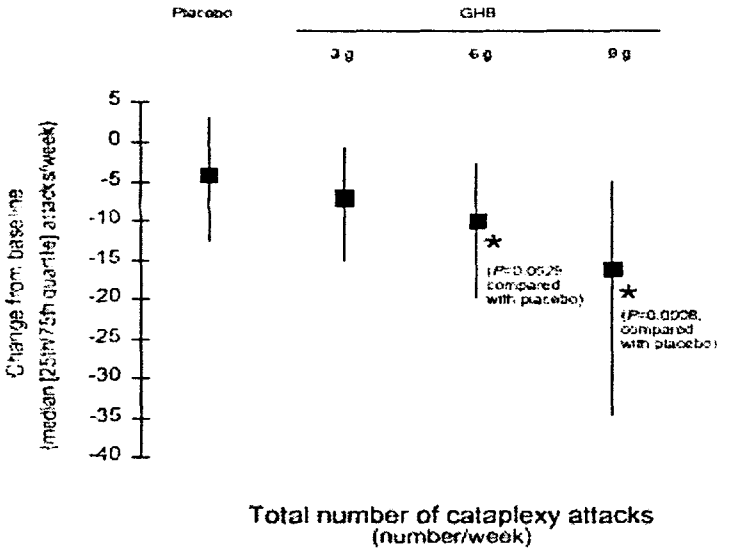
Baseline Clinical Global Impression of Severity results are in the next table. A statistical analysis comparing treatment groups has not been performed but the placebo group had a distinctly higher proportion of patients in the "extremely ill" category as compared with each of the groups receiving GHB.

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

6.11.7 Primary Efficacy Analysis

The results of the primary efficacy analysis, comparing the change in the total number of cataplexy attacks per week from baseline to endpoint between treatment groups, are presented in the next table and figure, both of which have been copied from the submission. **Note that the results of the analysis are based on ANCOVA using log-transformed data, and not on what was planned as the primary efficacy analysis in the original and amended protocols.**

		Observed		Change from baseline to endpoint	Comparison with placebo (p-value)
Dose group	Statistic	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	-8.9	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	

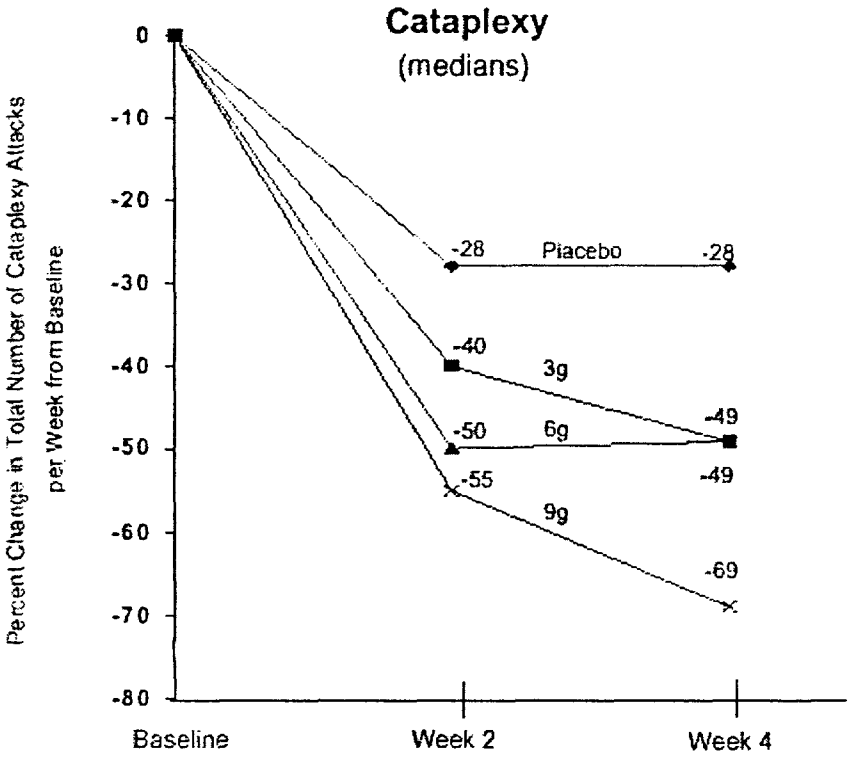


The overall treatment group comparison by ANCOVA was statistically significant at p = 0.021

As the table and figure above indicate:

- a dose-response relationship was observed across all treatment groups, based on the median change in total number of cataplexy attacks
- when each GHB dose-group was compared with placebo, the 9 g group showed a definite statistically significant superiority (p = 0.0008), and the superiority of the 6 g group approached statistical significance (p = 0.0529); however the difference between the 3 g and placebo groups was not statistically significant (the sponsor considers the difference between each of the GHB groups and placebo "clinically meaningful"; this may have a basis if the median change, but not the mean change is considered)

The time-course for the changes in the total number of cataplexy attacks was analyzed by the sponsor as follows. The percentage change in the median total number of cataplexy attacks was calculated based on the distribution of change values for each individual patient. The median of the individual differences is different from the median of the group differences. The mean change in the total number of cataplexy attacks (calculated by this method) at Weeks 2 and 4 for each treatment group is shown in the next figure and accompanying table



Treatment Group	Median Baseline Value	Median Week 2 Value	Median % Change from Baseline to Week 2	Median Endpoint Value	Median % Change from Baseline to Week 4
Placebo	20.2	15.0	28.0 %	15.2	28.1%
3g	20.0	8.75	39.7 %	9.9	49.3%
6g	23.0	16.0	50.0 %	8.0	49.2%
9g	23.5	16.69	54.6%	8.0	68.6%

The table and figure above indicate that the greater part of the change in all groups was evident by 2 weeks with smaller changes occurring between 2 and 4 weeks.

The within-group change in median from baseline to endpoint, in the total number of cataplexy attacks, was analyzed using the paired-t test. The change in each group was statistically significant as indicated by the following table

Treatment Group	P-value for within-group change from baseline to endpoint
Placebo	0.028
GHB 3 g	0.026
GHB 6 g	0.070
GHB 9 g	<0.001

6.11.8 Secondary Efficacy Analysis

The results of the secondary efficacy analysis are presented, in summary only, below. Most parameters are outlined in the next table

Parameters	Treatment	Change in Medians from baseline to endpoint	P-value for overall comparison *	P-value GHB group vs placebo
Excessive Daytime Sleepiness (Epworth Scale)	Placebo	-2.0	0.0006	
	3 g	-1.0		0.1137
	6 g	-3.5		0.1860
	9 g	-5.0		0.0001
Frequency of Daytime Sleep Attacks	Placebo	-0.26	0.0101	
	3 g	-0.20		0.1022
	6 g	-0.48		0.0497
	9 g	-0.48		0.0122
Duration of Daytime Sleep Attacks	Placebo	-3.10	0.0282	
	3 g	-5.00		0.9995
	6 g	-9.75		0.4413
	9 g	-7.95		0.0689
Number of Awakenings at Night	Placebo	+0.20	0.0217	
	3 g	-0.25		0.7628
	6 g	-0.21		0.5516
	9 g	-0.91		0.0035
Number of Hypnagogic Hallucinations	Placebo	-0.02	0.3092	
	3 g	-0.10		
	6 g	-0.15		
	9 g	-0.10		
Number of Sleep Paralysis Episodes	Placebo	0.00	0.3326	
	3 g	-0.07		
	6 g	0.00		
	9 g	-0.06		
Total Amount of Sleep Each Night	Placebo	8.57	0.6921	
	3 g	13.66		
	6 g	9.12		
	9 g	9.25		
Quality of Sleep	Placebo	-0.04	0.0009	
	3 g	-0.18		0.2446
	6 g	-0.42		0.0028
	9 g	-0.54		0.0010
Level of Alertness in the Morning	Placebo	0.00	0.0001	
	3 g	-0.13		0.6043
	6 g	-0.49		0.0006
	9 g	-0.42		0.0004
Ability to Concentrate	Placebo	-0.05	0.0012	
	3 g	-0.08		0.5440
	6 g	-0.29		0.0229
	9 g	-0.50		0.0007
Complete Cataplexy Attacks	Placebo	0	0.2131	
	3 g	-1.00		
	6 g	-1.62		
	9 g	-1.62		
Partial Cataplexy Attacks	Placebo	-2.72	0.0032	
	3 g	-3.69		0.5017
	6 g	-6.35		0.1494
	9 g	-10.00		0.0009

* based on ANCOVA

The above analysis indicates that at least one GHB dose group was superior to placebo at a nominally statistically significant ($p < 0.05$) level for the following

parameters: excessive daytime sleepiness, frequency of daytime sleep attacks, duration of daytime sleep attacks, number of awakenings at night, partial cataplexy attacks, quality of sleep, level of alertness in the morning, and ability to concentrate. However, given that there were 12 secondary efficacy measures, when adjustment was made for multiple comparisons only the following GHB-placebo comparisons continued to show statistical significance at the same level: Epworth Sleepiness Scale, quality of sleep, level of alertness, and ability to concentrate; for the Epworth Sleepiness Scale, quality of sleep and ability to concentrate it did appear that there was a dose-response with the 9 g/day dose being the most effective; for the Epworth Sleepiness Scale only the 9 g/day dose showed a statistically significant superiority to placebo.

The results of the Clinical Global Impression of Change in the severity of narcolepsy between baseline and endpoint are summarized in the following table which used the original categorical scale. The p-value for the overall treatment group comparison was 0.0010 based on the Cochran-Mantel-Haenszel test by Non-zero correlation

		GHB 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	2 (6%)	1 (3%)	0	2 (7%)
Much worse	0	0	0	0
Very much worse	1 (3%)	0	1 (3%)	0

A dichotomized analysis was then carried out. Responders were those in the "much improved" or "very much improved" original categories; those in all other categories were considered non-responders for purposes of the analysis presented below. The results of this analysis are presented below. The p-value is based on Fisher's exact test

		GHB 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	

As will be seen from the table above there was a statistically significant difference between the proportions of responders (who are much more numerous) and non-responders in the 9 g dose group

6.11.9 Statistical/Analytical Issues

- The data for a number of outcome measures, including the total number of cataplexy attacks, were not normally distributed; a log transformation was therefore performed
- Missing data were excluded from calculations; 16 patients received study medication but did not complete the study; these were included in the analysis at points prior to their discontinuation from the study
- No inter-site variability was seen
- Since the number of patients treated was small; no formal analyses were conducted between efficacy response and concomitant therapy or between response and past/concurrent illnesses

6.12 Safety Results

These were incorporated into the NDA Safety Review

6.13 Sponsor's Conclusion

- The 6 g nightly dose of GHB was marginally statistically significantly superior to placebo in regard to the reduction in total number of cataplexy attacks and the number of inadvertent naps during the day
- The 9 g nightly dose of GHB was superior to placebo at a statistically significant level in reducing the total number of cataplexy attacks, number of awakenings during the night, number of inadvertent daytime naps and excessive daytime sleepiness as measured by the Epworth Scale; and in reducing the patient's overall severity of illness as assessed by the CGI-C

6.14 Reviewer's Comments

6.14.1 Primary Efficacy Measures

- As noted above the primary efficacy analysis was not performed as specified in the original and amended protocols. Dr Sharon Yan, the statistical reviewer of this submission has however reproduced the per-protocol primary efficacy analysis using the sponsor's datasets. She has performed 2 types of analysis.